RABIES AND ENVENOMINGS

A NEGLECTED PUBLIC HEALTH ISSUE

Report of a Consultative Meeting

World Health Organization, Geneva

10 January 2007

World Health Organization

RABIES AND ENVENOMINGS

A NEGLECTED PUBLIC HEALTH ISSUE

Report of a Consultative Meeting
World Health Organization, Geneva
10 January 2007

World Health Organization

WHO Library Cataloguing-in-Publication Data

Rabies and envenomings : a neglected public health issue : report of a Consultative Meeting, WHO, Geneva, 10 January 2007.

1.Rabies – drug therapy. 2.Rabies – epidemiology. 3. Bites and stings – drug therapy 4.Bites and stings – epidemiology. 5.Immunization, Passive – utilization. 6.Antivenins – economics 7.Drug industry – economics. I.World Health Organization.

ISBN 978 92 4 156348 2 (NLM classification: WD 400)

ACKNOWLEDGEMENTS
This Report was developed by compiling the information provided at the WHO Consultative Meeting on RABIES AND ENVENOMINGS: A NEGLECTED PUBLIC HEALTH ISSUE that took place at WHO, Geneva on 10 January 2007. It was prepared by Professor D. Warrell, University of Oxford, Oxford, United Kingdom and Dr J-M Gutierrez, Universidad de Costa Rica, San José, Costa Rica that served as Rapporteurs and Dr A. Padilla, Project Leader, WHO.

Acknowledgements are due to all the participants for the information and comments provided during the Consultative Meeting. Special thanks are due to the speakers for their excellent presentations and written comments in support of the preparation of the Report.

Design & Layout: WHO Graphics
All photographs © Professor David Warrell
Printed in France

CONTENTS

SUMMARY

The people most affected by rabid dog bites, snake bites and scorpion stings usually live in poor rural communities where medical resources are often sparse. Because they lack a strong political voice, their problems tend to be overlooked by politicians and health authorities who are based in capital cities and are poorly informed about major public health issues affecting rural areas. Consequently, the impact of these health issues, although dramatic and economically significant, does not appear as a priority in the design of national public health programmes. These are therefore the most neglected among today's neglected global health problems.

The gravity of this situation should be discussed explicitly in national, regional and global health fora, in order to give these neglected diseases and their abandoned victims the attention they deserve. The situation is particularly poignant because, in contrast to some other diseases, a highly effective treatment already exists: the timely administration of specific antiserum. Rabies, for instance, is entirely preventable even after severe exposure, provided post-exposure prophylaxis, completed with rabies immunoglobulin, can be given. Similarly, the mortality and morbidity of snake bites and scorpion stings can be reduced to very low levels by timely administration of appropriate antivenoms.

The state of antisera production worldwide varies greatly. Public access to production technology following GMP standards, together with a concerted exchange process through workshops, direct technical assistance and innovation in specific aspects of manufacture and training, should allow the less developed manufacturing laboratories to strengthen their technical and production capacities. The possibility of partnerships should be promoted, including, in the case of antivenoms, the creation of groups developing the skills needed for the preparation of high quality venom pools and the subsequent preparation of antivenoms.

In summary, the current situation of the management of potentially rabid mammal bites and envenomings by snake bites or scorpion stings worldwide is a global public health emergency. There is a lack of awareness of the magnitude of the problem by health authorities and politicians alike, due to both the scarcity of adequate statistics on the real impact of these diseases, and the lack of advocacy by and on behalf of the affected groups, mostly children and rural agricultural workers. Worldwide production of these antisera has declined, due to economic constraints that have forced the withdrawal of some private producers, and to the weakening of public-sector manufacturers in the public sector in many countries. Moreover, the poor quality of some antisera and the resulting deficiency in their efficacy and safety, together with deficient distribution policies and inadequate training of medical and nursing staff requires an urgent international action. The gravity of this problem, and the complexity of its causes, demands from the public health community, and especially from the WHO and humanitarian international agencies, a concerted, rapid and effective global response to reduce the burden of human suffering incurred by rabies, and snake and scorpion envenomings.

INTRODUCTION

A meeting of stakeholders to discuss measures to ensure sustainable production of effective and safe therapeutic antisera[1] for treatment of rabid dog bites and envenomings due to snake bites or scorpion stings was convened by the Department of Medicines Policy and Standards, Health Technology and Pharmaceuticals Cluster, on 10 January 2007 at the World Health Organization (WHO) Headquarters, Geneva. This was the first meeting held by the WHO to address the need for strengthening the production systems of these biological preparations at a global level. Animal-derived antisera are the only effective treatments of envenoming, and are essential, in combination with vaccination and wound maintenance, for post-exposure rabies prophylaxis.

More than 40 participants from countries representing all WHO Regions were welcomed to the Consultative Meeting by Dr. Howard Zucker, Assistant Director General of the WHO Health Technology and Pharmaceuticals Cluster, and Dr. Hans Hogerzeil, Director, Medicines Policy and Standards Department. It was noted that there is a growing crisis in the production, accessibility and use of therapeutic antisera in regions where snake bites, scorpion stings and exposure to rabies have their greatest public health impact. These neglected public health conditions affect more than 14 million people annually, especially in the developing world; yet, effective treatment, critically dependent on therapeutic antisera (e.g. rabies immunoglobulin and antivenoms), is often unavailable or unaffordable, in particular in Africa and Asia. This results in high mortality and morbidity with grave socioeconomic consequences. Children and young agricultural workers are the worst affected by these conditions. Therapeutic antisera are included in the WHO Essential Medicines List (1).

The shortage of therapeutic antisera has become a critical global health issue. Many manufacturers in the developed world have abandoned production of antisera because of market limitations in countries with developed economies. In developing countries, the remaining producers of antisera are vulnerable to fluctuations and uncertainties in market demand, to private takeover of former national companies, and to the lack of financial investment to upgrade the facilities to comply with good manufacturing practices (GMP). As a result, the world is at risk of losing a critical mass of skill, experience and production capacity that is vital to the maintenance of an adequate supply of antisera of assured quality.

The crisis in the availability of rabies immunoglobulin and antivenoms calls for an international effort to ensure expertise in developing countries and, when needed, facilitate the transfer of technology. There is also a need to address major logistic problems in distribution, particularly to ensure maintenance of an adequate cold chain. In addition, it is recognized that a lack of knowledge about the correct medical management of dog bites, as well as bites and stings by venomous animals, including the appropriate use of antisera, is further compromising the efficient clinical use of the limited quantity of product available.

WHO was recognized as the health agency most qualified to lead development and implementation of a global strategy on therapeutic antisera. This meeting represented the first effort to identify and bring together existing and potential partners, including clinicians, epidemiologists, manufacturers, government representatives, regulators and nongovernmental and international organizations.

[1] For the sake of simplicity, the term antiserum (plural antisera) is used throughout this document to refer to animal derived (usually equine) therapeutic preparations constituted of purified IgG molecules or products of their enzyme digestion used in the treatment of snake bite or scorpion sting envenomings or in the post-exposure prophylaxis of rabies.

Chapter 1

RABIES AND ENVENOMINGS: neglected diseases

Rabies and envenomings are diseases that result from bites by rabid mammals or bites and stings by venomous animals, especially snakes and scorpions. In all cases, appropriate early treatment, including therapeutic antisera, can prevent life-threatening systemic spread of the virus or venom toxins.

RABIES

In most parts of the world, rabies is endemic (Figure 1). Rabies virus, a rhabdovirus present in infected animal's saliva is inoculated into the bite wounds (Figure 2a), enters peripheral nerves and spreads to the central nervous system where it causes a lethal encephalomyelitis (Figure 2b). Once clinically established, rabies encephalomyelitis is almost invariably fatal, but the disease is entirely preventable provided that complete post-exposure prophylaxis is implemented promptly (2).

The regimen of post-exposure prophylaxis for people bitten by rabid mammals that is currently recommended by WHO consists of a combination of wound cleaning, active immunization with a tissue culture rabies vaccine and passive immunization with equine (or, rarely, human) rabies immunoglobulin (3). This has proved highly effective in preventing infection. Inclusion of rabies immunoglobulin in the post-exposure regimen is regarded as mandatory for WHO "category 3" exposures (bites or scratches that break the skin and contamination of mucosae with saliva) which constitute about 60% of all cases. The efficacy of equine rabies

Figure 1 Global distribution of classic rabies virus (Genotype 1) and European and Australian bat lyssaviruses

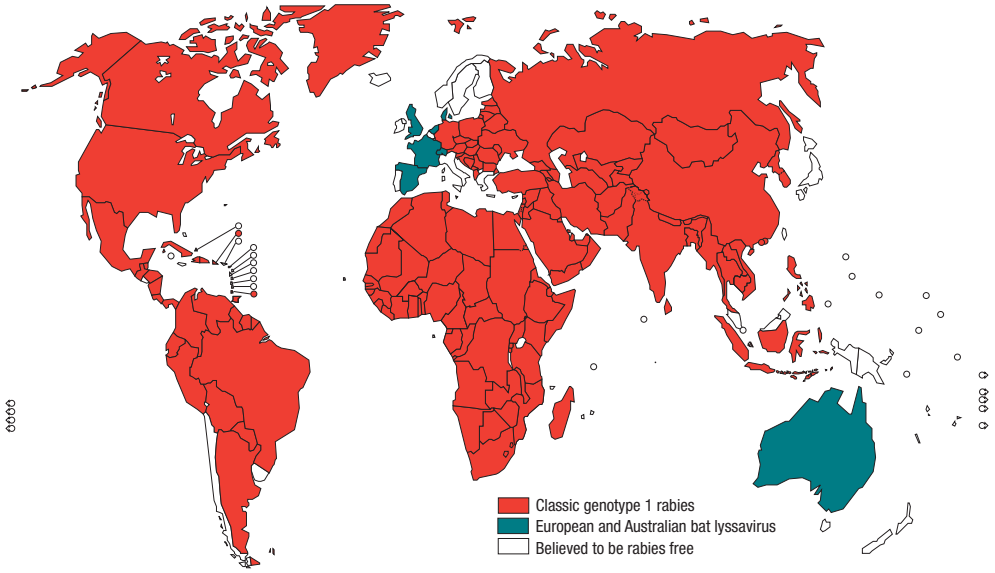


Figure 2a Facial bite wounds inflicted by a rabid dog and carrying a high risk of rabies

