Envenoming: Neglected Issues in Health

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Envenomings are diseases that result from bites by rabid mammals or bites and stings by venomous animals, especially snakes and scorpions etc. In all cases, appropriate early treatment, including therapeutic antisera, can prevent life-threatening conditions and even spread of the virus or venom toxins in the body. This will reduce a lot of deaths occurring especially in areas where health care is at a distance or is unavailable.

Rabies is seen in most parts of the world as an endemic disease. The Global distribution of classic rabies virus (Genotype 1) and European and Australian bat lyssaviruses has been depicted in the figure below:

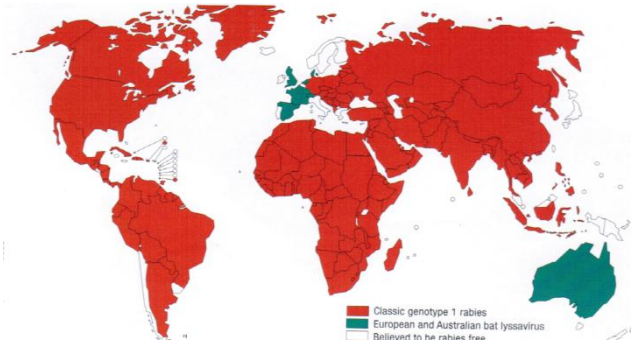

Figure 1.Map of Endemic countries of Rabies

It is well known that clinically established, rabies encephalomyelitis is almost invariably fatal. It is also known that the disease is entirely preventable with complete post-exposure prophylaxis. This type of curable envenomed disease needs to be eradicated completely, particularly where the disease is an end-disease and has an effective vaccine available.

Snake bites, similarly, induce an envenomingand create medical emergencies involving multiple organs, depending on the species of the snake bite. Most severe types of snake bites are due to bites by members of the families Viperidae (pit vipers and true vipers) and Elapidae (cobras, kraits, mambas, coral snakes, Australasian species andsea snakes). Venomous snakes are widely distributed throughout the world (fig. 2) except for a few islands, frozen environments and high altitudes.[1,2]

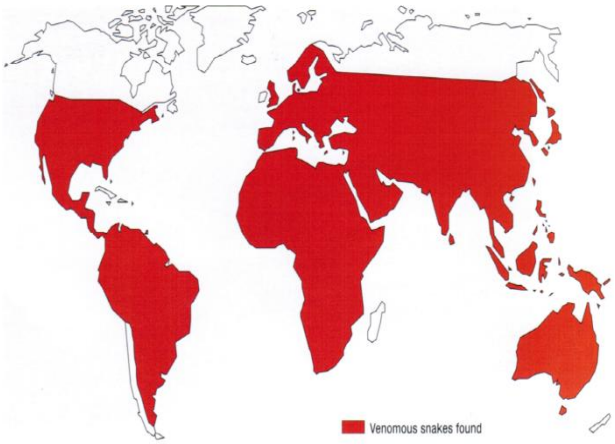

Figure2.Map of Countries showing dangerously venomous snakes

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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. Viperid snake venoms cause local extravasations 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, edema, 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 hemorrhage (e.g. into the brain or gastrointestinal tract), secondary to micro vascular 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 venomprovokes systemic myotoxicity, associated with myoglobinuria, hyperkalemia and acute renal failure.[3]

The clinical management of snake bite envenoming is centered on the intravenous administration of antivenom, together with a series of ancillary interventions that may include ventilatory support for neurotoxic envenoming, fluid replacement for hypovolemic 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.

Epidemiology and theBurden of Envenoming Diseases

Globally, rabies is the tenth leading cause of death due to infection in humans. Predominantly, it affects poor people in developing countries, particularly in rural India and other developing countries.The true incidence of the disease is not known and available data are often underestimated. In the year 2005, there were reports estimating that nearly 60,000 human fatalities occur each year mostly in Asia and Africa.[4] A WHO-sponsored multicentric study estimated that at least 20,000 deaths occurred annually in India alone.[5] In China, rabies has, since May 2006, become the leading cause of infectious disease mortality, killing 3,293 people in 2006, which is 27% more than in 2005.

As per WHO,2007, the lack of supplies of rabies immunoglobulin and vaccination of "right dose-duration-time", calls for more than 55,000 people (90% confidence interval = 24,000-93,000) worldwide each year to die an agonizing death from rabies. Even this figure might have beenan underestimation. WHO quotes,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 to be USD 583.5 million (90% CI = USD 540.1-626.3 million) in Asia and Africa alone.[4]

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 and scorpion stings are well-known medical emergencies in many parts of the world where these animals are distributed. Agricultural workers and children are the most prone individuals affected by snake bites. The true worldwide incidence of snake bite envenoming is presently impossible to estimate because of unavailability of exact information. 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.[6]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 bysnake bites do not seek hospital treatment but

prefer traditional remedies. Snake bite victims in rural areas may die at home unrecorded.[7]

The community-based studies, in the Eastern Terai region of Nepal, showed 162 snake bite deaths per 100,000 population per year,[8] in Nigeria, the incidence of snakebites was 497 per 100,000 people per year, with a fatality rate of 12.2% , in Malumfashi, Nigeria, showed that there were 40-50 snakebite cases, with 4 deaths per 100,000 population per year. Nineteen percent of them developed persistent sequelae and only 8.5% sought hospital treatment,[10,11] 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.[12]

