Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206**
Sch. Acad. J. Pharm., 2013; 2(3):252-259

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Review Article

Snake Bite Problem in India: An Overview

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Abstract: Snakebite is a medically and socially significant issue in India. Even in the 21st century India still is an agrarian country. Indian farmers are vulnerable to snake attacks as they mostly work bare foot with limited protection. There are currently seven pharmaceutical laboratories in India which produce anti-venom against four medically important Indian snake species Cobra (Naja sp.), Krait (Bungarus sp.), Russell's viper (Daboiarusselii) and Sawscaled viper (Echiscarinatus sp.), the 'big four' further exasperates the situation. The price is also out of reach of most people.
In this Review article we are highlighting about the fact that India has the worst snakebite problem in the world, largely affecting poor people and children from rural communities & in India there is need for superior techniques for making anti- venoms.
Keywords: Snake-bite, anti-venom, first-aid , India.

INTRODUCTION

Indian subcontinent being subtropical harbors, a wide variety of snakes are present. Snakes here are no only feared but also are revered. Snakes in most parts of the country are worshipped and devotees consider snakes very sacred. In 2009 the World Health Organization added snakebite to its list of neglected tropical diseases, hoping toreduce its burden on so many marginalised populations. [1, 2] According to SB Management in Asia and Africa produced in 2010 by the International Medical Research Council, 11,000 deaths from snakebite occur every year in India.

Snakes in Indian Culture --History

Snakes worship is common in religions like Buddhism and Hinduism in India. The Cobra referred to as "Nag" represents rebirth, death and mortality, due to its casting of its skin and being symbolically "reborn". The Nairs of Kerala and Tulu Bunts of Karnataka in South India still carry out many sacred ancient customs. The Nāga is a deity or class of entity or being, taking the form of a very great snake.Nag panchami is an important Hindu festival associated with snake worship which takes place of the fifth day of Shravana. Snake idols are offered gifts of milk and incense to help the worshipper to gain knowledge, wealth, and fame. Shesha, the 1,000 headed snake, upholds the world on his many heads and is said to be used by Lord Vishnu to rest. Shesha also sheltered Lord Krishna from a thunderstorm during his birth. The Hindu mythology is replete with stories of various forms of snakes.

Poisonous Snakes in India

Spectacled cobra Common krait Russell's viper Saw-scaled viper.

Figure No. 1: Showing poisonous Indian snake species.

SNAKE BITE

Venom is a precious resource for venomous snakes. Snake envenomation is a completely voluntary process. A venomous snake can deliver a dry bite (a bite without venom) if it feels envenomation is not necessary The frequency of dry bites varies with species and environmental conditions. Snakes do not ordinarily prey on humans. Unless startled or injured, most snakes prefer to avoid contact and will not attack humans. With the exception of large constrictors, nonvenomous snakes are not a threat to humans. The bite of a nonvenomous snake is usually harmless; their teeth are not designed for tearing or inflicting a deep puncture wound, but rather grabbing and holding. Although the possibility of infection and tissue damage is present in the bite of a non-venomous snake, venomous snakes present far greater hazard to humans.

Anatomy of Venomous Snakes [3]
The anatomy of venomous snakes is widely varied, but some aspects are universal. All snakes have similar venom delivering apparatus systems comprised of venom glands, a duct and fangs for venom delivery.

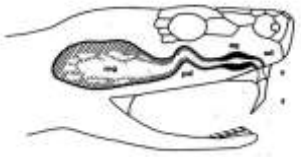


Figure No 2: Showing schematic drawing of the venom apparatus of Crotalidae
[Reference for fig. --Rattlesnake Venoms, copyright 1982. Marcel Decker Inc.]

Venom is synthesized & stored in the main venom gland (mg) & transported by the primary duct (pd) through the accessory gland (ag) & secondary duct (sd)which exits into a fang sheath pocket 9s) ,diverting a venom into & through the fang (f).The loop in the primary duct accommodates the movement of the fang.All of these features occur bilaterally.

