Venom, antivenom production and the medically important snakes of India

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Snakebite is a medically and socially significant issue in India, but the quality of treatment and reporting protocols need to be upgraded to international standards. There are currently seven pharmaceutical laboratories in India which produce antivenom against four medically important Indian snake species (cobra (Naja sp.), krait (Bungarus sp.), Russell's viper (Daboia russelii) and saw-scaled viper (Echis carinatus sp.), the 'big four'. Most venom for antivenom production is sourced from Chennai, South India. While the 'big four' are responsible for a majority of serious and fatal bites, the situation is actually much more complex. In this article, we review the production of venom and antivenom in India and suggest areas of improvement. We show that several factors complicate the treatment of snakebite in India. The first is geographic, intra-species variation in venoms of cobras and Russell's vipers. Secondly, there are four species of cobra, eight species of kraits, two distinct sub-species of saw-scaled viper. In view of these observations, it is felt that identifying, evaluating and implementing changes to venom and antivenom production protocols, public education, snakebite treatment and policy in India should be an immediate priority.

Keywords: Antivenom, snakebite, snakes, venom.

'IN January 1870, being then in Calcutta, I collected statistical information which afforded proof that the loss of human as well as animal life in India from the bite of venomous snakes was very great; and as it seemed to me that this ought to be, to a great extent, preventable, I extended my investigations with the view of obtaining accurate information as to the characters and peculiarities of the venomous snakes themselves, the localities in which they most abound; the modus operandi of the poison; the circumstances under which the bites are inflicted; the value of any known remedies in the treatment of those bitten, and what measure might possibly be devised for diminishing this serious evil….'[1]

Snakebite in India has been a subject of considerable interest and debate for centuries. During the colonial era, several physicians and naturalists were remarkably prescient in their observations and strived to alleviate the trauma and suffering inherent in what has been identified as a common rural occupational hazard. A study reports 19,060 human deaths from snakebite in India in 1880 (ref. 1). The author petitioned the government of the time not to cut and clear jungles near villages, but rather to offer rewards for killing venomous snakes and to provide identification and information charts in colour. Altogether, 467,744 snakes were killed for rewards during 1880 and 1881. This, the author asserted, resulted in lesser human deaths (18,610) on 1881, though the methodology for data collection is not given. It seems likely that a majority of the snakes (if indeed venomous species) brought in for rewards were saw-scaled vipers, the only species of venomous snake in India that occurs abundantly in several places[1]. The *Dictionary of the Economic Products of India* (1892) states that there were 22,480 snakebite deaths in India in 1889 and an average of about 20,000 per year 'for the past 10 years' (when India had a population of about 250 million people). The editor makes the astute observation that the 'Death rate is higher or lower more in relation to the habits of the people than to the prevalence of poisonous snakes.'[2]

A century later, it is still acknowledged that snakebite is a serious medical problem in rural India and in April 2009, snakebite was added to WHO's list of 'neglected tropical diseases'[3]. A recent study reported that worldwide, the total number of snakebites could be as high as 5.5 million with 94,000 deaths[4]. Reliable statistics for India are available only now, thanks to the Million Death Study, an initiative of the Registrar-General of India and the Centre for Global Health Research at St Michael's Hospital and University of Toronto, Canada. Based on this study, the upper estimate for snakebite deaths in India is a staggering 50,000 per annum[5].

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Reasons for such a high incidence of snakebite and resultant mortality in India include the following:

- High numbers of snake species of medical importance in agricultural areas.
- Inadequate distribution/availability/publicity of anti-venom serum (AVS).
- Reliance on traditional and quack treatments.
- Walking at night without light, no adequate footwear, sleeping on ground mats.
- Lack of widely disseminated, standardized first aid and treatment protocols.
- Geographic variation in venom composition.
- Lack of knowledge about snake habits and behaviour.
- Inadequate training of clinicians in dealing with snakebite.