The Current Antisera

Extensive scientific knowledgeis available on envenomings by snake bites and scorpion stings. The clinical, pathophysiological, biochemical and immunological characteristics of venoms are well known now. The species responsible for most snake and scorpion envenomings in the different regions of the world have been identified. There is also abundant scientific literature on the cross-reactivity of antivenoms against venoms from different species of snakes within a specific geographical region. It can be applied to the design of immunizing mixtures to raise effective neutralizing antisera for a given area or geographical region. With regard to the rabies virus, this is an excellent immunogen. This knowledge can be helpful to the manufacturers of animal-derived antisera in order to improve the quality and safety of these products in case of snake and scorpion stings also. The most important weaknesses are low volumes of production; poor safety and efficacy of some products anddeficient or non-existent regulation and control of antisera in some countries.

Antiserum safety is another aspect that demands careful attention. Upon parenteral administration, antisera may induce early or late adverse reactions. 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 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 and 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.[13] The incidence of reactions 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. Equine rabies immunoglobulin has proven extremely safe with a reaction rate of 1.13% 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.[14]

Late adverse reactions (LARs) 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 centers 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 poorly refined antivenom and where a thorough follow-up was possible, it was seenthat 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).[15] 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 sanitization

of equipment and clean rooms, and the design of all production systems should strictly follow GMP principles. Failure to fulfill 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 program should be established for strengthening technical expertise in local and regional laboratories aimed at the implementation of GMP in all manufacturing facilities.

WHO Initiative to improve Availability of Safe Antisera[14]

- The development of WHO guidelines on the production, control and regulation of antisera**,** 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 development of national and regional technical capacity to manufacture safe and effective antisera isadvised to benefit the national regulatory authorities and manufacturers of antisera, especially laboratories in developing countries.
- The implementation of an international technological cooperation strategy has 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.
- The implementation of a prequalification scheme for antisera producers and 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. Regardinglaboratories 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.
- The improvement in the clinical management of rabies and envenomings should include a component aimed at acquiring in-depth knowledge of the public health impact of these diseases at global, regional and national levels. 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 are highly needed. 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, clinical management of envenomings and rabies post-exposure prophylaxis.
- The improvement in the logistics of antiserum distribution 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 implementation of a financially-sustainable strategy 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 programs in the affected countries.

References

1. WarrelDA. Clinical Toxicology of snake bite at Africa and Middle East / Arabian Peninsula, Handbook of clinical toxicology of animal venoms and poisons, *CRP Press, Florida*, 1995.
2. WarrelDA. Injuries, envenoming poisoning and allergic reactions caused by animals, Oxford Textbook of Medicine,*Oxford*, 2003: 923-46.
3. WarrelDA.Epidemiology,clinical features and management of snake bite in central and south Americas, Venomous reptiles of Western hemispheres,Ithaca,*Cornell University Press*, 2004.
4. Konobel DL, Cleaveland S, Coleman PG etal. Reevaluating the burden of Rabies in Africa and Asia.*WHO Bulletin* 2005;83(5).
5. Sudarshan MK, Madhusudana SN, Mahendra BJ etal.Assessing the burden of human rabies in India: Result of national multi-center epidemiological survey.*International Jr.Infectious Diseases* 2007;11:29-35.
6. ChippauxJP. Snake bites: Appraisals of the global situation and determinants of fatal outcomes.*WHO Bulletin* 1998;76(5):515-24.
7. Gutierrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snakebite envenoming: The need for a Global partnership. *PLoSJrMedicine* 2006; 3(6): 727-31.
8. Fox S, Rathuwithana AC, KasturiratneA etal. Underestimation of snake bite morbidities in hospitalsin the Monaragala,Srilanka. *Transaction of Royal Society of Medicine* 2006;100(7): 693-95.
9. Sharma SK, Chappuis F,Jha N etalImpact of snakebites and determinants of fatal outcomes in southern Nepal. *AmJrTropMed & Hygiene* 2004; 71(2): 234-38.
10. WarrelDA,Arnett C. The importance of bite by the saw scaled or carpet viper:Epidemiological study in Nigeria.*ActaTropica* 1976; 33(4): 307-41.
11. Pugh RN, Theakston RDG. Malumfasi endemic diseaseresearch project report XIII,Epidemiological studies in Nigeriaand a review of world literature.*Annals of TropMed& Parasitology* 1980; 74(5): 523-30.
12. Snow RW,Bronzan R, Roques Tetal.The Prevalence and morbidity of snake bite and treatment seeking behaviouramong rural Kenya population.*Annals of TropMed& Parasitology* 1994; 88(6):665-71.
13. Sutheriand SK. Serum Reactions, An analysis of commercial antivenomsand the possible role of anticomplementary activity in de-novo reactions to antivenoms and antitoxins.*Med J Aust* 1977; 1(17): 613-15.
14. WHO. Progress of the standard of venom and antevenom, *WHO offset publication*, 1981.
15. Corrigan P, Russell FE, Wainschel J. Clinical reactions to antivenin.*Toxicon* 1978: 1,457-65.