Snake Venom [4]
Snake venom is highly modified saliva containing zootoxins used by snakes to immobilize and digest prey or to serve as a defense mechanism against a potential predator or other threat. The venom produced by the snake's venom gland apparatus is delivered by an injection system of modified fangs that enable the venom to penetrate into the target

Venom Composition [5].
More than 90% of snake venom (dry weight) is protein. Each venom contains more than a hundred different proteins: enzymes (constituting 80-90% of viperid and 25-70% of elapid venoms), non-enzymatic polypeptide toxins, and non-toxic proteins such as nerve growth factor

Venom enzymes
These include digestive hydrolases, hyaluronidase, and activators or inactivators of physiological processes, such as kininogenase. Most venoms contain l-amino acid oxidase, phosphomono- and diesterases, 5'-nucleotidase, DNAase, NAD-nucleosidase, phospholipase A and peptidases.

Zinc metalloproteinase haemorrhagins : Damage vascular endothelium, causing bleeding.
Procoagulant enzymes: Venoms of Viperidae and some Elapidae and Colubridae contain serine proteases and other procoagulant enzymes that are thrombin-like or activate factor X, prothrombin and other clotting factors. These enzymes stimulate blood clotting with formation of fibrin in the blood stream. Paradoxically, this process results in incoagulable blood because most of the fibrin clot is broken down immediately by the body's own plasmin fibrinolytic system and, sometimes within 30 minutes of the bite, the levels of clotting factors are so depleted ("consumption coagulopathy") that the blood will not clot. Some venoms contain multiple anti-haemostatic factors. For example, Russell's viper venom contains toxins that activate factors V, X, IX and XIII, fibrinolysis, protein C, platelet aggregation, anticoagulation and haemorrhage.

Phospholipase A_2 (lecithinase): The most widespread and extensively studied of all venom enzymes. It damages mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular endothelium, and other membranes, produces presynaptic neurotoxic activity, opiate-like sedative effects, leads to the auto-pharmacological release of histamine and anti-coagulation.

Acetylcholinesterase: Although found in most elapid venoms, it does not contribute to their neurotoxicity.

Hyaluronidase: Promotes the spread of venom through tissues.

Snake Anti Venom [6]
ASV is the immunoglobulin (usually the enzyme refined F (ab) 2 fragment of IgG) purified from serum or plasma of horse or sheep that has been immunized with the venoms of one or more species of snake. Polyvalent or polyspecific anti-venom neutralizes the venoms of several different species of snakes, usually the most important species in a particular geographical area. ASV treatment is recommended if and when a patient with proven or suspected snake bite develops one or more signs of systemic envenomation – hemo or neurotoxicity.

SYMPTOMS OF SNAKE BITE [7]
Fang marks, Pain, Oedema at site, Weakness, Numbness, Tingling, Tachycardia, Nausea, Vomiting, Confusion, Muscle fasiculations.

Problems and Possible Solutions In India
The problems with anti-venoms and their possible solutions are given below:

A. Statistical Variation [8, 9]
In 1869 Joseph Fayrer of the Indian Medical Service tracked 11416 snake bites across half of British India ranging from Pakistan to Burma. In 2005 the WHO estimated that 35000- 50000 snake deaths in India. A report published in the Public Library of science of Neglected Tropical Diseases journal in April 2011 put the toll to 45900 that surveyed about 1.1 million houses across the country.

