Can we solve the snakebite crisis in India?

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CAN WE SOLVE THE SNAKEBITE CRISIS IN INDIA?

India has the capacity and skills to solve the problem but it will require political will, co-ordinated action and a well-funded programme which encourages co-operation between research groups, and does not neglect the urgent need for basic research.

Spectacled cobra in a rice field in West Bengal: W Wüster

SNAKEBITE MITIGATION AND INNOVATIVE WAYS TO DEVELOP EFFECTIVE ANTI-VENOM

1-3 DEC 2017, CSIR-CENTRE FOR CELLULAR AND MOLECULAR BIOLOGY, HYDERABAD

SnakSymp, an annual symposium of the Toxinology society of India (TSI), attracts diverse interest groups including medical doctors, scientists working on aspects of snake biology, venom proteins and their actions, and novel approaches to snakebite treatment, NGOs working for human and animal welfare, and conservationists interested in reducing human-wildlife conflict. SnakSymp-2017 was inaugurated by Mr. Jogu Ramanna, Minister for Forest and Environment, Telangana State. Concurrently with the symposium, 60+ invited participants took part in a discussion workshop with the objective of reviewing the current situation around underpinning research, clinical management, anti-venom manufacturing, epidemiology and education/awareness, and to identify an action-oriented plan for mitigation of snakebite.

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WHY IS SNAKEBITE SUCH A BIG PROBLEM IN INDIA?

Recent estimates put the number of deaths from snakebite in India at **45,900 per year**, the vast majority occurring in the rural population[1]. However, official Government of India figures based on hospital records are c. 30 times less than this. Surviving bite victims may be **permanently disabled** and suffer considerable **economic losses**[2].

The key to clinical management of snakebites is timely administration of an appropriate anti-venom. However, as toxins in snake venoms vary between and within species, the design and production of anti-venom requires information on the diversity and distribution of venomous snakes and their toxins, which is not currently available.

Polyvalent anti-venom (effective against the venom of the "Big 4" species: the common Indian or spectacled cobra, the common Indian krait, Russell's viper and the saw-scaled or carpet viper) is made in India by a number of manufacturers. However, major regions of India are occupied by different species, and genetic evidence suggests that some of the Big 4 themselves may contain more than one species.

Venom for manufacture of anti-venom is predominately sourced from one licensed supplier based in Tamil Nadu and clinical evidence suggests that the current anti-venom does not neutralize the life-threatening effects of snakebite caused by the Big 4 species in other regions due to differences in venom composition.

The presence of non-immunoglobin (Ig) equine proteins in all commercially available anti-venoms results in a high risk of adverse effects such as anaphylactic shock which can kill a patient if not treated promptly.

Many stakeholders need to be involved to address the problem effectively, including field herpetologists, Forest Departments, researchers (genetics, protein biology, epidemiology, health economics, behavioural change), clinicians, anti-venom manufacturers, drug regulatory agencies, rural health workers, traditional healers, snake rescue organisations, public health authorities, procuring agencies and educators.

Basic research

Research on venomous snakes and their venoms requires collection of samples of snakes in the wild but requires permits from Forest Departments due to their protected status in India, a difficult and slow process.

Other permits, sometimes from different agencies, are required for moving venom across State boundaries and for foreign researcher/institution involvement.

Forest Departments can be reluctant to grant permits for collection (even when non-lethal protocols are used) as substances said to be snake venom and claimed to have high economic value are regularly confiscated,

Multiple applications from different research groups to the same states creates tension and wasted effort while lack of research funding available to laboratories to analyse collected samples delays progress.

Use of differing methodology, geographical sampling, and lack of verification of species involved, reduces the value of existing scientific studies on venom variation.

Russell's viper

ACTIONS

Short-term: A Global Snakebite Initiative India ((GSI-I) Research Working Group should be formed to co-ordinate collecting effort, establish standard methodology for analyses, and agree a sample and data sharing protocol.

GSI-I should work with experts on the Wildlife Protection Act (1972) to establish a website for researchers outlining the procedures required for applying for permits per State.

Researchers should work with State Forest Departments to confirm if venom is present in smuggling seizures. If so, establish a database of toxins to allow identification of species involved and their geographic origin.

Medium term: A biorepository for snakebite research samples should be established at the ICAR-National Bureau of Animal Genetic Resources, Haryana.

Longer-term: Govt. of India should simplify access to samples from venomous snakes for medical research by removing this from the control of the Forest Departments.

ACTIONS

Short-term: An existing WhatsApp snakebite treatment group for telephonic consultation exists and should be publicized widely.

