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Snake bite envenoming in Bangladesh and the challenge of biodiversity

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Envenoming caused by the bites of snakes is a common and serious public health problem and, although eminently treatable, a major neglected disease of the 21st century (Gutiérrez et al., 2006). Compared to most other countries where snake bite is hyperendemic, Bangladesh is in the fortunate situation of having consensus guidelines and protocols for treatment of snake bites and a variety of education materials to assist teaching programmes in medical and nursing schools (Faiz et al., 2000a-d). Detailed instructions can also be found in the WHO/SEARO guidelines for the clinical management of snake bites in the Southeast Asian region (Warrell, 1999) which are available free on the internet. This presentation focuses on the situation in Bangladesh with particular reference to the clinical and epidemiological challenges posed by the great species diversity of venomous snakes in this country and its dependence on imported antivenom from India.

The incidence of snake bites in Bangladesh is unknown. Published estimates (Huq et al. 1995; Sarkar et al., 1999) contrast sharply with the results of population surveys in the lowlands of eastern Nepal (Sharma et al., 2004) that revealed a dramatically high annual incidence, morbidity and mortality (1,162 snake bites including 604 envenoming bites and 162 deaths per 100,000). As the venomous snake fauna of the lowlands of Nepal is very similar to that of Bangladesh, and its population exposed in a similar manner to the hazard of snake bites, it is reasonable to suspect that the true incidence of snake bites in Bangladesh is close to these latter figures.

Like in other tropical countries, snake bite envenoming in Bangladesh is an occupational disease of the young and especially male rural poor people who suffer bites while engaged in physical work (Faiz, 2004; Faiz et al., 1995, 1997; Islam et al., 1999). The morbidity and mortality or long-term disability in such young people must have a profound effect on the productivity of the country. Snake bites are most common during the monsoon season from May to October, and they may peak during floods when humans and snakes are confined to the few spots that remain over water. Children have a particularly high risk of dying from snake bite envenoming (Faiz et al., 1999b).

The majority of snake bites in Bangladesh are non-envenoming bites (60–80% in hospital-based studies; Faiz, 2005; Faiz et al., 1995, 1997; Islam et al., 1999; Majumder et al., 2000). These include bites that are caused by nonvenomous snakes, and incidents in which venomous snakes do not inject venom during a bite. Traditional treatment by "ozhas", whenever it is not harmful or lethal in itself, will appear to be fully effective in these cases. This "success rate" along with the lack of medical treatment for snake bites in the past explains why treatment by "ozhas" is popular enough in Bangladesh to result in relatively few hospital admissions.

Venomous snakes of Bangladesh: underestimated biodiversity

A historically undercollected and understudied fauna

Among the epidemiologically relevant front-fanged venomous snakes, a review of the zoological literature from 1852 to 2004 (F. Tillack, unpublished) revealed about 40–50 species of Elapidae and Viperidae recorded from the geographic area of Bangladesh. The Elapidae include both terrestrial and marine species. About 25 species of highly venomous sea snakes occur in the Bay of Bengal, coastal waters and estuaries of Bangladesh, and up to several kilometres upstream in rivers. Among the terrestrial elapid snakes, cobra and krait are widely known to the public in Bangladesh. However, there are actually about a dozen species of terrestrial elapids in Bangladesh, including two species of cobra (the Indian or Spectacled Cobra, *Naja naja*, and the Monocellate [or Monocled] Cobra, *Naja kaouthia*), at least five different species of krait (*Bungarus*), the King Cobra (*Ophiophagus hannah*) and perhaps four species of coralsnakes (*Sinomicrurus*). The pitvipers and true vipers are represented by about six species in Bangladesh, among them Russell's Viper (*Daboia russelii*) and several species of green pitviper. The records of 4–5 more viperid species require verification.

The literature records of venomous snakes in Bangladesh are especially difficult to evaluate as most are not based on preserved museum specimens, which are the only permanent and reliable source of information for biodiversity studies and for demonstrating the existence of a given species in a particular locality. Voucher specimens are also the only hard evidence that may be relatively easy to obtain in a proportion of hospital admissions for snakebite envenoming, and, if properly preserved, will allow multiple researchers including those of future generations to re-evaluate their identification under aspects that may change as our knowledge of biodiversity and evolution increases over time.

As most zoological collecting in the region over the past 200 years took place in West Bengal or Assam, and because many species are difficult to distinguish from one another without the advice of a specialist or the use of modern methods of identification, the geographic distribution of venomous snakes in Bangladesh, even of the most common ones, is virtually unknown. This is particularly discomforting from a medical point of view. Not surprisingly, the question of snake species identification has been recognized as an important problem and future research priority in several of the early pioneering studies on snake bites in Bangladesh (e.g., Faiz et al., 1995; Islam et al., 1999).