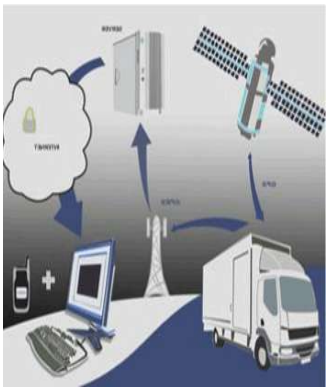
The statistics vary due to poor accessibility to rural areas, no reporting of cases, and improper reporting of

cases. The figure most likely is around 30000-5000 deaths. The problem is utter ignorance and negligence of the Union government towards this issue. In fact the deaths are invisible to the government reports. Union Health minister GhulamNabi Azad told the LokSabha in April 2012 that there had been 1440 deaths due to snake bites in India. The startling gap is consistent with central bureau of health intelligence report that recorded a 1350 snake bites deaths. WHO, however, predicts as many as

1,84,1000 envenomings and 94,000 deaths globally, with India having the most of any country, with an estimated 81,000 envenomings and 11,000 deaths a year. This staggering and appalling gap points the dismissive attitude of authorities towards this important issue. In April 2009, snakebite was added to WHO's list of 'neglected tropical diseases' which indicates the fact that snake bite is a serious medical problem in rural India. It is high time the Indian government acknowledges the problem too.

The first steps towards solving the problem is recognizing and considering it to be a problem. As the species of snakes differ in various parts of the country so does the anti-venom which makes management difficult. Hence local communities should be empowered using financial and educational help. Collection of data is important for proper strategic planning. This will help in distribution and management.

In the modern era novel methods of data collection include usage of GPS and by development of an information gathering model as shown in the figure-3 below.



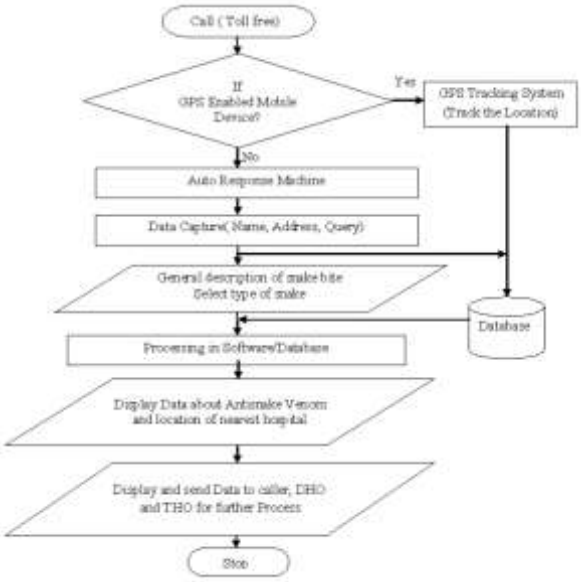


Figure no.3: Describes RAC (rural assistance Centre flow chart model)

B. Venom production [10-13]

Venom is necessary for the production of anti-venom. 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. 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 anti venom. Venom collection is very difficult due to lack of trained persons and also due protection of all snakes under the Wildlife Protection Act. One of the possible solutions could be formation of communities which collect snakes and extract their venom under legal supervision.

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 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. The ISCICS account for 80% of India's anti-venom. 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 · N.S. and Associates, Sehore, Madhya Pradesh is another institute established in 2004 with limited venom collection.

C. Anti-venom Production [14-16]

The national demand for ASV is between 4-5 million vials but the production remains less than 1.5 million vials. This statistics paints the sad story about acute shortage of ASV in India.

The poor supply of venom in terms of quality as well as quantity in turn affects anti venom production. There is a huge deficit of anti-venom production in India. The installed production capacity of ant venom 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.

All Indian anti-venom labs produce polyvalent serum of equine origin against the four most common and widely distributed medically important Indian snake species. 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 anti-venom in the USA (at over US$ 1900 per vial) or CSL anti-venom in Australia (at US$ 1500 per vial**)** is supplied by Indian anti-venom producers to government hospitals at Rs. 115 per vial (US$ 2.50). Though the cost of vial is considerably low the concentration of ASV is quite low too. This is according to government standards set up in 1950s. So while 4 vials of ASV produced by Cro Fab can neutralize viper bite in USA, a cobra bite can require anything between 13-165 vials (according to amount and concentration of venom injected) made by Indian companies. This not only increases medical cost but ultimately over exposes the victim to potentially dangerous side effects of ASVs.