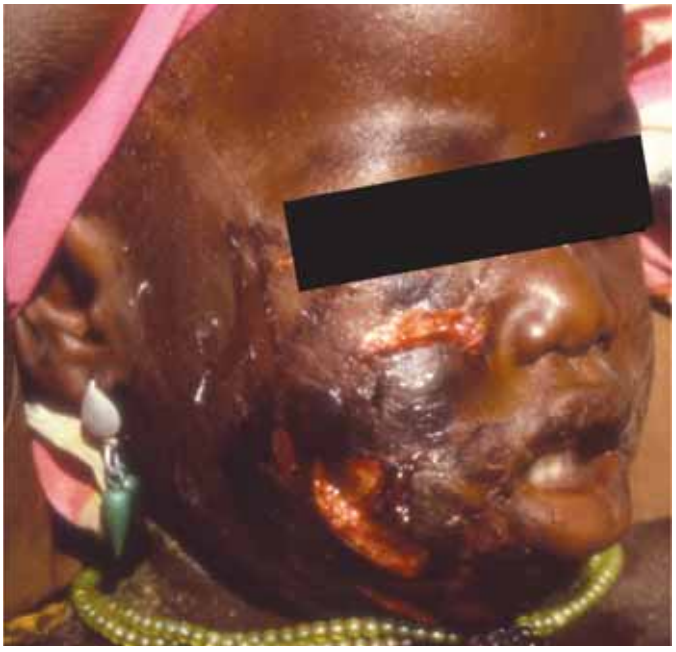
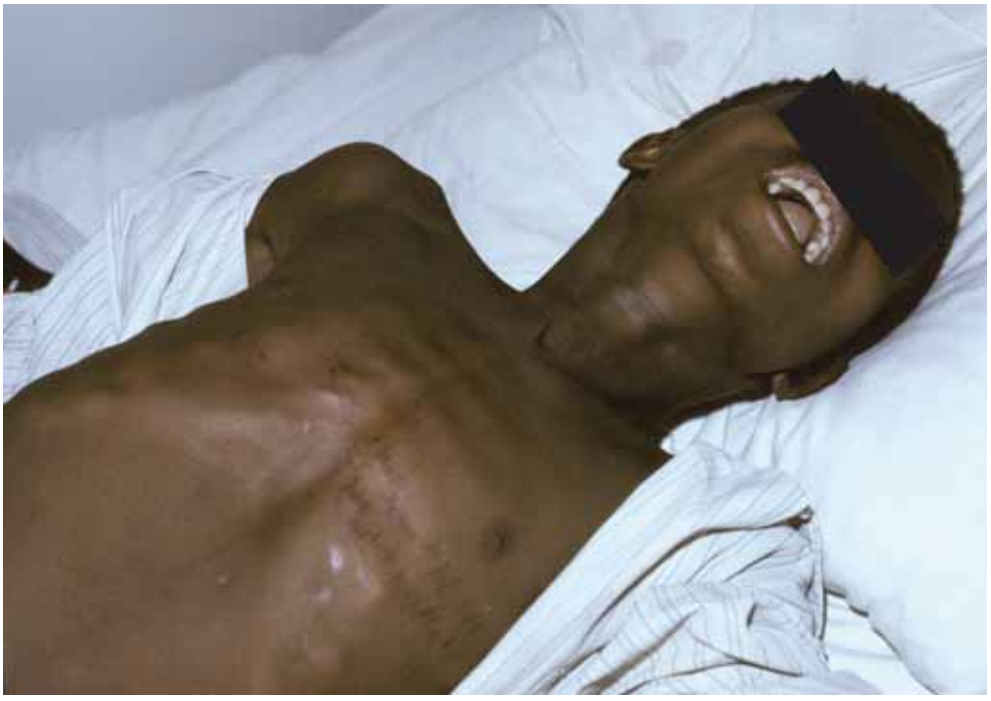


Figure 2b Rabies encephalomyelitis: hydrophobic spasm



immunoglobulin was established by studies of Iranian patients who had been attacked by rabid wolves (4,5). Rabies immunoglobulin is infiltrated around the bite wounds and any residual immunoglobulin solution is injected intramuscularly.

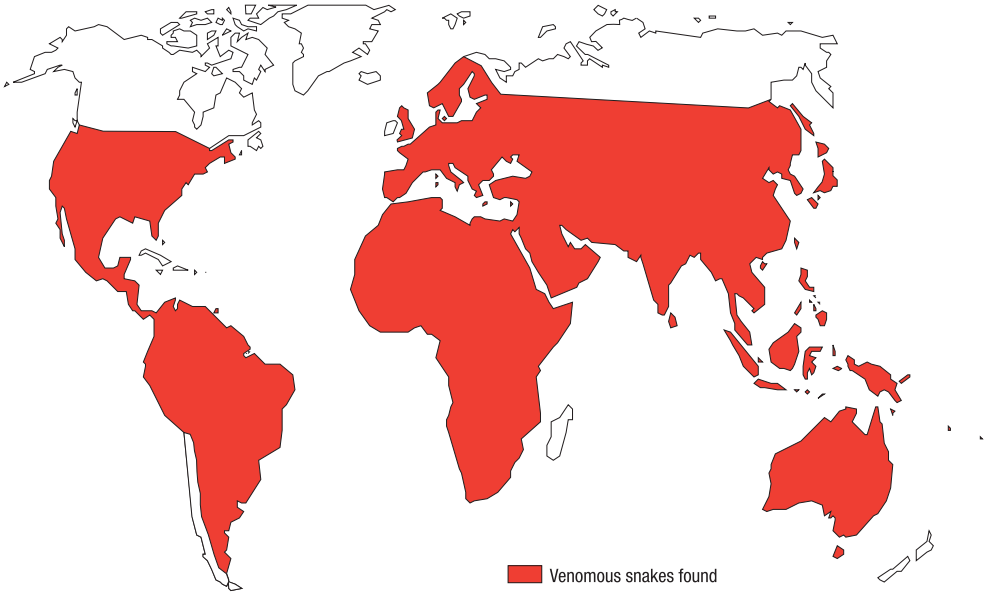
SNAKE BITES

Envenomings by snake bite create medical emergencies that involve different organs and tissues, depending on the species responsible for the bite. Most severe cases result from bites by members of the families Viperidae (pit vipers and true vipers) and Elapidae (cobras, kraits, mambas, coral snakes, Australasian species and sea snakes). Venomous snakes are widely distributed throughout the world (Figure 3) except for a few islands, frozen environments and high altitudes (6,7,8).

Life-threatening effects of snake bite envenoming include shock, spontaneous systemic bleeding, paralysis involving respiratory muscles, generalized break down of skeletal muscle (rhabdomyolysis), acute renal failure and infection of necrotic tissue at the site of the bite (Figure 4a,b). Viperid snake venoms cause local extravasation of plasma and blood into the bitten limb, inflammation and tissue damage, due to the action of toxins on muscle, skin and blood vessels, resulting in pain, oedema, blistering, bleeding and necrosis of skin, subcutaneous tissues and muscle. Some elapid snake venoms (e.g. African spitting cobras and some Asian cobras) can also cause extensive local necrosis. Viperid snake venoms induce spontaneous systemic haemorrhage (e.g. into the brain or gastrointestinal tract), secondary to microvascular damage, coagulopathy and platelet dysfunction, together with cardiovascular shock and renal failure. Elapid snake venoms usually cause neurotoxicity, in particular descending paralysis that may lead to respiratory failure. Some venoms provoke systemic myotoxicity, associated with myoglobinuria, hyperkalaemia and acute renal failure.

Since these local pathological effects develop rapidly and irreversibly after venom injection, those who survive snake bite may suffer permanent sequelae including the results of the locally necrotic effects of viper and some elapid venoms, requiring amputation of digits or limbs

Figure 3 Global distribution of dangerously venomous snakes



(Figure 5a,b) and causing contractures (Figure 6a), tendon damage, arthrodeses and chronic infected ulcers and osteomyelitis that may cause malignant transformation (squamous cell carcinoma) (Figure 6b). Chronic renal failure, chronic pituitary-adrenal failure and neurological sequelae from haemorrhagic strokes also occur.