Morbidity, including loss of limbs and other serious disability could affect further hundreds of thousands of victims of venomous snakebite, but there are no reliable data. Inexplicably however, the Government of India's 'National Health Profile' reports a total of more than 1,400 snakebite deaths for all of India[6]. Since 2008, the Government of West Bengal has given Rs 1 lakh compensation to families of persons killed by snakebite. In 2011/2012, the total amount disbursed was Rs 4 crores 11 lakhs, indicating a minimum of 411 snakebite deaths in that state alone (source: West Bengal State Health Bureau).

As important as it is for accurate compilations of snakebite data to aid our understanding and guide snakebite management, there is sufficient data to demonstrate the urgent need to bring together key stakeholders: clinicians, venom researchers, antivenom producers, venom producers, health authorities and wildlife authorities (all snakes are protected in India). Some of the important issues to address are as follows:

- Reliable supply of quality snake venoms.
- Reliable supply of quality, high potency antivenom and its publicity.
- Regional variation in venoms.
- Regional differences regarding species responsible for bites.
- Review of snake species of medical importance.
- Training in snakebite first aid and treatment.

What follows is a review of available data on the production of snake venom and antivenom in India and the species responsible, based on existing literature and communication with colleagues in the field. The main purpose is to provide a guide to the current production of venom and antivenom in India. The second purpose is to encourage further effort in this direction so that the production of appropriate venom and antivenom can be based on robust science rather than heresay or mere repetition of established, but not optimum, production protocols and potency standards. Lastly, it is acknowledged that the advancement in snakebite treatment with antivenom has never been a subject of importance in training clinicians nor has it been conveyed to the public at large. Publicity and knowledge sharing about prevention and treatment of snakebite at the clinical, village and rural levels is an essential part of the national mitigation initiative that is the need of the hour. Community education about snakes and their habits, sensible behaviour to avoid bites such as using a torch at night, sleeping under a mosquito net and watching where you walk are basic requirements to reduce what is a tremendous health burden for India.

Competition from unregistered 'medical practitioners'

Before the widespread usage of an effective antivenom in the early 20th century, a plethora of 'remedies' were available to victims of snakebite. Delving into the literature, it can be seen that a century ago, it was already ascertained that none of the existing 'cures' had any value. A. J. Wall who, in the footsteps of Joseph Fayrer and others, tested many of the existing 'remedies' states: 'In regard to remedies…, it is impossible to exaggerate the uselessness of each of them.'[7]

Amazingly, today it is as easily possible to go for treatment of a life-threatening venomous snakebite to a shaman, herbalist or other 'healer' in India, as it was a hundred years ago. Traditional Indian medical systems of ayurveda, siddha and the introduced homeopathic system have sophisticated treatments for many ailments, developed over time. However, antivenom, prepared by immunizing horses or sheep is the only medically accepted remedy for systemic snake envenomation[8]. When practitioners of other medicine systems purport to be able to treat systemic symptoms of serious venomous snakebite, it becomes dangerous, life-threatening quackery.

Purveyors of bogus snakebite remedies have a ready market amongst the superstitious in rural and semi-rural communities, and there do not seem to be any effective laws to prevent the sale and use of these 'treatments'. Serious envenomation or mortality occurs in less than 10% of the snakebite victims which makes the 'quack' appear quite successful and flourish in his trade. Figure 1 is an illustrative example of a well-known bogus 'remedy' for snakebite available in India and used even by educated people. Although exact numbers are not known, several authors estimate that 20–70% of snakebite victims go to unregistered medical practitioners (read 'quacks') for treatment often resulting in tragedies[8,9]. A relevant question is why the purveying of such quack 'remedies' is not considered a criminal offence.

Widely publicizing the efficacy of antivenom treatment for snakebite victims will certainly improve the current situation. In addition, clinicians with rural patients need to familiarize themselves with the latest WHO update on snakebite treatment protocol[10] (http://www.searo.who.int/LinkFiles/BCT_Snake_Bite_Guidelines.pdf) and the snakes of medical importance in their area. Efforts towards community education and promoting sensible activity and awareness of snake movement and habits amongst farmers and their families are of utmost importance.