State Governments should supply free ASV in government hospitals in all states.

Medical Council of India should introduce compulsory Continuing Medical Education on snakebite for doctors' license renewal.

Medium term: The Clinical Establishments (Registration and Regulation) Act 2010, which sets the standards for all health facilities in the country, should be reviewed to ensure Level 2 hospitals are equipped to deal with snakebite emergencies.

Trauma counselling should be included in post-emergency care provided.

Registrar General of Births and Deaths should make snakebite notifiable using the diagnosis code T63.0 (toxic effect of snake venom) and the external cause code X20 (contact with venomous snakes and lizards).

MoHFW should revise and improve the National Snakebite Treatment Protocol and develop simple aids (e.g., flowcharts) for doctors.

Anti-venom production

Currently several AVS manufacturers, largely private companies, provide liquid and/or lyophilized product. There is wide variation in total protein content, potential for adverse reactions, potency, and endotoxin content.

The cost, quality and consistency of supply of venom hampers manufacturers' ability to improve the product.

The limited availability of venom from only major licensed source also fails to account for geographical variation in venom composition.

The low neutralizing capacity per vial is designed to allow flexibility in dosage given the large variation in potential venom yields (from milliliters for a large cobra to microliters for a saw-scaled viper), but high doses of horse proteins are delivered where larger number of vials are used.

The high frequency of adverse reactions experienced is a major obstacle to the successful treatment of victims and is a consequence of presence of non-Ig horse proteins in the final product.

Clinical Management

Training of doctors, especially junior doctors stationed at primary health care (PHC) facilities, is currently inadequate and should include basic life-saving procedures (e.g., diagnosis and monitoring (including proper use of WBCT20 20-minute whole blood clotting test[3]; Rational use of anti-snake venom serum (ASV); signs and proper treatment of adverse reactions; Intubation and use of artificial ventilation).

Training modules for PHC doctors are currently only taught in West Bengal and Tamil Nadu but could be extended to other states in the form of online webinars.

Diagnostic tests for the identification of biting species is not necessary for advancing early treatment with anti-venom, and will add additional cost to patients.

Simple clinical algorithms that guide diagnosis of systemic envenoming are needed to inform early anti-venom decision making. Diagnosis need only be "envenomed" vs "non-envenomed" when treatment is via a polyvalent product.

There is a marked lack of evidence on which to base recommended treatments and robust trials will be needed for testing new anti-venom formulations.

ACTIONS

Short-term: Manufacturers should switch from bottles to disposable bags for plasma collection and include tests for bacterial contamination.

Medium-term: stablish regional venom collection and supply centres (e.g., based on public-private partnerships) with strict protocols for snake husbandry and venom collection procedures, and certification of venom quality.

Manufacturers should implement strict current Good Manufacturing Practice (cGMP) to the entire process, with stricter and independent Quality Control by the Central Drugs Standard Control Organization applied on bulk and final product, to reduce incidence of hypersensitivity.

Longer-term: Pre-clinical and clinical testing of products should be mandatory, with Phase IV studies for ongoing surveillance of licensed products.

ACTIONS

Short-term: NCDC should develop simple and clear questionnaires for use in hospitals and provide assistance to doctors to analyse and publish snakebite data.

GSI-I working group should lobby State Govts. to standardize levels of compensation available, and align it with compensation for other types of human-wildlife conflict.

MoHFW should review amount available for snakebite treatment under the national health insurance scheme to ensure it is adequate.

MoHFW should set up an agency to manage the supply chain of ASV in the public sector and monitor stocks.

Medium-term: MoHFW should fund further research on social and environmental risk factors, and effectiveness of various interventions in reducing snakebite.

Health economists should develop alternative more realistic measures of ASV cost-effectiveness than price per vial.

Public Education and Awareness

Prevention of snakebite should be the top priority, and is in line with the move from the curative to the preventative approach to public health in India[4].

The GSI-I working group should recruit health economists and behavioural change experts to investigate effectiveness of use of mass and social media to promote use of torches at night, sleeping on raised platform with use of tucked-in mosquito nets to reduce krait bite risk, use of footwear when outdoors, and rodent control on reducing numbers of bites.

School-children should be targeted through the curriculum as well as through specific programs as they are among the most affected section of society. This should include the importance of snakes in the ecosystem, what to do if a snake is encountered, snakebite as a medical emergency and anti-venom as the only cure, discredited and proper methods of first aid, awareness of free ambulance service or alternative methods for rapid transport to hospital.