Figure 4a Snake bite paralysis: life-threatening total flaccid paralysis requiring assisted ventilation (Malayan krait *Bungarus candidus*)

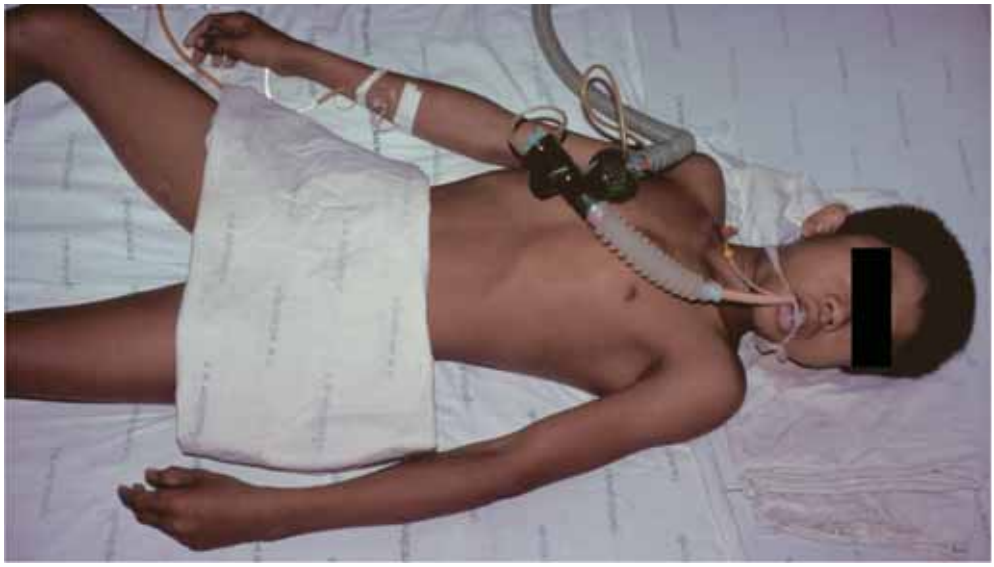
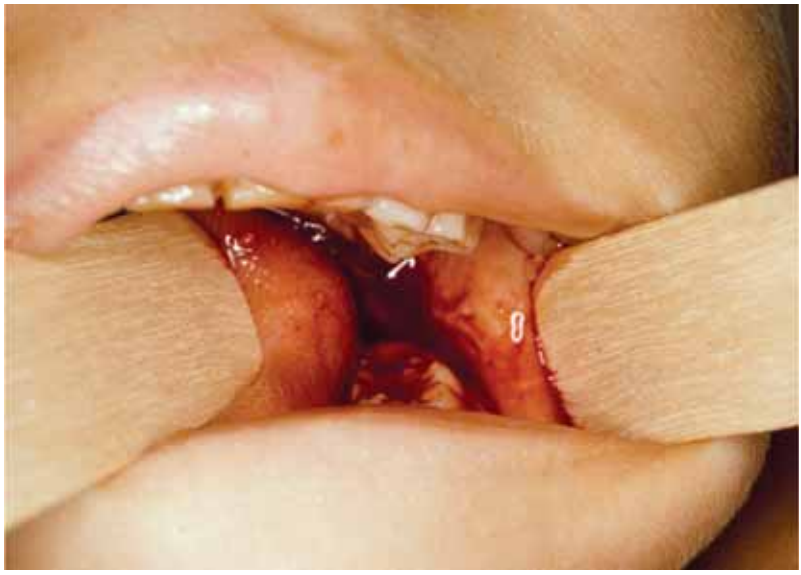


Figure 4b Snake bite haemorrhage from the gingival sulci (Malayan pit viper *Calloselasma rhodostoma*)



The clinical management of snake bite envenoming is centred on the intravenous administration of antivenom, together with a series of ancillary interventions that may include ventilatory support for neurotoxic envenoming, fluid replacement for hypovolaemic shock, dialysis for acute renal failure, tetanus prophylaxis and antibiotics for local wound infection and surgical debridement of necrotic tissue, followed by rehabilitation to restore full function in the bitten limb. Because of the large inter- and intra- specific variation in venom composition and immunogenicity, antivenoms are manufactured using the venoms that are most relevant for a given geographical region. They are therefore specific for snake species of a given region, and are usually ineffective in other regions inhabited by different species of snakes.

Figure 5a Necrosis – gangrene of a limb caused by neglected terciopelo (*Bothrops asper*) bite

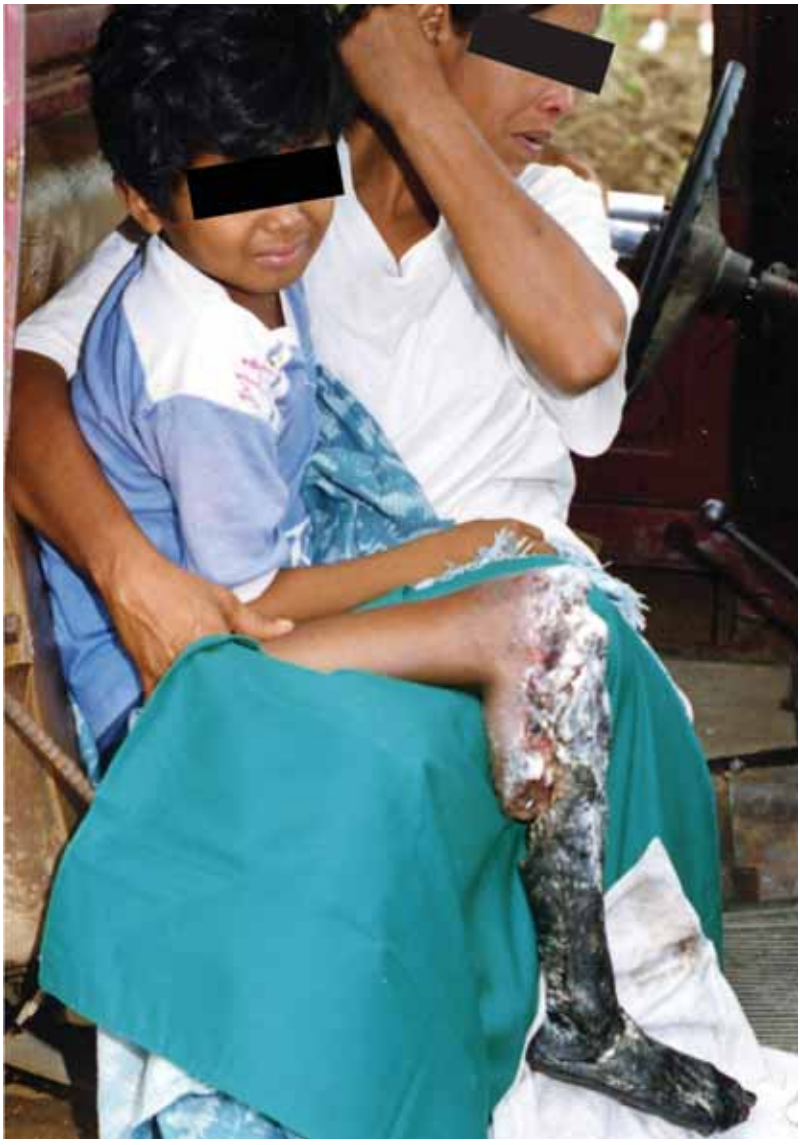


Figure 5b Amputations of gangrenous limbs from common lancehead (*Bothrops atrox*) bites

Figure 6a Hypertrophic scar following black-necked spitting cobra (*Naja nigricollis*) bite

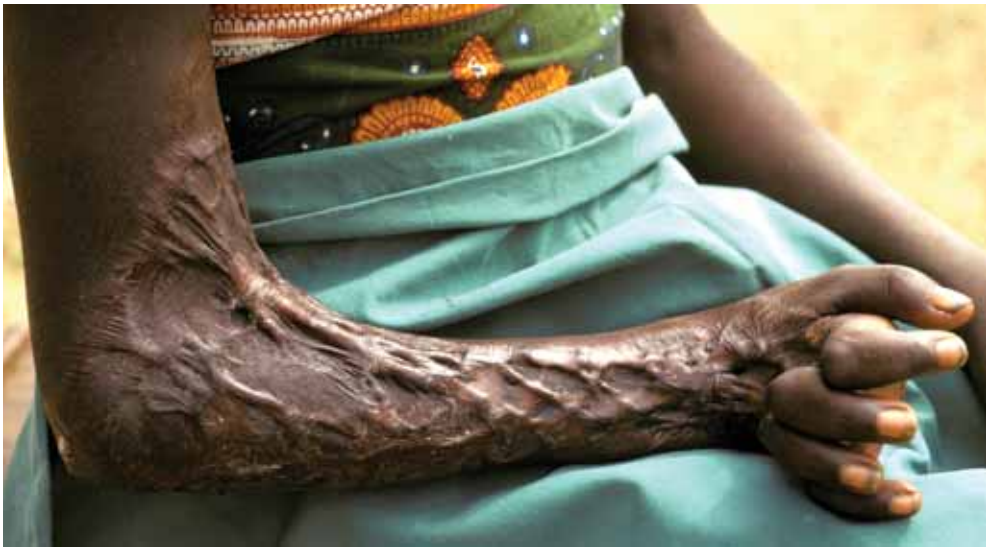


Figure 6b Malignant transformation (Marjolin's ulcer) to squamous cell carcinoma in a chronic snake bite ulcer (*Naja nigricollis*)

SCORPION STINGS

Envenomings by scorpion stings are also an important, yet neglected, health issue in many parts of the world, particularly in the extreme Northern and Southern parts of Africa, the Middle East, Southern states of USA, Mexico and parts of South America, and the Indian sub-continent. Scorpion venoms, which are especially lethal in young children, release autonomic nervous system mediators causing myocardial damage, cardiac arrhythmias, pulmonary oedema, shock, paralysis, muscle spasms and pancreatitis. Early administration of antivenom is highly effective, together with intensive care support in severe cases. However, the rapid tissue distribution of scorpion venom toxins and their ability to cause early death especially in young children, demands early treatment with antivenom and full cardio-respiratory support.