Venom production

In India, all snakes are protected under the Wildlife Protection Act and as such, snakes cannot be collected or venom extracted without the permission of the state wildlife authorities[11]. There is no scientific study that adequately quantifies snake abundance (though the export of up to 10 million snake skins per year in the 1960s gives some indication), which has resulted in a conservative stance by the wildlife authorities in some states and a general reluctance to permit capture of large numbers of snakes for venom extraction to produce AVS.

Case study A – the Irula Snake Catchers Industrial Cooperative Society

The Irula Snake Catchers Industrial Cooperative Society (ISCICS), which operates in two districts of Tamil Nadu totalling 7,850 sq. km, is a tribal self-help project set up in 1978 (ref. 12). The Society is licensed by the Tamil Nadu Forest Department to capture an average of 8,000 snakes per year of the four most medically important species, the 'big four'. Snakes are kept in captivity for 3–4 weeks and venom extracted four times from each snake. Snakes are then released back to the wild. Table 1 gives the average annual sales made by the society for the period 2000–2009 for antivenom production.

The number of snakes permitted to be caught under the state forest department license determines the relative quantities of venom produced. This has resulted in a perennial surfeit of cobra and Russell's viper venom, hence the Irula Cooperative stipulates that buyers must purchase venom in a ratio of 5 : 5 : 1 : 1 (*Naja* : *Daboia* : *Bungarus* : *Echis*). For buyers who wish to purchase only krait or saw-scaled viper venom, the price is an astronomical US$ 3888 per gram[13]. Antivenom producers have expressed concern over the high venom prices (see Table 2) and purchase of Irula Cooperative venoms dropped considerably in 2010 (ref. 14). New methods of immunization require much less venom to produce the same results which will of course reduce demand even further[8]. In comparison, prices for Indian snake venoms produced in the USA are US$ 150 per gram for spectacled cobra, US$ 600 for Russell's viper and US$ 400 for saw-scaled viper (Kentucky Reptile Zoo).

The Irula Cooperative now produces a major portion (an estimated 80%) of India's venom needs (for the production of antivenom) from snakes found within two districts of Tamil Nadu[14]. Therefore, it would be advantageous to expand the scope of the cooperative activities to other parts of the country by becoming a multi-state cooperative in order to include other snake catching communities under its wing. This will benefit both marginalized snake catchers as well as being a big step forward in dealing with the complex and life-threatening problem of regional venom variation and address the possibility of other species of snakes being medically important. However, it is to be noted that the standards of venom production and protocols of the cooperative have considerable scope for improvement in conformity with WHO guidelines[8].

Case study B – N.S. and Associates, Sehore, Madhya Pradesh

This is a small venom production unit started in 2004, with the capacity to keep 100 to 150 snakes. The snakes

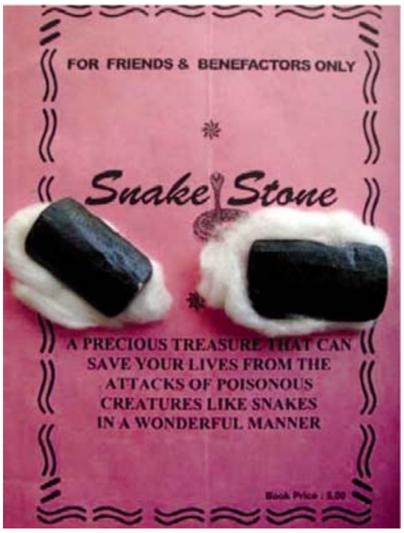

Figure 1. The infamous 'snake stone' from a clinic in Kerala, India.

Table 1. ISCICS venom sales (average annual sales for 10 years, 2000–2009)

Species	Quantity (grams)[14]
Naja naja	274
Bungarus caeruleus	38
Daboia russelii	262
Echis carinatus	36

Table 2. ISCICS venom prices per gram (lyophilized) (July 2010)

Species	Price per gram (US$)[13]
Naja naja (spectacled cobra)	511
Bungarus caeruleus (common krait)	888
Daboia russelii (Russell's viper)	666
Echis carinatus (saw-scaled viper)	1,000

(only *Naja naja* and *Daboia russelii*) are caught locally in houses and gardens in response to villagers' requests. Till 2008, a total of 295 ml of *N. naja* and 51 ml of *D. russelii* liquid venom had been sold to an antivenom manufacturer[15].