The government should provide incentive to companies to produce anti venom and the standards of Indian anti-venom should improve in accordance with global standards. In an effort to quantify total anti-venom production capacity in India, along with projected production estimates of Indian anti-venom 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 laboratoriesin India which produce snake anti-venom; Table 2 shows their stated projected production estimates for 2011/2012

Table 2: Showing 2010–2011 production estimates of Indian polyvalent anti- venom

Name of Company	Vials produced (NO.)
Public sector	
Haffkine Institute, Mumbai	180,000
King Institute, Chennai	3,300
Central Research Institute, Kasauli	0
Bengal Chemicals and Pharmaceuticals Ltd, Kolkata	NR [not received]
Private sector	
Serum Institute of India, Pune	0
Biological E Ltd, Hyderabad	200,000
Bharat Serum and Vaccine, Mumbai	1,500,000
VINS Bioproducts Ltd, Hyderabad	No projection
Mediclone Biotech (Chennai)	75,000
Total	**1,958,000**

The Madras Crocodile Bank Trust and Centre for Herpetology (MCBT), in collaboration with scientists at the Indian Institute of Science (IIS) and National Center for Biological Sciences (NCBS) and the Global Snakebite Initiative has begun a project that will initially concentrate on Russell's viper which is responsible for many serious and fatal bites. Venom will be collected from ten different geographic areas around India, quickly frozen using a new GSI-developed protocol and then transferred to toxicologists at the Indian Institute of Science for studies of how effectively it is neutralized by Indian anti-venoms. Detailed proteomic studies will follow. Results of these studies should improve the quality and potency of Indian anti venoms.

Institute	Installed capacity (10 ml vials) 2007–08 2008–09	Actual production	
Public sector		2007–08	2008–09
Central Research Institute, Kasauli	30,000	2,500	0
Haffkine Institute, Mumbai	393,000	1,600	396,500
Bengal Chemicals and Pharmaceuticals Ltd, Kolkata	6,000	400	NR
King Institute, Chennai	75,000	0	0
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	**6,78,000**	**4,500**	**4,08,200**

Shortage in government center's-The shortage of ASVs at government health clinics is due to a court case that apparently led to the current short supply situation dates back to 2008 when government put a condition that it will purchase medicines from only those companies whose annual turnover is over Rs 10 crore. Challenging the caveat, certain small-scale industries obtained a stay order from the HC, which stalled government's further procurement deal with new companies. Those which already had agreements with the government till 2007-08 continued to supply medicines at rates decided then. However, since the cost of anti-venom vials shot up, they stopped supply in 2011. Cost of a vial of anti-venom has gone up from Rs 154 in 2008 to Rs 350 now. Among others, the short-supply situation is similar for saline drips, whose cost went up from Rs 8.8 to Rs 12. However, it is widely available in the open market and the cost is not very high. After a recent review the government has authorized the chief district medical officers (CDMOs) to buy from the open market locally at their level in case of shortage. However, hospitals may not find the vials available in the market easily as very few chemists keep it. "Since it is a free government supply medicine, very few chemists keep it.

D. Standards of Anti venom

As mentioned in the last section the standards of ASV production in India are drastically low when compared with International standards. For example, an Australian anti-venom producer uses 2 mg of taipan (*Oxyuranusscutellatus*) venom to yield the equivalent of 1,600 10 ml vials of anti-venom from horses. This means that 2 million vials could be produced by their methodology using a mere 2.5 g of venom! If the standards for production of ASVs are improved the requirement of venom is also low due to advanced technology. As collection of anti- venom from snakes is difficult, improving the efficiency of ASV production could drastically improve the situation.

E. Variation in snake venom of same species [17, 18]

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. Anti-venom prepared from venom from south India failed to protect experimental animals against venom from *D. russelii*of other parts of India. 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. Other studies showed significant variation in the composition of *D. russelii*and *N. naja*venoms.

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 anti-venoms.