Chapter 2

EPIDEMIOLOGY: the burden of disease

RABIES

Globally, rabies is the tenth leading cause of death due to infection in humans. The threat of rabies exists in most parts of the world (Figure-1). Predominantly, it affects poor people in developing countries and its true incidence may be underestimated. In the year 2005, there were reports estimating that nearly 60,000 human fatalities occur each year mostly in Asia and Africa (9). A WHO-sponsored multicentric study estimated that at least 20,000 deaths occurred annually in India alone (10). In China, rabies has, since May 2006, become the leading cause of infectious disease mortality, killing 3,293 people in 2006, 27% more than in 2005.

More than 99% of all human deaths from rabies occur in the developing world (11) and almost half of those dying of rabies and requiring rabies immunoglobulin are children less than 15 yrs old. The lack of supplies of rabies immunoglobulin and training in its correct use, condemns more than 55,000 people (90% confidence interval (CI) = 24,000-93,000) worldwide each year to die an agonizing death from rabies. Even this figure underestimates the full burden of human suffering as millions of victims of potentially rabid bites suffer protracted anxiety resulting from the uncertain and sometimes very long incubation period of this infection (up to 6 years or more) (12). Deaths due to rabies are responsible for an estimated health burden of 1.74 million DALYs ('Disability adjusted life years') (90% CI = 0.75-2.93). Morbidity and mortality following side-effects of nervous-tissue vaccines account for an additional 0.04 million DALYs. The annual cost of rabies is estimated USD 583.5 million (90% CI = USD 540.1-626.3 million) in Asia and Africa alone (9).

Assuming that 60% of post-exposure prophylaxis regimens require the administration of an average number of two vials of rabies immunoglobulin (dose according to body weight), the estimated annual requirements for this antiserum are: 1,200,000 vials for Africa, 350,000 for the Americas, 200,000 for East Mediterranean region, 4 million for the West Pacific, including China, and 3.2 million for South-East Asia, including India, thus resulting in a grand total need for approximately 9 million vials every year. These calculations are based on available epidemiological data that undoubtedly underestimate the size of the problem.

SNAKE BITES

Snake bites and scorpion stings are well-known medical emergencies in many parts of the world where these animals are distributed (Figure-3). Agricultural workers (the countries' food producers) and children are the most affected. The true worldwide incidence of snake bite envenoming has proved difficult to estimate. It has been reported that there are 5 million snake bites, resulting in 2.5 million envenomings, 125,000 deaths and perhaps three times that number of permanent sequelae in the world each year (13). The incidence of snake bite mortality is particularly high in Africa, Asia, Latin America and New Guinea. In India alone there may be as many as 50,000 snake bite deaths each year. Many estimates of snake bite mortality and resulting permanent morbidity are based on hospital returns, which greatly underestimate the real impact of this health problem, since most people affected by snake bites do not seek hospital treatment but prefer traditional remedies (14). Snake bite victims in rural areas may die at home unrecorded (15). A number of community-based studies have begun to disclose the true burden of snake bite mortality. For example, in the Eastern Terai region of Nepal, there were 162 snake bite deaths per 100,000 population per year (16), and in a region of Nigeria, the incidence of snakebites was 497 per 100,000 people per year, with a fatality rate of 12.2% (17). A study performed in Malumfashi, Nigeria, showed that there were 40-50 snakebite cases, with 4 deaths per 100,000 population per year. Nineteen percent of those bitten developed persistent sequelae and only 8.5% sought hospital treatment (18) while in Kilifi District in coastal Kenya, 68% of snake bite victims consulted a local muganga (“witch doctor”), only 27% went to hospital and 36% were left with permanent sequelae (19). Therefore, the actual impact of this neglected health problem on a global basis is much higher than has been previously realized. Analysis of the burden of human suffering attributable to these envenomings from a broader public health perspective reveals their greater impact. Evaluated using DALYs , the impact of envenomings is very high (estimated in 2 million DALYs per year for sub-Saharan Africa), because most victims are children or young agricultural workers, many of whom are left for the rest of their lives with permanent physical or psychological consequences of envenoming. The impact of snake bite as an occupational disease on the economy is also highly significant, as many of the affected people are agricultural workers (food producers) whose families, community and country are highly dependent on the products of their physical activity.

SCORPION STINGS

The true incidence of scorpion sting envenoming is not known because many cases do not seek medical attention. However, it has been estimated that there are approximately 1 million stings per year. In Mexico alone, 250,000 scorpion stings are reported yearly, but fatalities have declined from 2,000 to less than 50 per year following widespread distribution of antivenoms. In Tunisia 40,000 stings, 1,000 hospital admissions and 100 deaths are reported each year. There is a high incidence in other parts of Northern Africa, the Middle East (notably Iran), India and Latin America. In Khuzestan, south-west Iran, where scorpion stings are the fourth leading cause of death, 12% of the 25,000 stings treated each year and more than 95% of the fatalities are attributable to *Hemiscorpius lepturus* (Hemiscorpiidae) (20). In Brazil, 37,000 scorpion stings and 50 deaths were reported in 2005 and, in this country, scorpion stings are an emergent health problem, due to the adaptation of some scorpion species to the urban environment.

THE NEED FOR THERAPEUTIC ANTISERA

On the basis of the epidemiological figures presented above, the current annual need for antisera for post-exposure rabies prophylaxis and for the treatment of snake bite and scorpion sting envenomings amounts to 9 million vials of rabies immunoglobulin and 10 million vials of antivenoms. Unfortunately, the present worldwide production capacity is well below these needs. There are various reasons for this situation: governments and health authorities ignore antisera because of their neglected status; a number of private producers have stopped manufacture because of market instability and unprofitability; the prices of some products are completely unaffordable by the health systems of developing countries; some former public manufacturers have been privatised, with a consequent drop in antiserum production because is perceived to be unprofitable. Furthermore, the weakening of public health budgets has resulted in deterioration of infrastructure and equipment for antisera production in public institutions. This resulted in a global reduction in antisera production and accessibility. This trend should be reversed through concerted actions by national, regional and world health authorities and manufacturers.

Chapter 3

PRODUCTION AND CONTROL OF THERAPEUTIC ANTISERA

The therapeutic use of antisera started at the end of the 19th century, following the pioneering work of von Behring, Kitasato, Roux and Calmette. The first antivenoms were developed by Calmette and Phisalix and Bertrand in 1894 (21). At the dawn of immunology, it was observed that animals immunized with specific toxins or venoms developed an antibody response that could be beneficial to the treatment of many different diseases, from tetanus and diphtheria to snake bite envenomings and rabies. Thereafter, passive immunization, or serotherapy, became a powerful therapeutic tool based initially on the use of non purified serum that caused a high incidence of adverse effects. During the 20th century, with the development of methods to purify serum proteins, fractionation protocols were introduced in the production of antisera and therapeutic preparations were obtained of either intact antibodies (IgG) or antibody fragments [F(ab')2] against antigens of clinical relevance.

Table 1 Treatment and diagnostic applications of animal derived hyper-immune antisera

Infections	Rabies, tetanus, diphtheria, botulism, gas gangrene
Poisoning	Drugs (digoxin) and plants containing cardiac glycosides
Venomous bites and stings	Snakes, lizards, scorpions, spiders, bees, caterpillars, fish, jellyfish, ticks
Emerging pathogens	Potential for treatment and diagnosis of some emerging diseases
Bio-terrorism agents	Diagnosis and antidote for specific bioterrorism agents

CURRENT SITUATION

High quality preparations of heterologous immunoglobulins (intact IgG molecules), or products of their enzyme digestion, can now be manufactured following methods largely in the public domain. Many laboratories prepare horse-derived antisera using various modifications of the original Pope method (22), based on pepsin digestion and ammonium sulphate precipitation, to yield F(ab')2 antibody fragments (23, 24). Other preparations consist of intact IgG molecules, purified by caprylic acid precipitation of non-IgG serum proteins (25, 26). Additional steps such as ion-exchange chromatography have been incorporated by some manufacturers (23, 24).

Manufacturers therefore use very different methods, some of which are based on traditional plasma fractionation protocols, others on more complex steps, as shown at a WHO workshop convened to discuss antivenom production and control procedures (27). A recent workshop of Latin American public laboratories also highlighted the variety of techniques

used in antivenom manufacture (28) and their respective impact on product yield, safety and quality. The information available showed ample opportunities for technology transfer as well as the need for improved production processes and training of manufacturers in the developing world.

A list of antivenoms available in 1995 was prepared by Meier (29) but several laboratories have stopped manufacture since then. Currently, many laboratories face significant difficulties in pursuing the manufacture of antisera, improving the quality of the products or increasing the production capacity. Some production centres require extensive upgrading of the infrastructure, equipment and manufacturing technologies, to meet required quality and safety standards, others lack qualified staff. Those with more advanced manufacturing methods require a clearer definition of the size and markets needs in order to design reliable long-term manufacturing strategies.

The diverse scenarios outlined above support the development of a worldwide strategy to increase antiserum production to respond to clinical needs. A detailed analysis of the situation is required together with the design and implementation of different approaches which should be adapted to product needs.