There are several other producers of snake venom in India, but the status of their legality is questionable and some reportedly supply liquid or 'light-bulb dried' venom to antivenom producers. The WHO protocol for venom standards and production for the manufacture of antivenom is unfortunately, not yet implemented in India. In 2009, the Maharashtra State Forest Department announced plans, via a press release, to set up a Snake Venom Research and Extraction Centre in Nashik, utilizing the snakes caught by 'snake rescuers', often attached to local animal welfare bodies[16]. The current status of this initiative is unknown, but considering the popularity of snake rescue in many parts of India, this is an obvious potential source of snakes for venom production.

Production of antivenom

In an effort to quantify total antivenom production capacity in India, along with projected production estimates of Indian antivenom producers, a simple questionnaire was sent, via e-mail, to all these producers, with follow-up phone calls required for most respondents. There are currently at least seven laboratories in India which produce snake antivenom; Table 3 shows their stated projected production estimates for 2011/2012.

Antivenom production statistics from the Indian Central Bureau of Health Intelligence (ICBHI) for the years 2008–2009 are shown in Table 4 (ref. 17). These statistics when compared with the results of the author-conducted survey, suggest that installed capacity for the production of AVS has increased by at least 260% over a period of 3 years. This figure, however, does not accurately quantify the actual situation, as data is missing from both the data sets. This further illustrates the need for a standardized, data collection, collation and display system to process all data related to the production and use of antivenom.

Earlier production estimates (2001–2004) are also published by ICBHI[18]. These figures, as originally published, are somewhat difficult to interpret as different units have been used, sometimes within individual data sets. For ease of representation, they have all been converted into the same units and are presented in this paper as thousands of vials (10 ml vials are standard antivenom doses in India) as in Table 5.

The installed production capacity of antivenom producers in India appears to have dropped by nearly 300% from 2001 to 2008; following this, there has been an increase of at least 260% in installed capacities from 2009 to 2011. Reasons for the decline include the fact that the Serum Institute of India, one of the biggest producers, stopped production for many years. The subsequent increase in production from 2009 to 2011 could be explained by several factors, including the emergence of new producers (for e.g., Mediclone Biotech, Chennai), and an increase in production capacity by others – most notably Bharat Serums and Vaccines, whose installed capacity increased almost four-fold from 400,000 vials in 2001, to 1,500,000 vials in 2010.

Two antivenom producers have recently stopped production.

- Serum Institute of India, Pune – Polyvalent for 'big four', lyophilized, average annual production >100,000 vials. Also lyophilized polyvalent for two species of African snakes combined (for reasons unknown) with Indian *Daboia* and *Echis*. Production of antivenom was stopped in 2008, reportedly in view of the stringent conditions which were implemented by the Committee for the Purpose of Control and Supervision of Experiments on Animals (India) CPCSEA. Venom source (India): Irula Cooperative.
- Central Research Institute, Kasauli (Government of India) – Polyvalent for 'big four', lyophilized, average annual production was 25,000 vials. Production discontinued on 2007. Venom source: Irula Cooperative.

All Indian antivenom labs produce polyvalent serum of equine origin against the four most common and widely distributed medically important Indian snake species, referred to for brevity as the 'big four'. It has been observed that 2010 prices for a 10 ml vial of Indian polyvalent AVS range from about INR 300 to 500 (US$ 6.50–11.00), which is a fraction of the cost of a vial of CroFab antivenom in the USA (at over US$ 1900 per vial) or CSL antivenom in Australia (at US$ 1500 per vial)[15,19,20].