F. Fradulent techniques

Lack of qualified persons to administer ASV leads to a lot of quacks, phony doctors, bhopas sadhus and other phony doctors exploiting illiterate people in most villages of India.

G. Large cases of Adverse Drug Reaction

Adverse drugs reactions of AS such as Type 1 and 2-Early anaphylactic reactions, Type2 Pyrogenic reactions and Late Serum sickness type reactions are not uncommon in patients administered with ASVs. The deaths due to ASV reactions are wrongly attributed to envenomation.

These would tend to understate the current level. The quantity of ASV to be administered depends on the venom injected by the snake. The only way to detect this amount is by observation of the patients symptoms. This method is thus very highly unreliable. The number of ADRs can be reduced by stringent laws and ensuring high

Standards of quality control during ASV production.

Pharmacovigilance centre	ADRs to ASV
JIPMER, Pondicherry	20
SriDevarajUrs Medical College, Kolar	3
Manipal College of Pharmaceutical Sciences, Manipal	4
Annamalai University, Chidambaram	2

(Reported from RPC (South) JIPMER, Pondicherry, during April to November, 2005)

H. Awareness and Management

Lack of awareness makes most victims vulnerable to snake venom. Creation of awareness among villagers can reduce the number of snake bites, decrease irrational killing of snakes, decrease number of quacks and thereby save lives.

Awareness techniques include

1. How can snake bites be avoided
2. Implementing preventive strategies for community education.
3. Identification of venomous snakes.
4. First Aid and intermediate support and care.
5. Information about nearest center where ASVs are available.

TREATMENT [19-22]

Snake Identification

Identification of the snake is important in planning treatment in certain areas of the world, but is not always possible. Ideally the dead snake would be brought in with the person, but in areas where snake bite is more common, local knowledge may be sufficient to recognize the snake. Polyvalent anti venoms avoid the need for snake identification in most countries.

First Aid

Snake-bite first aid recommendations vary, in part because different snakes have different types of venom. Some have little local effect, but life-threatening systemic effects, in which case containing the venom in the region of the bite by pressure immobilization is desirable. Other venoms instigate localized tissue damage around the bitten area, and immobilization may increase the severity of the damage in this area, but also reduce the total area affected; whether this trade-off is desirable remains a point of controversy. Because snakes vary from one country to another, first aid methods also vary.

However, most first aid guidelines agree on the following:

- Protect the person and others from further bites. While identifying the species is desirable in certain regions, risking further bites or delaying proper medical treatment by attempting to capture or kill the snake is not recommended.
- Keep the person calm. Acute stress reaction increases blood flow and endangers the person. Panic is infectious and compromises judgment.
- Call for help to arrange for transport to the nearest hospital emergency room, where anti venom for snakes common to the area will often be available.
- Make sure to keep the bitten limb in a functional position and below the victim's heart level so as to minimize blood returning to the heart and other organs of the body.
- Do not give the person anything to eat or drink. This is especially important with consumable alcohol, a known vasodilator which will speed up the absorption of venom. Do not administer stimulants or pain medications to the victim, unless specifically directed to do so by a physician.
- Remove any items or clothing which may constrict the bitten limb if it swells (rings, bracelets, watches, footwear, etc.)
- Keep the person as still as possible.
- Do not incise the bitten site.
- Many organizations, including the American Medical Association and American Red Cross, recommend washing the bite with soap and water.India developed a national snake-bite protocol in 2007 which includes advice to:Reassure the patient. 70% of all snakebites are from non- venomous species. Only 50% of bites by venomous species actually envenomate the patient.
- Immobilize in the same way as a fractured limb. Use bandages or cloth to hold the splints, not to block the blood supply or apply pressure. Do not apply any compression in the form of tight ligatures, they don’t work and can be dangerous!
- Get to Hospital Immediately. Traditional remedies have no proven benefit in treating snakebite.
- Tell the doctor of any systemic symptoms, such as droopiness of a body part, that manifest on the way to hospital.