STRENGTHS AND WEAKNESSES OF CURRENT ANTISERA MANUFACTURE

Technologies for the fractionation of animal serum and the purification of intact IgG or F(ab')2 fragments are available in the public domain and production protocols have been reported in international publications. Relevant guidelines on the principles of GMP are also available (30) and can be adapted to the manufacture of animal-derived antisera. The openness of this technological field, and the fact that many groups involved in research, development and production of antisera are public institutions, brings further possibilities for the establishment of a dynamic process of training and transfer of technology .

In the case of envenomings by snake bites and scorpion stings, there is extensive scientific knowledge on the clinical, pathophysiological, biochemical and immunological characteristics of venoms. The species responsible for most snake and scorpion envenomings in the different regions of the world have been identified and many of their venoms partially characterized. There is also abundant scientific literature on the cross-reactivity of antivenoms against venoms from different species of snakes within a specific geographical region. Such information can be directly applied to the design of immunizing mixtures to raise effective neutralizing antisera against the most relevant venoms from a given area or geographical region.

With regard to the rabies virus, this is an excellent immunogen which readily induces strong immune responses in horses, facilitating the preparation of rabies immunoglobulins.

In addition, the field of human immunoglobulin preparations for intravenous use has witnessed great advances in the plasma fractionation methodologies and viral reduction procedures introduced in the production processes (31, 32). This knowledge can be helpful to the manufacturers of animal-derived antisera in order to improve the quality and safety of these products.

On the other hand, the production of antisera faces difficulties that need to be addressed and solved to guarantee adequate global supply. The most important weaknesses are:

(1) low volumes of production;
(2) poor safety and efficacy of some products and;
(3) deficient or non-existent regulation and control of antisera in some countries

Many manufacturers in the public sector operate on a small production scale, and, as such, are unable to satisfy the national demand. This highlights the need for substantial investment in equipment, infrastructure and training of technical and administrative staff to ensure self-sufficiency.

ANTISERUM POTENCY

Effective treatment of rabies and envenoming is critically dependent on the availability of good quality antisera. Deficient quality assurance and quality control practices, together with the lack of regulatory policies in some countries, result in the production or importation of antisera with low neutralizing potency. Ineffective antivenoms may also be prepared because of an inappropriate selection of the venoms used as immunizing mixtures. This illustrates a lack of information on the snake fauna of the area or region as well as on the composition and immunochemistry of venoms. The problem is aggravated by the lack of preclinical control of many antivenoms.

The neutralization by antivenoms of the most relevant toxic activities of the venoms with greatest medical significance in a particular territory should be assessed. For example, several groups in Latin America have succeeded in the preclinical characterization of antivenoms against venoms from different areas in the region. As a result, the neutralizing ranges of many antivenoms have been established and used to support the distribution of antivenoms within, and occasionally, among countries (33, 34). However, this information is lacking for many antivenoms and venoms throughout the world.

The control of the biological activity of antivenoms depends, among others, on the preparation of representative venom pools obtained from the snakes and scorpions species targeted (27). This requires concerted efforts among zoologists, toxinologists, manufacturers and regulators to establish protocols for the maintenance in captivity (and ideally for the reproduction) of snakes and scorpions, the appropriate venom collection and storage, the design of representative venom pools and the testing of venoms toxicity. In order to guarantee an appropriate geographical spectrum of efficacy of an antivenom, it is essential to know in which parts of the country or region the specific envenoming is predominant. The control of the neutralizing ability of an antivenom preparation should be performed using pools of well-characterized venoms, taking into account the known causes of intra-specific variation in venom composition and antigenicity (35). Currently, there are many lacunae in the preparation and use of venom pools for antivenom standardization and control. This explains the discrepancies in the potency tests carried out in different laboratories. To solve this problem, a network of quality control laboratories should be formed and the sharing of standard venoms for use in assays should be encouraged (36,37). The experience in Brazil, where a well-defined national standard venom of the jararaca snake *Bothrops jararaca* is prepared and distributed to manufacturers and quality control laboratories, is a good example of national and inter-laboratory coordination.

The regulatory overview and quality control of rabies immunoglobulin is poor or absent in some countries. Preclinical characterization can provide only preliminary guidance about therapeutic efficacy which can be established only through clinical studies or post-marketing surveillance information.

ANTISERUM SAFETY

Antiserum safety is another aspect that demands careful attention. Upon parenteral administration, antisera may induce early or late adverse reactions.

Early adverse reactions (EARs):

Intravenous administration of antisera results in EARs in a variable proportion of patients. These are best categorized as anaphylactic reactions. Clinical features include urticaria, itching, fever, tachycardia, vomiting, abdominal colic, headache, bronchospasm, hypotension and angioedema (38, 6). The incidence of EARs depends on the quality, dose, protein content, route of administration and speed of intravenous injection or infusion (38). Unless patients are observed closely during at least 2 hours after intravenous antivenom administration, EARs may not be detected. This lack of surveillance leads to underreporting of side effects. With antivenoms of good quality profile, there is a low incidence (less than 10%) of generally mild EARs, mostly urticaria and itching. However, for other products, the incidence of such reactions may be as high as 85%, including potentially life-threatening systemic disturbances such as hypotension and bronchospasm (6). EARs are attributable, in part, to the physicochemical characteristics of the particular antivenom preparation. The presence of protein aggregates is believed to contribute to complement activation (39) and to the onset of EARs (38). The formation of such aggregates often reflects deficiencies during fractionation or freeze-drying of products. Likewise, the presence of contaminant proteins contributes to the reactogenicity of antisera, as well as the total amount of protein administered which is related with the incidence of both EARs and late antivenom reactions (LAR). The incidence of EARs would not be attributable to the use of intact IgG, since antivenom immunoglobulin preparations purified by caprylic acid fractionation of horse plasma present a good safety profile (40).

Equine rabies immunoglobulin has proven extremely safe with a reaction rate of 1.13% (41) because it is never administered intravenously and the total amount of equine protein injected is relatively low. Some antisera carry the risk of causing pyrogenic reactions, implying poor manufacturing practices (6).

Late adverse reactions (LARs):

These resemble classical serum sickness and are also described as a consequence of antiserum therapy. Their true incidence is poorly known, mostly because patients leave health centres within the first few days after treatment, and the manifestations of serum sickness do not appear until 7-14 days post-treatment. However, in one series of patients who received a poorly refined antivenom and where a thorough follow-up was possible, it was shown that the incidence of serum sickness increased to almost 100%, proportionally to the total dose of antivenom infused and, the interval between treatment and the appearance of symptoms decreased (42).

There have been no reports of infectious diseases transmitted to humans by the administration of animal antisera, but the microbiological safety of these products is of growing concern. There is an urgent need to validate the capacity for viral removal and/or inactivation that can be achieved by currently-used manufacturing processes of antisera. Preliminary results from a limited number of studies suggest that some of the production steps currently

used, such as acid pH, pepsin digestion, caprylic acid precipitation and possibly others, can be effective in virus reduction (43, 32). However, this area requires significant collaborative efforts among manufacturing laboratories and research groups, to perform viral validation studies and transfer of know-how for correct implementation.

Problems associated with poor safety of some antisera preparations are clearly linked to failures or lack of GMP. The principles of GMP should cover all steps in antiserum production, including the handling and care of animals used for immunization, the preparation of the appropriate venom and immunization protocols, the bleeding of horses, the blood and plasma collection procedures, the plasma fractionation process as well as the steps of aseptic filling and freeze-drying of the final product. Similarly, the production of water, the cleaning and sanitisation of equipment and clean rooms, and the design of all production systems should strictly follow GMP principles. Failure to fulfil these requirements results in poor quality and safety profiles. These problems are also associated with defective training of the staff involved in antiserum production, lack of technological innovation and lack of investment in the implementation of GMP.

There are ample opportunities for improving the production of antisera at a global level. A WHO coordinated training programme should be established for strengthening technical expertise in local and regional laboratories aimed at the implementation of GMP in all manufacturing facilities.

CLINICAL STUDIES

The serious lack of well-designed, controlled clinical trials in the evaluation of the efficacy and safety of antivenoms is a deficiency that needs to be addressed at a global level. Some clinical studies have been published, the first in 1974 (44), and provided valuable information on relative efficacy of various antivenoms, initial dosage, pharmacokinetics and safety profile (40,45). Quite often, antivenoms are introduced in a given country or region without appropriate clinical validation of their efficacy or safety and in absence of regulatory oversight. This may have serious public health implications. The reported use of counterfeit products and imported geographically-inappropriate non-specific antivenoms in some countries, notably in Africa, further aggravates the problem. The therapeutic failure of these products leads to a loss in confidence in medical treatment of envenomings within the population and a return to the use of ineffective and sometimes dangerous traditional methods.

Chapter 4

DISTRIBUTION AND APPROPRIATE USE OF THERAPEUTIC ANTISERA: failure to supply those at greatest need

Failures in the distribution of antisera to places where they are needed are another factor contributing to the gravity and complexity of this public health problem. In some instances, antisera are held in the main cities, where rabies and envenomings are rare, instead of being distributed to peripheral health clinics in rural areas where dog and snake bites, and scorpion stings are frequent. This reflects defective distribution planning which is associated with a lack of coordination between those who understand the epidemiological pattern of the disease and those responsible for the antiserum distribution. As a consequence, antivenoms are sent to places where there are no snake bites or where the particular antivenoms are ineffective. Furthermore, rural health facilities may lack sufficient antivenoms to treat even a single case of envenoming, because the health authorities are uninformed of treatment protocols.