Table 3. 2010–2011 production estimates of Indian polyvalent antivenom (responses from an author-conducted survey)

Institute	Production estimates (10 ml vials)
Public sector	
Central Research Institute, Kasauli	0
Haffkine Institute, Mumbai	180,000
King Institute, Chennai	3,300
Bengal Chemicals and Pharmaceuticals Ltd, Kolkata	NR
Private sector	
Serum Institute of India, Pune	0
VINS Bioproducts Ltd, Hyderabad	No projection
Biological E Ltd, Hyderabad	200,000
Bharat Serum and Vaccine, Mumbai	1,500,000
Mediclone Biotech (Chennai)	75,000
Total	1,958,000

NR, Not received.

Table 4. Production values of Indian polyvalent antivenom serum for 2007–08 and 2008–09

Institute	Installed capacity (10 ml vials)	Actual production 2007–08	Actual production 2008–09
Public sector			
Central Research Institute, Kasauli	30,000	2,500	0
Haffkine Institute, Mumbai	393,000	1,600	396,500
King Institute, Chennai	75,000	0	0
Bengal Chemicals and Pharmaceuticals Ltd, Kolkata	6,000	400	NR
Private sector			
Serum Institute of India, Pune	40,000	NR	NR
VINS Bioproducts Ltd, Hyderabad	30,000	NR	NR
Bharat Serum and Vaccine Pvt Ltd, Mumbai	84,000	NR	NR
Biological E Ltd, Hyderabad	20,000	NR	11,700
Total	678,000	4,500	408,200

NR, Not received.

Table 5. Actual production values of Indian polyvalent antivenom serum for 2001–02 and 2002–03, proposed production for 2003–04 (1000s of vials)

Institute	Installed capacity (10 ml vials)	Actual production 2001–02	Actual production 2002–03	Proposed production 2003–04
Public sector				
CRI, Kasauli	35	70.9	26.4	36
HBPCL, Bombay	453	143.1	143.3	250
KIPM, Chennai	75	4.3	0	20
Bengal Chemicals and Pharmaceuticals Ltd, Kolkata	623	231.9	NR	NR
Private sector				
SII, Pune	550	110.4	NR	NR
VINS Bioproducts Ltd, Hyderabad	25	10.4	25	50
Biological E Ltd, Hyderabad	100	0	34	30
Bharat Serum and Vaccine Pvt Ltd	400	226.9	419.4	876
Total	2,261	797.9	648.1	1262

AVS is supplied by Indian antivenom producers to government hospitals at Rs 115 per vial (US$ 2.50)[15]. Some labs produce both liquid and lyophilized sera and some have produced bivalent sera in the past. While this relatively low cost makes Indian antivenom more accessible, it does have certain inherent problems, which are dealt with under a separate heading below.

Venom and antivenom requirements for India

It will be advantageous to ascertain exactly how much venom is required to produce an adequate quantity of antivenom for India in order that venom supply permits and protocols can be worked out. Based on a production breakdown provided by an antivenom producer (though subject to considerable variability depending on the immunization procedures used and other factors), production of 10,000 vials of antivenom requires approximately 2 g each of *N. naja* and *D. russelii* venom and 0.2 g each of *Bungarus caeruleus* and *Echis carinatus* venom[21]. Production of 2,000,000 vials (estimated output for 2011/2012 based on responses from antivenom producers) would therefore require an annual production of at least 400 g each of *N. naja* and *D. russelii* venom and 40 g each of *B. caeruleus* and *E. carinatus* venom (see the next section).

Using these estimates, it is inferred that the Irula Cooperative supplies only about half of India's *N. naja* and *D. russelii* venom requirements, but almost all of its *B. caeruleus* and *E. carinatus* venom requirements. However, it must be noted that there was considerable variability in estimates provided by two other antivenom producers: the second data set indicates that the production of 2,000,000 vials would require 2,260 g of *N. naja*, 1,508 g of *D. russelii* and 300 g each of *E. carinatus* and *B. caeruleus* venoms[22]. The third dataset indicates that the production of 2,000,000 vials of antivenom would require 250 g of *N. naja* and *D. russelii* venom with 76 g each of *B. caeruleus* and *E. carinatus* venom[23]. Efforts to

Table 6. Number of snakes required to meet 2011/2012 antivenom production requirements, (two million vials) using AVS statistics from Bharat Serums and Vaccines[21]

Species	Venom yield (g) per snake (average)	Total grams required (g)[21]	Total snakes required*
Naja naja	0.330	400	1,212
Bungarus caeruleus	0.0227	40	1,762
Daboia russelii	0.200	400	2,000
Echis carinatus	0.00625	40	6,400
Total		880	11,374

*Total snakes required = total venom required (g)/average venom yield (g).