Other techniques

The following treatments have all been recommended at one time or another, but are now considered to be ineffective or outright dangerous. Many cases in which such treatments appear to work are in fact the result of dry bites.

- Application of a tourniquet to the bitten limb is generally not recommended. There is no convincing evidence that it is an effective first aid tool as ordinarily applied.[1] Uninformed tourniquet use is dangerous, since reducing or cutting off circulation can lead to gangrene,

which can be fatal. The use of a compression bandage is generally as effective, and much safer.

- Cutting open the bitten area, an action often taken prior to suction, is not recommended since it causes further damage and increases the risk of infection.
- Sucking out venom, either by mouth or with a pump, does not work or may harm the affected area directly. Suction started after 3 minutes removes a clinically insignificant quantity—less than one thousandth of the venom injected—as shown in a human study. The well-meaning family member or friend may also release bacteria into the victim's wound, leading to infection.
- Immersion in warm water or sour milk, followed by the application of snake-stones (also known as *la Pierre Noire*), which are believed to draw off the poison in much the way a sponge soaks up water.
- Application of potassium permanganate.

Bites by cobras, king cobras, kraits, Australasian elapids or sea snakes may lead, on rare occasions, to the rapid development of life-threatening respiratory paralysis. This paralysis might be delayed by slowing down the absorption of venom from the site of the bite. The following techniques are currently recommended:

Pressure-immobilization method [23]

Ideally, an elasticized bandage, approximately 10 – 15 cm wide and at least 4.5 meters long should be used. If that is not available, any long strips of material can be used. The bandage is bound firmly around the entire bitten limb, starting distally around the fingers or toes and moving proximally, to include a rigid splint. The bandages bound firmly (at a pressure of 50-70 mmHg), but not so tightly that the peripheral pulse (radial, posterior tibial, dorsalispedis) is occluded or that the patient develops severe (ischemic) pain in the limb.

Pressure pad [23]

A rubber and/or folded material pad approximately 5 cm square and 2-3 cm thick is placed directly over the bite site anywhere on the body and bound in place with a non-elastic bandage at a pressure of at least 70 mmHg.

CONCLUSIONS & RECOMMENDATIONS

Snake bites constitute 0.5% of the total deaths in India and as previously discussed this number is drastically deviates from reality. Snake bite deaths are underestimated and unacknowledged. This menace can be curbed by creation of co-operative societies on a large scale like the Irula society in Tamil Nadu. This will ensure safe and supervised large scale collection of venom. There is also a desperate need for superior techniques for making anti- venoms.

It is recommended that ASV should be made available in the public as well as private sector, clinics/hospitals particularly in the rural areas where snake bites are prevalent.

The Million Death Study puts it in a nutshell*: "*Snakebite remains an underestimated cause of accidental death in modern India. Community education, appropriate training of medical staff and better distribution of anti-venom, especially to the 13 states with the highest prevalence, could reduce snakebite deaths in India.*"*

We need to act now to deal effectively with this problem, which causes severe disability, brings misery to families, and which kills thousands of people." However, policy makers, clinicians, and the general public have largely ignored the snakebite problem, even though it kills thousands of people each year and causes social, economic, and personal misery to many more.

GLOSSARY

WORD	MEANING
Zootoxins	A poisonous substance from an animal, such as the venom of snakes, spiders, and scorpions.
Prey	An animal hunted and killed by another for food.
ASV	Anti- snake venom
Envenomation	The process by which venom is injected into some animal by the bite (or sting) of a venomous animal.
GPS	Global positioning system- A space-based satellite navigation system that provides location and time information in all weather conditions, anywhere on or near the Earth where there is an unobstructed line of sight to four or more GPS satellites.
Equine	A family of genus Equdae which includes horses, donkeys, zebras.
GSI	Geological survey of India
Instigate	Bring about or initiate (an action or event)
Splints	A device immobilizing part of the body
Droopiness	To bend or hang downward

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