Snakes of principal medical importance in Bangladesh

Certainly the most diverse group of venomous snakes in Bangladesh and perhaps the most abundant, sea snakes constitute an occupational hazard for fishermen but the incidence of their bites is unknown in Bangladesh. Patients with sea snake envenoming may present with paralysis, muscle pain, and/or dark brown urine and renal failure.

On land, bites by the Monocellate Cobra (*N. kaouthia*) and green pitvipers (*Cryptelytrops* [previously *Trimeresurus*] *erythrurus* and possibly others) were the most commonly identified ones in Chittagong and Cox's Bazar District (Faiz et al., 1997) and might be the commonest in much of Bangladesh. Neurotoxic envenoming by cobras (*N. kaouthia* and *N. naja*) and kraits (*Bungarus* species) is the principal cause of snake bite mortality probably also in most parts of Bangladesh.

Using a syndromic approach of diagnosis, nightly bites on sleeping people on land that result in paralysis with no or only minimal local swelling may be interpreted as a likely case of krait envenoming. Exactly which of the five different species of krait known from Bangladesh caused the bite cannot be determined by this approach. However, this information is relevant for the management of the patient because the venom of only one species of krait (*Bungarus caeruleus*) is used in the production of the polyvalent antivenoms that are manufactured in India. *Bungarus caeruleus* is so far known with certainty only from a few localities in western Bangladesh. In fact, recent studies at the Chittagong, Dhaka and Khulna Medical College Hospitals (Faiz et al., unpublished) revealed that two species of krait that were not previously known from Bangladesh (the Greater Black Krait, *Bungarus niger*) or whose distribution in the country had been unknown (Wall's Krait, known as *Bungarus sindanus walli* or *Bungarus walli*) were each involved in several cases of severe envenoming including fatalities, with no clinically apparent response to Indian polyvalent antivenom.

Bites by *N. kaouthia* in Bangladesh have been observed to cause neurotoxicity (80% of cases) and local swelling that often (53%) leads to soft tissue necrosis (Faiz et al., 1996, 1998). In contrast to krait envenoming, treatment with polyvalent antivenom and anticholinesterase usually reversed the neurotoxicity, with comparatively short periods of respiratory paralysis in severe cases, but it could not prevent local tissue necrosis following cobra bites in Chittagong and Cox's Bazar Districts (Faiz et al., 1998). The geographic ranges of *N. kaouthia* and *N. naja* in Bangladesh are unknown; they are expected to overlap considerably so that large regions of Bangladesh may be inhabited by both. *Naja kaouthia* should be expected to occur throughout the country; it has so far been the only species of *Naja* found in the wild in Chittagong and Cox's Bazar Districts. The distribution of *Naja naja* might be restricted to western and northern Bangladesh.

Most cases of envenoming with local pain and swelling in the presence (or absence) of coagulopathy, and without paralysis, are very likely caused by various species of green pitvipers in most parts of Bangladesh. Antivenom to treat green pitviper envenoming is available in Thailand (Warrell, 1999) but fortunately its use would rarely seem to be indicated.

However, local pain and swelling with bleeding/clotting disturbances are also characteristic for Russell's Viper (*D. russelii*) envenoming, which is much more severe, may be accompanied by a range of different clinical features depending on the particular geographic region (e.g., shock, dark brown urine and renal failure, even neurotoxic signs like ptosis, external ophthalmoplegia, facial paralysis, etc.) and is associated with high mortality (Warrell, 1989). The distribution of Russell's Viper, although sometimes referred to as "widespread" in Bangladesh in the zoological literature, might actually be patchy and/or restricted to western and northern parts of the country. There have been no recent reports of proven cases of Russell's Viper envenoming in Bangladesh. However, among numerous very short anecdotal notes published by Banerji (1929), several of those relating to localities in Bangladesh are attributable to Russell's Vipers. Characteristic signs in these cases of severe envenoming included the vomiting of blood and bleeding from the eyes, gums and nose. Most of these occurred in the southwest under Assasuni and Shamnagar police stations in Satkhira District and under Koyra and Paikgacha police stations in Khulna District. Russell's Vipers thrive in agricultural lands and cause numerous bites with fulminant envenoming where they occur (Warrell, 1989). Thus, the possibility of an unrecognized regional public health problem involving this species warrants further investigation.