Table 7. Number of snakes required to meet 2011/2012 antivenom production requirements, (two million vials) using AVS statistics from Haffkine Institute[22]

Species	Venom yield (g) per snake (average)	Total grams required (g)[22]	Total snakes required*
Naja naja	0.330	2,260	6,848
Bungarus caeruleus	0.0227	300	13,215
Daboia russelii	0.200	1,508	7,540
Echis carinatus	0.00625	300	48,000
Total		4,368	75,603

*Total snakes required = total venom required (g)/average venom yield (g).

trace the rest of the venom supply in India have yielded minimal information. A recent, state by state estimate of AVS requirements in India totals 1,200,500 vials[24]. Further refinement of the estimated needs will help both venom and antivenom producers fulfil India's actual requirements.

ICBHI estimates antivenom 'demand' (it is unclear as to whether this can be equated to 'requirements') for India to be just 110,000 doses for 2007–08 and 128,133 doses for 2008–09 (ref. 17). This is an entire order of magnitude lower than the estimates made by antivenom producers. We see the need, again, based on these figures, for standard methods of reporting production, demand (requirements) and supply details for all antivenom producers and purchasers.

Are our antivenom producers up to date?

Indian antivenom producers have to upgrade their production protocols that have not changed much since the 1950s. For example, an Australian antivenom producer uses 2 mg of taipan (*Oxyuranus scutellatus*) venom to yield the equivalent of 1,600 10 ml vials of antivenom from horses. This means that 2 million vials could be produced by their methodology using a mere 2.5 g of venom!

Irula Cooperative statistics[13] using their standard average of four venom extractions from each snake while it is in captivity for 3–4 weeks, have been compared to antivenom production statistics of two producers. Tables 6 and 7 show the approximate number of snakes required to produce 1 g of venom (lower estimate of all three antivenom production data sets).

Table 6 provides the most conservative output in terms of the number of snakes required to meet the antivenom production requirements for India. Conversely, Table 7 shows a much greater estimate of the number of snakes required – it is not possible, with the existing information to determine which data set is most accurate, but it is possible that an average of the two outputs provides a reasonable overview of the situation.

Tables 6 and 7 illustrate the need for accurate reporting, and also the potential variability between antibody yield and venom requirement in the production of antivenom. All snakes are protected under India's Wildlife Protection Act and permits for snake capture for the essential purpose of antivenom production, have in the past been difficult to obtain. The process urgently needs to be streamlined by the state forest departments[11].

Issues related to Indian antivenoms

Several studies have demonstrated regional variation in *D. russelii* venom. A study shows that *D. russelii* venom from northern and western parts of India was twice as toxic as venom samples from the south[25]. Antivenom prepared from venum from south India failed to protect experimental animals against venom from *D. russelii* of other parts of India[26]. Similarly, *N. naja* venom from the eastern part of India was more lethal than that of western and northern forms and available antivenom (made mainly with venom sourced from the south) could not neutralize venoms from the eastern and northern parts of the country[27]. Other studies showed significant variation in the composition of *D. russelii* and *N. naja* venoms[28–30].

Inadequate attention to these long-understood geographic variations in venoms is one of the reasons for the increasingly common reports from clinicians about the ineffectiveness of commercially available antivenoms[31–33]. Other issues include the sourcing of venom from unlicensed producers, misleading/outdated medical information in the instruction leaflets, noncompliance with WHO standards and protocols for venom and antivenom production. The export/sale of India-specific antivenoms to other countries including Cambodia, Nigeria and Papua New Guinea is another serious issue raised in various national and international fora regarding antivenom production in India[34,35].