Epidemiology and Public Health

Many regions of India currently lack snakebite data (e.g., northeastern and northern states[1], where considerable uncertainty about the biting species exists). Epidemiological data is particularly urgently needed to evaluate the requirement for a different anti-venom in these regions.

The Ministry for Health & Family Welfare (MoHFW), through the Integrated Disease Surveillance Programme (IDSP) of the National Centre for Disease Control (NCDC), should leverage existing district-level health surveillance networks to evaluate factors such as gender bias in seeking treatment.

Sample sizes needed for epidemiological studies are difficult to achieve but can be increased by including significant non-lethal endpoints.

Antibody-based immuno-assays for identification of biting species are limited by within-species venom variation in venom and nucleic-acid based alternatives (aptamers) could be quickly developed.

GVK-EMRI, who operate the free 108 ambulance service in 16 states and 2 Union Territories, collect data which can be leveraged for retrospective and prospective epidemiological studies.

ACTIONS

Short-term: State Education Boards should add snakebite awareness to existing school curricula.

GSI-I should provide templates of short videos and well-designed posters[5] for translation and dissemination through State Panchayats and community health networks e.g. Accredited Social Health Activists (ASHA).

GSI-I should provide training material[5] for snake rescue networks to reduce risk of snakebite.

Medium-term: GSI-I should lobby state Governments which do not yet offer a free ambulance service, and review adequacy of provision of PHC in rural areas.

GSI-I should work with traditional healer associations to encourage them to direct snakebite victims to hospital without delay.

WHAT CAN WE DO NOW?

Funding agencies should ensure that the knowledge gap in underpinning basic research is addressed with a mix of short-to-medium term and longer term funding, and should encourage co-operation and standardization of approach by targeting funding at consortia of minimum size that involve key stakeholders.

The Ministry of Environment, Forests and Climate Change (MoEFCC) should work with the Global Snakebite Initiative (India) working groups to ensure that adequate amounts of essential samples can be collected in a reasonable timeframe. A biorepository for snakebite research samples should be established at the ICAR-National Bureau of Animal Genetic Resources to reduce the need for repeated collection from the wild.

The Ministry of Health and Family Welfare (MoHFW) and its associated agencies should improve snakebite surveillance by making snakebite a notifiable disease that it reported using the appropriate diagnostic codes.

Indian Council of Medical Research should fund further research on social and environmental risk factors, effectiveness of various interventions in reducing snakebite and true cost-effectiveness of anti-venom.

The Medical Council of India should require continuing medical education (CME) courses on snakebite to be taken as a condition of license renewal, introduce a specific module in basic medical training which includes practical life-saving procedures, and provide simple clinical guides for diagnosing envenomation.

Regional venom collection and supply centres should be established with strict protocols for snake husbandry and venom collection procedures, and certification of venom quality.

Anti-venom manufacturers should implement strict current Good Manufacturing Practice to the entire process, with stricter independent quality control by the Central Drugs Standard Control Organization.

State Education Boards should add snakebite awareness to existing school curricula and posters in local languages should be distributed through State Panchayats and community health networks (e.g. ASHA).

Snakebite patient, who died within 20 hrs after receiving 20 vials of anti-venom. Dr. Shyamal Kundu.

References

1 Mohapatra B et al. 2011. Snake bite mortality in India: A nationally representative mortality survey. PLoS Negl Trop Dis 5(4):e1018. **2 Vaiyapuri** et al. 2013. Snakebite and Its Socio-Economic Impact on the Rural Population of the Tamil Nadu, India. PLoS ONE 8(11): e80090. **3 World Health Organization** 2016. Guidelines for the Management of Snake-bites 2nd Ed. WHO Regional Office for South-East, New Delhi, India. **4 Indian Council of Medical Research**, Public Health Foundation, and Institute for Health Metrics and Evaluation 2017. India: State of the Nations' States – The India State-level Disease Burden Initiative. New Delhi, India.

Further Information and Useful Resources

World Health Organisation factsheet on snakebite envenoming: http://www.who.int/mediacentre/factsheets/fs337/en/

The Global Snakebite Initiative, an internationally-active non-profit organisation dedicated to improving access to good quality, safe and effective antivenoms in the world's poorest communities: http://www.snakebiteinitiative.org/

Report by Health Action International, which conducts research and advocacy to advance policies that enable access to medicines and for all people: "THEORY OF CHANGE REPORT: Preventing and Treating Snakebite in Resource-Poor Settings – An Action Plan for Change" available at http://haiweb.org/what-we-do/global-snakebite-initiative/

Bangor University BITES project website: bites.bangor.ac.uk

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