Management implications

Awareness programmes

When scientific studies on snake bites were initiated in Bangladesh in the 1990s, almost all hospitalized bite victims had seen one or several traditional healers ("ozhas") prior to admission and this is still very common today. Besides being ineffective, their traditional practices complicate both diagnosis and treatment. Inadequate first aid measures and delayed admission to hospital caused by first seeing "ozhas" are usually observed in those cases that have resulted in the death of the patients before arrival at hospital (Faiz et al., 1999b). Also of great concern is the widely practiced use of often multiple tourniquets (Faiz et al., 1997). Their destructive potential (e.g., ischaemic damage to the limb and peripheral nerve injury) is multiplied by snake venoms that damage local tissues, adding to the overall morbidity and increasing the risk of permanent disability. Recommended first-aid techniques are detailed in the national guidelines for the management of snake bites in Bangladesh (Faiz et al., 2000), and in the WHO/SEARO guidelines (Warrell, 1999).

Several studies and hospitals in Bangladesh noted dramatically increased admissions after the regional population had become aware of the fact that effective medical treatment for snake bites was available at hospitals (Islam et al., 1999; Faiz, 2005). The treatment at Chittagong, Rajshahi and Khulna Medical College Hospitals could reduce the mortality of hospitalized cases to less than 2% (Faiz, 2004) from the 20–22% reported by Huq et al. (1995) and Sarkar et al. (1999). The provision of such treatment and awareness programmes by Chittagong Medical College Hospital increased the annual number of snake bite victims admitted to that centre from 44 cases in 1993/94 (Faiz et al., 1995) to 307 cases in 1999. Even metropolitan hospitals like Dhaka Medical College Hospital nowadays see increasing numbers of snakebite victims (e.g., 61 cases in 2004; Faiz, 2005), many of whom are brought directly or referred by other hospitals from distant rural localities. Education programmes, media reports and the testimony of fully recovered snake bite victims after their return to the villages all contribute to this changing trend.

Integrating "ozhas"

Because of their traditional key role in the popular response to snake bite, "ozhas" instead of delaying and hampering medical treatment could be converted into the first line of defence in the fight against snake bite morbidity and mortality in Bangladesh. If properly trained (e.g., in cardiopulmonary resuscitation) and integrated into the present health care system, such "modern ozhas" might, for example, apply appropriate first-aid measures, help organize prompt referral to the nearest medical facility where treatment is available, and accompany patients during transport keeping their airways clear and providing live-saving mouth-to-mouth respiratory support whenever no qualified paramedics are available.

Primary health care for snake bites

Strengthening primary health care centres in Bangladesh by ensuring that the basic facilities for the successful treatment of snake bites are available, and by providing training of primary care physicians working in thana health complexes on various aspects of snake bite, should be simultaneous priorities. This may increase awareness among the general public that the treatment of most cases of snake bite is possible locally, and could further contribute to reducing the critical interval between the bite and the start of medical treatment.

Such local capacity-building could go hand in hand with the systematic use of standardized data entry forms and snake bite registers as well as the establishment of specialized wards or clinics in hospitals that are designated to treat all snake bite cases admitted to the respective centre.

In the past, antivenom to treat snake bite envenoming has often been unavailable in thana and district level hospitals and even at large medical college hospitals (e.g., Ahmed et al., 2005). Thus, medical personnel providing care at different levels of the health system might not be familiar with the use and application of antivenom in adequate doses, or the practice of providing respiratory support by intubation and manual ventilation (e.g., by Ambu bag) in cases of neurotoxic envenoming. As a consequence, it has not been a rare situation to see severely envenomed patients admitted to major tertiary care facilities in distant cities after long journeys that included visits to several "ozhas", thana and district level hospitals but no adequate medical treatment.

Voucher specimens: adding hard evidence to snake bite research

While most hospitalised victims of snake bites in Bangladesh had not seen the snake that bit them, and those who had could not identify it, it was observed that in about 10% of all cases the victims or their attendants brought the dead snake (Faiz et al., 1997; Majumder et al., 2000). This percentage may appear low. However, if snake bite victims and their attendants are routinely asked whether the snake was killed, and requested to bring it if this was the case, followed by systematic preservation of every snake that is brought to hospital in formalin or alcohol (most importantly, along with durable and precise labeling that will allow future researchers to link the specimen to a case history and locality), a wealth of relevant epidemiological information can be obtained (Faiz et al., 1997). Also, based on such specimens a key for the rapid in-ward identification of venomous species can be developed to aid the attending physician in making treatment decisions.