The quality and potency of South Asian antivenoms have been largely unchanged for more than 55 years[36]. A review of the situation[35] highlights the fact that poor manufacturing standards persist, and products have minimal efficacy and unacceptably high adverse reaction rates[37]. There is, therefore, an urgent need for regional partners to come together, perhaps with external collaboration, to develop a robust, potent, high quality pan-Asian polyvalent antivenom that provides broad coverage against the venoms of the major venomous species throughout the region. The WHO has recently published Guidelines for the *Production, Regulation and Control of Snake Antivenom Immunoglobulins,* and produced a complementary website with a number of resources[8,10]. As one author puts it, ‘a new antivenom for South Asia that meets these rigorous standards, could fulfil the needs of all governments across the region, and at the same time significantly improve patient outcomes, while substantially reducing treatment costs[35]’.

The current antivenom potency requirements (set by Indian Government regulators in the 1950s) of 0.45–0.6 mg/ml are woefully inadequate, given the venom yields of most of the species responsible for envenoming[35]. While it is true that India produces the cheapest antivenom in the world (averaging US$ 10 per vial, retail), simple calculation shows that treatment can actually be very expensive. For example, the range of venom yields for cobras reported in one study was 58–742 mg (ref. 38), which translates to a need for 13–165 vials (a treatment cost of US$ 130–1,650 or INR 6,500–82,500). To corroborate this, one study in northern India reported the median number of vials used for bites by elapid snakes (kraits and cobras) as 90, for a treatment cost of US$ 900 or INR 45,000 (ref. 39). As venom yields measured during venom extraction may far exceed the average (but always unknown) quantity of venom injected in a defensive bite, it is obviously vital that antivenom potency must be adequate (and affordable) for a ‘worst case’ scenario.

Table 8. Venom yields of some medically important species[42]

Species	Average venom yield (mg)
Naja naja (black form)	198.6
Bungarus sindanus	13.0
Trimeresurus malabaricus	16.5
Echis carinatus sochureki	51.2
Peltopelor macrolepis	5.1

In addition to this disparity in venom yields, variations in venom composition and yield geographically and with sub-species of the ‘big four’ are understudied phenomena, which have significant implications for snakebite treatment. There are at least four medically significant species of *Bungarus* (kraits), viz. *B. caerulus*, *B. sindanus*, *B. niger* and *B. walli*[40,41], two of *Naja* sps., viz. *N. kouthia* and *N. oxiana* and one sub-species of *Echis*, *E. carinatus sochureki*[37]. We are currently looking at structural differences between these venoms and aim to determine ED50 (effective neutralizing dose of antivenom) of Indian antivenom against these and other species of possible medical significance[42]. Table 8 illustrates venom yields from the first extractions conducted by the Centre for Herpetology as part of a collaborative effort to quantify structural differences in venom composition geographically.

These average venom yields indicate that, although antivenom is not made specifically for these species/variants, all of them (with the exception of *P. macrolepis* and *T. malabaricus*, for which there are no recorded fatalities) can inject potentially lethal quantities of venom.

Discussion

Snake venom production for antivenom in India was done solely by the Haffkine Institute in Mumbai prior to the establishment of ISCICS outside Chennai[12]. There are currently seven laboratories producing antivenom in India with a total production capacity estimated at two million, 10 ml vials[15,22–24]. Based solely on venom sales by the Irula Cooperative, requirements to fulfil this capacity are approximately 1,330 g each of *N. naja* and *D. russelii* and 133 g each of *B. caeruleus* and *E. carinatus.* However, these figures are subject to confirmation and requirements based on data from antivenom producers are significantly different. One data set indicates a requirement of about 2,260 g of *N. naja*, 1,508 g of *D. russelii* and 300 g each of *E. carinatus* and *B. caeruleus*[22].

The current potency of Indian antivenoms is 0.60 mg/ml for cobra, while prior to the 1950s, it was 4 mg/ml. In Russell’s viper venom, it was 2 mg/ml and is now a mere 0.45 mg/ml. When and why was this changed by the government antivenom potency regulators? This issue of antivenom potency needs urgent attention.