Ensuring adequate supply of antisera will inevitably incur some wastage, as products become expired. Pharmacies should have sufficient stocks to cover contingencies such as seasonal epidemics of snake bites. In Brazil, where approximately 4% of all antivenom is misused (wrong species or non-venomous snake bite), double the expected antivenom requirement (cases x average dose) is supplied to health centres. Therefore, an adequate distribution policy of antiserum demands some form of epidemiological surveillance programme and close communication between clinicians, other health workers, epidemiologists, governmental procurement offices and manufacturers. Also, inadequate storage and transportation of antisera may result in physical destruction of vials and ampoules (e.g. by freezing of liquid antisera). The lack of an adequate cold chain may result in deterioration and inefficacy of liquid antisera and cold chain facilities created for other health needs (e.g. vaccines) should be used more thoroughly. Decisions on distribution of liquid and freeze-dried antisera, when both formulations are available, should be based on careful and detailed analysis of the prevailing conditions in each region and health clinic facilities. The design of effective strategies for distributing antisera is thus an essential component of any global effort to confront this serious crisis.

Inadequate access to therapeutic antisera is also related to the lack of health facilities in many rural regions of Africa, Asia, Latin America and New Guinea, together with a lack of adequate transportation of patients to the nearest health post. This difficult and dangerous situation becomes even worse when rural populations are uninformed about how to proceed when someone is bitten by a possibly rabid dog or a snake, or is stung by a scorpion. Community public education campaigns are needed to address this problem.

Besides the inadequate supply, distribution and accessibility of safe and effective antisera, another major issue is the lack of training of health workers on how to use these products and how to conduct appropriate clinical management of these medical emergencies. In many countries, medical and nursing school curricula do not include the treatment of rabies and envenomings. These subjects are also omitted from the training programmes implemented in rural hospitals where these conditions are common. The development of national and regional guidelines for the treatment of envenomings, based on consensus views, has been largely neglected; exceptions include the Guidelines from the WHO Regional Office for South East Asia (SEARO) (46). Efforts need to be made for a wide distribution of guidelines among physicians and nurses in rural hospitals. The end-result of all these deficiencies is a dearth of standardized and adequate treatment protocols and, consequently, the existence of a significant diversity in clinical practice and a profusion of empirically-derived protocols. Another problem associated with antivenom treatment is the uncertainty about the criteria for rational use and initial and repeated dosage. In some hospitals, a small dose of antivenom is given routinely to every patient presenting a snake bite, irrespective of whether there is any evidence of envenoming. This practice squanders scarce resources and unnecessarily exposes unenvenomed people to the risk of antivenom reactions. In other situations, excessive doses are administered without justification, thus wasting this precious commodity. The results of any programme of medical staff training and improved access to antisera should be monitored by continuous surveillance of the appropriateness of antisera usage.

Chapter 5

SCALES OF PRODUCTION: the need to strengthen capacity

Various types of support are needed to improve the quality and the production capacity of antisera to meet worldwide needs. Some producers are likely to have 'global' market perspectives, i.e. a willingness to produce antivenoms for different regions of the world, based on demand, humanitarian needs and on agreements with national and regional health authorities. A strategy towards the consolidation of 'regional' laboratories should also be considered. These regional manufacturers should have reliable manufacturing processes and ability to ensure regional distribution of antisera of consistent quality and safety, in accordance with GMP standards. They should be encouraged and supported to increase production output and to demonstrate the efficacy of the antivenoms against the species of snakes and scorpions of greatest medical importance in the regions of distribution. Similar objectives prevail for the manufacture of safe and effective rabies immunoglobulins. Fostering 'regional' producers could be complemented by the strengthening of production laboratories, at national level, willing to improve product quality and to cover the national demand. This scenario, involving local, regional and global producers alike, and supported and coordinated by national and world health authorities, would guarantee an adequate and sufficient supply of safe and effective antisera.

THE CRITICAL CASE OF AFRICA: need for a multifaceted approach

The crisis in antiserum supply and correct use is most critical and urgent in sub-Saharan Africa. The number of antisera manufacturers supplying this region has decreased dramatically and the total amount of antiserum being offered is insufficient to cover even the most basic needs in this region. Moreover, the price of a vial of antivenom ranges between $50 and $150, which often represents a high portion of the yearly income of a rural worker. Since an average adequate treatment usually involves the administration of at least 3 vials of antivenom, plus the use of ancillary therapeutic interventions, the cost of treating a single envenomed patient in Africa may reach around $200. In addition, some products imported to Africa are inappropriate and ineffective for the treatment of envenomings by African snakes. This situation, together with the poor development of health facilities and training of doctors, nurses and dispensers responsible for treating snakebites, have deterred many people suffering a snake bite from seeking medical treatment and driven them instead, to seek the help of traditional healers. A similar situation occurs regarding the procurement of rabies post-exposure prophylaxis. This combination of factors has created a self-perpetuating vicious cycle which needs to be urgently interrupted and corrected (47).

The solution to this disastrous situation should be multifaceted, involving simultaneously the various strategies discussed above. First, there is a need to involve a number of manufacturers, both within Africa and in other regions, to commit themselves to a quota of antivenom production for Africa. An increase in overall antivenom supply to a level of 200,000 doses per year should be achieved by the year 2010. This effort should be combined with the transfer of manufacturing technologies to countries in Africa willing to start local production. The high cost of antivenoms for national health systems is another critical issue. Antivenom prices need to be affordable and international agencies and non-governmental organizations should commit to the purchase and donation of antivenoms. Achievement of these goals would break the vicious cycle by building up confidence in the use and supply of antivenoms. Concomitantly, antivenom distribution should be optimized and guided by appropriate epidemiological information. The development of regional treatment guidelines and the continuous training of health workers in the correct use of antivenom should complete the multifaceted strategy. Local community organizations should participate in all these efforts. The serious current crisis in antiserum supply and use in sub-Saharan Africa should involve global, regional and local manufacturers, public-private partnerships, local and regional health authorities and health workers in coordination with WHO.

Chapter 6

PREQUALIFICATION OF ANTISERA: the way to improve access to quality and safe products

WHO has developed a programme of prequalification of essential medicines aimed at expanding patients' access to drugs for the treatment of HIV/AIDS, tuberculosis and malaria. This programme ensures the quality, efficacy and safety of medicines procured by United Nations agencies, such as UNICEF. The concept of prequalification may be beneficial in the field of therapeutic antiserum as a means to assure the quality and safety of products distributed on the international market. Furthermore, it would stimulate antisera manufacturers, including those in developing countries, to improve their products.

The basic principles of the prequalification programme of medicines are: (a) it is voluntary, i.e. the manufacturers decide whether to participate or not; (b) it is based on general procedures and standards approved through WHO Expert Committees involving WHO member states and WHO Governing bodies; (c) it has been widely discussed and is supported by the International Conference of Drug Regulatory Authorities (ICDRA); (d) it is transparent, since all the information is available on the web site (48); (e) it is open to both products developers and manufacturers of generic products; (f) currently, it has no costs for applicants; (g) it involves a component of capacity building as a key issue in the process, which is particularly relevant in the field of antiserum manufacture.

The expected outcomes of this programme of prequalification, whether applied to essential medicines or to antisera, include the publication of lists of products and manufacturers, which would help national, regional and large scale procurement agencies. This process will also promote capacity building and harmonization among national drug regulatory authorities, manufacturers, WHO treatment programmes, non-governmental organizations and procurement institutions. The programme includes continuous quality monitoring of production and control laboratories. In the long term, it is expected that such a process, applied to the field of antiserum manufacturers and regulators, would result in widespread improvement in the capacity of the laboratories in developing countries, as well as in the quality and safety of available products. This will guarantee fulfilling the needs of effective and safe rabies immunoglobulin and antivenoms procurement where they are most needed.

For the manufacturers, the prequalification programme allows a free-of-charge independent review of the quality, safety and efficacy of their antisera, together with free-of-charge training and technical assistance by international experts in the field to assure production of high quality antisera. The programme will also be helpful in building up market confidence in the quality of the products, and may contribute to the involvement of international procurement organizations in the purchase of antisera for regions whose governments are unable to obtain these life-saving products.

The processes in which the laboratories applying for prequalification will be involved could also benefit other laboratories, through transfer of technology and training workshops on manufacture, quality control and regulation, under the coordination of WHO. Therefore, if well structured, the capacity building of this initiative could have a great impact on antiserum producers worldwide.

Chapter 7

TOWARDS A GLOBAL SOLUTION: a WHO initiative to improve availability of safe antisera

Stakeholders participating at the consultation agreed that WHO should lead a global initiative to improve access to life-saving therapeutic antisera. This effort should promote transfer of technologies and building-up of technical capacity, skills and experience of regulatory authorities and manufacturers, where needed. A pre-qualification programme was considered essential to facilitate the procurement of antisera which quality and safety would be assessed by WHO.

The collaboration of other international organizations, including nongovernmental organizations, and the identification of financial resources are essential for the development of this global strategy aiming to ensure access to effective and safe therapeutic sera, and as such to reduce the mortality and disease burdens of these neglected public health conditions.

The dimension and complexity of this problem requires a multifaceted strategy for its solution, which should involve many partners at national, regional and global levels coordinated by WHO. This strategy should include the following components:

(1) The development of WHO guidelines on the production, control and regulation of antisera.

These guidelines should include all aspects of antiserum manufacture and control, from the starting materials to the large-scale implementation of manufacturing steps and the control of critical parameters to release products of assured quality and safety. The elaboration of such a consensus document should be achieved through a wide consultation process of manufacturers and regulators, at global level, together with a series of technical workshops.

(2) The development of national and regional technical capacity to manufacture safe and effective antisera.