Syndromic approaches and the problem of species distributions

Based on the analysis of cases of envenoming caused by reliably identified snakes, a syndromic approach to clinical diagnosis can be developed (e.g. Warrell, 1999; Faiz et al., 2000a; Majumder et al., 2000). However, there is considerable overlap of clinical features caused by venoms of different species and even genera of snake. The more diverse a venomous snake fauna that may be involved in bites, and the more fragmentary our knowledge of that diversity and the actual geographic distribution and habits of these species, the more limited the usefulness of syndromic approaches will be.

Immunodiagnosis

The diagnosis of the species of snake responsible for bites is also possible via detection of venom antigen by immunoassay, most commonly using the patients' blood serum. This method has the advantage of being suitable both for the retrospective screening of large numbers of patient samples, which may be stored frozen until analysis, and for the development of rapid and easy-to-use bed-side detection kits. The latter are used in Australia to assist in the choice of the right antivenom, but their discriminatory power in identifying particular species is limited. Raising diagnostic antisera in rabbits for immunodiagnosis requires the availability in captivity of several live individuals of each snake species to be tested, optimally from various geographic localities and over an extended period of time so that a sufficient quantity of venom can be collected. Thus, as desirable and promising as immunodiagnosis is for the management of snake bite envenoming in Bangladesh (Faiz, 2005, Faiz et al., 1995, 1997; Majumder et al., 2000), obtaining the necessary venom samples, and establishing a constant supply of such venoms over time if immunodiagnosis is to be used for clinical routine, is the first hurdle that needs to be taken in this direction.

Molecular diagnosis of biting species

Forensic molecular genetic analyses allow for the analysis of an offender's trace DNA on the skin of a victim. The same principles of analysis and detectability apply when the offender is a snake. Preliminary experiments using PCR-aided direct DNA sequencing have allowed the identification of closely related krait species based on the swabs collected at the bite sites of laboratory animals (Kuch et al., unpublished), warranting further study and validation of this method. Among the potential advantages of a bite-site swab PCR method are its specificity, the possibility of documenting and identifying, by phylogenetic analysis, even new species that had not previously been collected, and the possibility of identifying also the species involved in non-envenoming bites. Its disadvantages are the possibility that snake DNA may not be available in sufficient quantity if the bite site was washed, and that analytical speed approaching clinical utility for treatment decisions may only be developed using technologies like real-time PCR that rely on presently expensive instrumentation. However, once the planned network of forensic DNA profiling laboratories is established across Bangladesh, and if these are open to the analysis of clinical cases without referral by the police or judiciary, the necessary facilities and know-how to effectively process such samples using validated protocols will be widely available in the country.

Specific treatment: the critical issue of antivenom

The intravenous administration of animal-derived antivenoms continues to be the mainstay and the only specific treatment of snake bite envenoming. However, due to the large immunochemical diversity of snake venoms even within a given species, the efficacy of antivenoms is generally restricted to a limited geographical and biological spectrum (Gutiérrez et al., 2006). The only antivenoms to treat snake bite envenoming that are currently available in Bangladesh are polyvalent antivenoms imported from India, a country that actually faces the same if not worse problems understanding which species are responsible for morbidity and mortality. Although there are now seven different producers, most of them profit-oriented commercial companies, all of the Indian polyvalent antivenoms are raised against the venoms of the same four species only, i.e., *N. naja*, *B. caeruleus*, *D. russelii*, and the Saw-scaled Viper *Echis carinatus* (which fortunately does not seem to occur in Bangladesh), using snakes captured in a small geographic region of Tamil Nadu in south India (Simpson and Norris, 2007). To date, it has been impossible to convince these manufacturers to produce new antivenoms against other species of medical importance in India and Sri Lanka such as the hump-nosed pit viper, *Hypnale hypnale* (Simpson and Norris, 2007).

Regarding the case of Bangladesh, the inclusion in Indian antivenom production of species like *N. kaouthia* and the recently emerging *B. niger* and *B. walli* is even less likely, especially since neither occurs in southern India (Whitaker and Captain, 2004). Thus, developing a locally made, safe and affordable antivenom that is effective against the venoms of the principal medically important venomous snakes from various regions of Bangladesh should be seen as an urgent priority for public health planning, and as a possible opportunity for public-private partnerships (Gutiérrez et al., 2006). As Bangladesh, Nepal, Bhutan and India's northeastern states share many of their most dangerous venomous snake species (e.g., *N. kaouthia*, *B. niger* and *B. walli* are all wide-ranging), such a regional antivenom would not only benefit the Bangladeshi population, but may also prove to be effective when exported to neighbouring countries.

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