Since the start of antivenom production in India over 100 years ago, conventional wisdom was that the ‘big four’ are responsible for the majority of serious bites. While this is still true at the generic level, current taxonomy now recognizes four species of cobras, eight species of kraits, one species of Russell’s viper and two sub-species of saw-scaled vipers[43]. Also, considerable regional variation has been found in Russell’s viper venom which requires further study[25,26]. There are growing indications from clinicians that antivenom produced from venoms of the ‘big four’, mainly sourced from Irula Cooperative, may not effectively neutralize envenomation by the ‘big four’ and related species in other parts of the country[27,31,33,35]. Whether this is due to venom variation, bites by other species, low antivenom potency or a combination of these factors, needs to be determined.

In addition, several of the 22 species of pit vipers in India[43], a number of sea snakes and species such as the king cobra are capable of causing human and livestock disability and death. Though serious bites from most of these species are thought to be rare, snakebites which occur in more remote areas are often not reported. When bites occur from species other than the four used in India’s polyvalent antivenom production, clinicians are apt to use the available antivenom, even though there is a great likelihood that it is ineffectual. For example, a recent case of pit viper bite in the Himalayas was treated at a military hospital using 30 ampoules of polyvalent serum, which has no neutralizing effect on pit viper bites[44].

Snakebite is responsible for tens of thousands of deaths and disabilities every year in India[3–5,35,37]. In a somewhat complex ‘snakes-of-medical-importance’ scenario, there is an urgent need to address the following issues to improve the situation.

- Venom/antivenom research to establish venom toxicity, antivenom potency, minimum effective dose of antivenoms, cross-reactivity of antivenom among species and the important area of geographic variation of venoms.
- Venom production in sufficient quantities and to supply the demand, under WHO protocol to produce a high standard of venom with immediate attention to proven and likely geographic variations.
- To achieve the previous point it is suggested that India’s largest venom producer, the ISCICS be reconstituted as a multi-state cooperative under the central government so that snake venom for the production of antivenom can be collected from as wide a geographic area as possible in recognition of the fact that there is considerable regional variation in the composition of venoms and that there are species other than the ‘big four’ responsible for serious bites.
- Field studies on the distribution and abundance of the medically important snakes to guide antivenom manufacture (regionally specific, monovalent, bivalent, polyvalent) and effects on local populations, if any, on capture of large numbers for antivenom production.
- Designing a protocol acceptable to wildlife authorities for the capture of sufficient numbers of snakes for India’s antivenom needs, safety standards for venom extraction and humane treatment of captured snakes.
- Education and awareness campaign to publicize use and effectiveness of antivenom as opposed to local, quack remedies.
- Enforcement of stringent laws against bogus snakebite ‘treatments’ and appropriate public awareness against these practices.
- Inducing state and central government health agencies to ensure wider availability of antivenom on a subsidized/free distribution basis for the rural poor via primary health centres and other rural health facilities.
- Antivenom production to supply India’s needs under WHO protocol including additional species if venom research and clinical data proves their medical significance. Producing a pan-Asian antivenom – a high potency antivenom designed for several countries across the South Asian region, produced in large volumes and dispensed in single dose vials is a worthy goal.
- Training of clinicians in correct treatment and management of serious snakebites.

To effectively implement these strategies, it has been suggested to the Ministry of Health, Government of India that it convenes a series of regional and central meetings of the key stakeholders including the following

- Venom producers
- Venom researchers
- Antivenom producers
- Clinicians with snakebite experience
- State and central health authorities
- Environment/wildlife authorities
- WHO experts
- Herpetologists with local experience.

Finally, it is significant to note that despite efforts over a period of nearly 10 years, we have been unable to elucidate concrete information about any other venom production units in India. There is ample evidence to suggest that several other venom producers do exist, and several individuals involved in the production of antivenom have confirmed this. These venom producers are most likely illegal, as suggested by paucity of information concerning them and by their temporary nature. If mechanisms are complimented to better facilitate, and also regulate the creation of venom production facilities, it would go a long way in promoting the production of high quality venoms (following WHO protocol) and creating better systems of accountability and reporting.

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