The target groups to benefit from this initiative are the national regulatory authorities and manufacturers of antisera, especially laboratories in developing countries. This objective will be fulfilled through the organization of regional and inter-regional workshops focusing on GMP, on good animal husbandry practices, on collection and fractionation of animal plasma, on preparation and storage of antigens (rabies virus and venoms), and on the correct implementation of manufacturing steps aimed at assuring the efficacy and safety of the products.

(3) The implementation of an international technological cooperation strategy.

Because of the large variation in the capacities and skills of the laboratories involved in antisera production, there is a good opportunity to organize a dynamic process of innovation and transfer of technology between regions and countries. These activities may be based on training courses and exchange of information, technology and expertise among laboratories. An international distribution of tasks can be envisaged. For instance, some laboratories may be in charge of keeping collections of snakes and scorpions of medical importance, as well as preparing high quality antigens which would be used by other laboratories to immunize animals and fractionate the hyperimmune plasma for antiserum production. This type of arrangement should strengthen the parties, while guaranteeing the production of the required volumes of antisera.

(4) The implementation of a prequalification scheme for antisera producers.

On the basis of the experience gained by WHO in the process of prequalification of medicinal products, the implementation of such a scheme for antisera may represent an incentive towards the supply of sufficient quality products. This process is voluntary and does not involve any direct cost to the laboratories. For laboratories aiming to contribute to the global production of antisera, this process would help them to qualify as international providers of these products through different procurement schemes.

(5) The improvement in the clinical management of rabies and envenomings.

The global initiative should include a component aimed at acquiring in-depth knowledge of the public health impact of these diseases at global, regional and national levels. This includes the promotion and development of community-based epidemiological studies on the incidence of rabid dog bites and envenomings due to snake bites or scorpion stings. In addition, preclinical assessment of antivenoms, together with well designed clinical trials are required in order to gain precise knowledge of the spectrum of efficacy and safety of antivenoms and of the most relevant clinical manifestation of envenomings. These efforts should be linked to the development of regional guidelines for the clinical management of envenomings and rabies post-exposure prophylaxis, which should be widely distributed to the health workers in rural areas. Strategies of continuing education of health workers as well as public campaigns on prevention and management of the diseases should complement the guidelines.

(6) The improvement in the logistics of antiserum distribution.

A concerted effort is needed between epidemiologists at ministries of health, procurement agencies and antiserum producers to assure the design and implementation of distribution strategies for these products. This should include the design and maintenance of an adequate cold chain. The use of distribution channels already developed in the health systems for other products (e.g. vaccines) should be fostered, as well as the collaboration and help of international organizations that support the distribution of other medicines. The experiences of some countries with well-developed distribution systems should be shared, through collaborative efforts, with less developed regions.

(7) The implementation of a financially-sustainable strategy.

The solution to the lack of effective and safe antivenoms on a global basis demands the financial support of governments, non-governmental organizations and other international agencies. Without adequate financial support it will not be possible to pursue the objectives described in this plan of action. A concerted international effort, led by WHO, will guarantee full international exposure of this problem thereby attracting the attention of agencies devoted to solutions for health problems in the developing world.

Such a concerted international effort, involving producers, regulators, researchers, national and regional health authorities, international agencies and the community organizations, under the coordination of WHO, can be expected to result in:

- increased availability of safe and effective animal-derived antisera;
- enhanced technical capacity of regulatory agencies and manufacturers;
- guaranteed production of safe and effective antisera
- improved clinical management of rabid bites and envenomings
- optimal clinical use of antisera
- improved health programmes in the affected countries.

REFERENCES

1. 15th Model list of essential medicines. *Report of the WHO Expert Committee 2007*. http://www.who.int/medicines/publications/EssMedList15.pdf.
2. *WHO Expert Consultation on Rabies: First report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 931).
3. WHO Guide for post-exposure prophylaxis. *WHO Expert Consultation on Rabies: First report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 931 Annex 1).
4. Baltazard M, Bahmanya M (1955). Practical trial of antirabies serum in people bitten by rabid wolves. *Bulletin of the World Health Organization*, 13:747–772.
5. Fathi M, Sabeti A, Bahmanyar M (1970). Séroprophylaxie antirabique chez les sujets mordus par loups enragés en Iran. *Acta Medica Iranica* 13:5–9.
6. Warrell DA (1995). Clinical toxicology of snakebite in Africa and the Middle East/Arabian peninsula, Asia. In: Meier J, White J eds. *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Florida, CRC Press, pp. 433-594.
7. Warrell DA (2003). Injuries, envenoming, poisoning, and allergic reactions caused by animals. In: Warrell DA, Cox TM, Firth JD, eds. *Oxford Textbook of Medicine*. Oxford, OUP, 3rd ed. 2003, pp. 923-46.
8. Warrell DA (2004). Epidemiology, clinical features and management of snake bites in Central and South America. In Campbell J, Lamar WW eds. *Venomous Reptiles of the Western Hemisphere*. Ithaca, Cornell University Press; 2:709-761.
9. Knobel DL et al. (2005). Re-evaluating the burden of rabies in Africa and Asia. *Bulletin of the World Health Organization*, 83(5):360-8.
10. Sudarshan MK et al. (2007). Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. *International Journal of Infectious Diseases* (2007) 11:29-35.
11. *World survey of rabies*: No. 32 for the year 1996. Geneva, World Health Organization, 1998 (WHO/EMC/ZDI/98.4; accessed 16 August 2007).
12. Smith JS, Fishbein DB, Rupprecht CE, Clark K (1991). Unexplained rabies in three immigrants in the United States. A virologic investigation. *New England Journal of Medicine* 324(4):205-11.
13. Chippaux JP (1998). Snake-bites: appraisal of the global situation. *Bulletin of the World Health Organization*, 76(5),515-24.
14. Gutiérrez JM, Theakston RDG, Warrell DA (2006). Confronting the neglected problem of snake bite envenoming: the need for a global partnership. *PLoS-Medicine* Jun 6;3(6):0727-0731.e150.
15. Fox S, Rathuwithana AC, Kasturiratne A, Lalloo DG, de Silva, HJ (2006). Underestimation of snakebite mortality by hospital statistics in the Monaragala District of Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100(7):693-5.
16. Sharma SK et al. (2004). Impact of snake bites and determinants of fatal outcomes in southeastern Nepal. *American Journal of Tropical Medicine and Hygiene*, 2004, 71(2):234-238.
17. Warrell DA, Arnett C (1976). The importance of bites by the saw-scaled or carpet viper (*Echis carinatus*): epidemiological studies in Nigeria and a review of the world literature. *Acta Tropica*, 33(4):307-41.
18. Pugh RN, Theakston RD, Reid HA (1980). Malumfashi Endemic Diseases Research Project, XIII. Epidemiology of human encounters with the spitting cobra, *Naja nigricollis*, in the Malumfashi area of northern Nigeria. *Annals of Tropical Medicine and Parasitology*, 74(5):523-30.
19. Snow RW et al. (1994). The prevalence and morbidity of snake bite and treatment-seeking behaviour among a rural Kenyan population. *Annals of Tropical Medicine and Parasitology*, 88(6):665-71.
20. Radmanesh M (1998). Cutaneous manifestations of the *Hemiscorpius lepturus* sting: a clinical study. *International Journal of Dermatology*, 37(7):500-7.
21. Bon C (1996). Serum therapy was discovered 100 years ago. In: Bon C, Goyffon M, eds. *Envenomings and Their Treatments*. Lyon, Editions Fondation Marcel Mérieux, pp. 3-9.
22. Pope CG (1939). The action of proteolytic enzymes on the antitoxins and proteins in immune sera. I. True digestion of the proteins. *British Journal of Experimental Pathology*, 20: 132-149.
23. Grandgeorge M et al. (1996). Preparation of improved $F(ab')_2$ antivenoms. An example: new polyvalent European viper antivenom (equine). In: Bon C, Goyffon M, eds. *Envenomings and Their Treatments*. Lyon, Editions Fondation Marcel Mérieux, pp. 161-172.
24. Jones RGA, Landon J (2003). A protocol for 'enhanced pepsin digestion': a step by step method for obtaining pure antibody fragments in high yield from serum. *Journal of Immunological Methods*, 275:239-250.
25. Dos Santos MC et al. (1989). Purification of $F(ab')_2$ anti-snake venom by caprylic acid: A fast method for obtaining IgG fragments with large neutralization activity, purity and yield. *Toxicon*, 27:297-303.

26. Rojas G, Jiménez JM, Gutiérrez JM (1994). Caprylic acid fractionation of hyperimmune horse plasma: description of a rapid procedure for antivenom production. *Toxicon*, 32:351-363.
27. Theakston RDG, Warrell DA, Griffiths E (2003). Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon*, 41:541-557.
28. Gutiérrez JM, Higashi HG, Wen FH, Burnouf T (2007). Strengthening antivenom production in Central and South American public laboratories: Report of a workshop. *Toxicon*, 49:30-35.
29. Meier J (1995). Commercially available antivenoms ("hyperimmune sera", "antivenins", "antisera") for antivenom therapy. In: Meier J, White J, eds. *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Florida, CRC Press, pp. 689-721.
30. WHO (2007). *Quality assurance of pharmaceuticals, Good manufacturing practices and inspection*, Volume 2, second updated edition.
31. Burnouf T, Radosevich M (2000). Reducing the risk of infection from plasma products: specific preventive strategies. Blood Rev. 14, 94-110.
32. *WHO Expert Committee in Biological Standardization. Fifty-third report*. Guidelines for Viral Inactivation and removal procedures. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924, Annex 4:150-212).
33. Bogarín G et al. (2000). Neutralization of crotaline snake venoms from Central and South America by antivenoms produced in Brazil and Costa Rica. *Toxicon*, 38:1429-1441.
34. Laing GD et al. (2004). Preclinical testing of three South American antivenoms against the venom of five medically-important Peruvian snake venoms. *Toxicon*, 44:103-106.
35. Warrell DA (1997). Geographical and intraspecies variation in the clinical manifestations of envenoming by snakes. In: Thorpe RS, Wuster W, Malhotra A. eds. *Venomous snakes. Ecology, evolution and snakebite*. Clarendon Press, Oxford, pp. 189-203.
36. World Health Organization (1981). *Progress in the characterization of venoms and standardization of antivenoms*. WHO Offset Publ; No. 58.
37. Theakston RDG, Reid HA (1983). Development of simple standard assay procedures for the characterization of snake venoms. *Toxicon*, 41:541-557.
38. Malasit P et al. (1986). Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *British Medical Journal*, 292, 17-20.
39. Sutherland SK (1977). Serum reactions. An analysis of commercial antivenoms and the possible role of anticomplementary activity in de-novo reactions to antivenoms and antitoxins. *The Medical Journal of Australia*, 1(17):613-5.
40. Otero-Patiño R et al. (1998). A randomized, blinded, comparative trial of one pepsin-digested and two whole IgG antivenoms for Bothrops snake bites in Urabá, Colombia. *American Journal of Tropical Medicine and Hygiene*, 58:183-189.
41. Satpathy DM, Sahu T, Behera TR (2005). Equine rabies immunoglobulin: a study on its clinical safety. *The Journal of the Indian Medical Association*, 103(4):238, 241-2.
42. Corrigan P, Russell FE, Wainschel J (1978). Clinical reactions to antivenin. *Toxicon* (Suppl No. 1), 457-65.
43. Burnouf T et al. (2004). Assessment of the viral safety of antivenoms fractionated from equine plasma. *Biologicals*, 32:115-128.
44. Warrell DA et al. (1974). Bites by the saw-scaled or carpet viper (*Echis carinatus*): trial of two specific antivenoms. *British Medical Journal*, 4(5942):437-40.
45. Smalligan R et al. (2004). Crotaline snake bite in the Ecuadorian Amazon: randomised double blind comparative trial of three South American polyspecific antivenoms. *British Medical Journal*, 329(7475), 1129.
46. WHO/SEARO (1999). Guidelines for the clinical management of snake bites in the South East Asian region. *South East Asian Journal of Tropical Medicine & Public Health*, 30 (Suppl. 1): 1-85.
47. Chippaux JP (2002). The treatment of snake bites: analysis of requirements and assessment of therapeutic efficacy in tropical Africa. In: Ménez A, ed. *Perspectives in Molecular Toxinology*. New York, John Wiley & Sons, pp. 457-472.
48. WHO (2007) *Prequalification programme - priority essential medicines.* A United Nations Programme managed by WHO: http://www.who.int/prequal/

LIST OF PARTICIPANTS

Dr A. Alagón, Universidad Nacional Autónoma de México (UNAM) - Instituto de Biotecnologia, Cuernavaca, Morelos, Mexico

Dr S. Arsac, International Committee of the Red Cross (ICRC), Vernier, Switzerland

Dr M. Attlan, Traveller and Endemic Risk Franchise, Sanofi Pasteur, Lyon, France

Dr C. Bon, Muséum national d'Histoire naturelle (MNHN), Unité de Chimie et Biochimie des Substances naturelles (VMS 0502 & UMR 5154 CNRS), Paris, France

Dr L. Boyer, Venom Immunochemistry Pharmacology and Emergency Response (VIPER). Institute University of Arizona, Tucson, Arizona, USA

Dr J-P Chippaux, L'Institut de Recherche pour le Développement (IRD) La Paz, La Paz, Bolivia

Dr G. De Lemos, Ministère des Affaires Etrangères, Direction du Développement, Bureau de la Santé, Paris, France

Dr P. Evans, Department for International Development (DFID), London, United Kingdom

Dr H.W. Fan, Gerência Técnica de Animais Peçonhentos, Coordenação de Doenças Transmitidas por Vetores e Antropozoonoses, Secretaria de Vigilância em Saúde/Ministério da Saúde; Brasilia, Brazil

Dr D. Garcia, Agence Française de Sécurité, Sanitaire des Produits de Santé (Afssaps), Lyon, France

Dr J-M Gutierrez, Instituto Clodomiro Picado, Facultad de Microbiologia, Universidad de Costa Rica, San José, Costa Rica (Rapporteur)

Dr M. Assar, Institut Pasteur du Maroc, Casablanca, Morocco

Dr S.S. Jadhav, Quality Assurance & Regulatory Affairs, Serum Institute of India Ltd., Hadapsar, Pune, India

Mr P. Jakobsen, United Nations Children's Fund (UNICEF), Freeport, Copenhagen, Denmark

Prof. S. Khomvilai, Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok, Thailand

Dr C. Lajo, Médecins Sans Frontières Logistique, Merignac, France

Dr J. López de Silanes, Instituto Bioclon, Tlalpan, Mexico

Mr G. López-Maclellan, Mission permanente de l'Espagne auprès de l'Office des Nations Unies à Genève et d'autres Organisations internationales en Suisse, Genève, Switzerland

Dr K.R. Mani, Central Drugs Laboratory, Kasauli, Solan, India

Dr J.R. Marcelino, Instituto Butantan, São Paulo, Brazil

Dr A.S. Nasidi, Special Projects, Federal Ministry of Health, New Federal Secretarial Complex Phase III, Garki-Abuja, Nigeria

Mrs K.D. Nguyen, Immunology Laboratory, Pasteur Institute, Ho Chi Minh City, Vietnam

Dr A. Sabouraud, Sanofi Pasteur, Lyon, France

Ms P. Saunders, Department for International Development/OXFAM (DFID/OXFAM), Essential Drugs Project, London, United Kingdom

Dr S. Seddik, Egyptian Company for Production of Vaccines, Sera & Drugs (EgyVac), Giza, Egypt

Mrs A. Segura, Permanent Mission of the Republic of Costa Rica to the United Nations Office and other International Organizations at Geneva, Genève, Switzerland

Dr S.K. Sharma, Department of Internal Medicine; B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal

Dr T. Sindik-Milošević, Institute of Immunology, Zagreb, Croatia

Ms N. Stuewer, Permanent Mission of Canada to the United Nations Office and other International Organizations at Geneva, Genève, Switzerland

Mme M-H Tissier, Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps), Lyon, France

Dr M. Toriba, Japan Snake Institute, Ota, Gunma, Japan

Prof. D. Warrell, University of Oxford, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford, United Kingdom (Rapporteur)

Dr O.Wimalaratne, Department of Rabies Diagnosis and Research Medical Research Institute, Danister de Silva Mawatha, Colombo-8, Sri Lanka

Dr C. Xuanlin, Lanzhou Institute of Biological Products, Lanzhou, Gansu, People's Republic of China

Dr S. Zhang, Division of Serum, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, People's Republic of China

SECRETARIAT

Dr H. Zucker, Assistant Director General, Health Technology and Pharmaceuticals

Dr H. Hogerzeil, Director, Department of Medicines Policy and Standards

Dr A.J. Belotto, Chief, Veterinary Public Health Unit, WHO Region of the Americas, Washington DC, USA

Dr H. Langar, Regional Adviser for Vaccines and Biologicals, Vaccine Unit, Division of Health System and Services Development, WHO Eastern Mediterranean Region, Cairo, Egypt

Dr C. Ondari, Coordinator, Policy, Access and Rational Use; Department of Medicines Policy and Standards (Chairman)

Dr A. Padilla, Scientist, Quality Assurance and Safety: Blood Products and related Biologicals; Department of Medicines Policy and Standards (Project Leader)

Dr L. Rago, Acting Coordinator, Quality Assurance and Safety: Blood Products and related Biologicals; Coordinator, Quality Assurance and Safety: Medicines; Department of Medicines Policy and Standards

Ms J. Tempowski, Scientist, Chemical Safety, Department of Protection of the Human Environment

Dr F-X Meslin, Coordinator, Department of Food Safety, Zoonoses and Foodborne Diseases

Dr D. Wood, Coordinator, Quality, Safety and Standards; Department of Immunization, Vaccines and Biologicals

The aim of this Consultative Meeting was to discuss strategies for improving the quality and quantity of therapeutic antisera, essential drugs for the effective treatment of suspected rabid dog bites and envenoming by snake bites and scorpion stings. Inadequacies in the efficacy, safety and production of these antisera have created a major global public health crisis, especially in Africa and Asia. Each year, millions of people are bitten by dogs or snakes or stung by scorpions and the failure to provide antisera costs at least 200,000 lives and at least as many cases of permanent physical handicap. The solution to this crisis demands an international effort to promote transfer of technology to affected countries, to improve standards through the WHO's prequalification scheme and to facilitate distribution of antisera and training of medical personnel in their optimal use.

Quality Assurance and Safety: Blood Products and Related Biologicals
Department of Medicines Policy and Standards
Health Technology and Pharmaceuticals Cluster
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27, Switzerland

Telephone 41 22 791 3892/ 3395
Fax 41 22 791 4730
e-mail: PSMinfo@who.int
http://www.who.int/bloodproducts
http://www.who.int/medicines

ISBN 978 92 4 156348 2