Indian Journal of Emergency Pediatrics
Volume 2 Number 2, April - June 2010

Perspectives

The Absence of Progress for both Children and Adults in Global Snakebite Management; Scrabbling for Funding and Business as Usual Ignores Available Solutions

Simpson Ian D.[1,2,3]

Jacobsen Ingrid M.[4]

ABSTRACT

For 50 years despite frequent initiatives, meetings and reports, WHO and their expert advisers in this field have failed to find a solution to the problem of reducing snakebite mortality and morbidity for both children and adults in developing countries. This situation has arisen from three main problem areas that have dominated the debate: 1. The problem of epidemiology –the belief that high mortality numbers are necessary to convince donors to provide funds, 2. The problem of policy – that always asking the same experts the same questions will somehow generate new answers. 3. The problem of sustainable and affordable anti snake venom provision. In the key area of epidemiology, which provides data on the requirements for anti snake venom little progress has been made. This has impacted on anti snake venom provision. Alternative approaches, which demonstrate effective methods of achieving, sound epidemiology for anti snake venom volume estimation and in the provision of the product itself have been largely excluded. This paper provides a review of the current approach and how the long sort for reductions in mortality and morbidity can be achieved.

Key words: Snake Bites, World Health Organisation, Envenoming, Antivenoms, Health

.

INTRODUCTION

The global snakebite crisis seems an enduring one. Nearly 60 years after Swaroop and Grab's famous epidemiology study little has changed and the many doctors today who are dealing with a child or adult with snakebite face the same problems[1]. At another recent initiative in Melbourne involving 'the worlds leading authorities on snakebite' and anti snake venom provision, including the World Health Organisation (WHO), the following comments by experts centrally concerned with strategy to deal with snakebite, including one who carried out a previous major epidemiology exercise are deeply disturbing [3].

With regard to the latest W.H.O. epidemiology exercise- [2]

"Frankly we don't have reliable data" [2]

"Re-excavating the same well-worn data and trying to reconstruct them into something more convincing is perhaps a stale process" [2]

"How can we make our quantitative argument more convincing"? [2]

"I think we first have to define two things. The first, methodology of epidemiological surveys and studies and the definition or criteria or indicators for example mortality and morbidity".[2]

With regard to anti snake venom (ASV) - [2]

Author's affiliations: [1]West Bengal Snakebite Taskforce, Kolcata, India, [2]Tamil Nadu Snakebite Taskforce, Chennai, India, [3]Snakebite Advisor, Pakistan Medical Research Council, Islamabad, Pakistan, [4]Indian Snakebite Research Initiative, Kerala, India.

Corresponding Author: Simpson Ian D, Kooran House, Nayathode, Kerala 683572, India, Phone: 0091-9947131374, E-mail: iandsimpson@gmail.com

(Received on 10.04.2010, accepted on 04.06.2010)

"For each of the regions, for each of the groups of snakes, we really do not understand the dosing, the dosing intervals and what we are actually hoping to achieve with antivenoms" [2].

With regard to the approach to life saving, funding and other diseases like SARS –

"A few deaths here and there, six deaths in Singapore and immediately $10 million gets pumped into that" [2].

The recognition that poor rural communities "lack a strong political voice", according to W.H.O. and their team of experts in 2007, is scant consolation to those who face snakebite with a poorly trained doctor with no ASV, and they will surely gain no comfort from the above statements [2,4].

This state of affairs has resulted primarily from three major problems, epidemiology, policy and provision of anti snake venom that have dominated W.H.O. and expert thinking for the last 40 years. The purpose of this paper is to outline the current problems within the approach and recommend alternative actions to promote progress based on success in India and other developing countries.

THE PROBLEM OF EPIDEMIOLOGY

Snakebite epidemiology remains in disarray and we cannot reliably determine just how many victims or even children as a subset of victims are affected. Despite three W.H.O. sponsored exercises, the numbers remain elusive, widely ranged and "our figures are so vulnerable" (Table I) [1-3,5].

SOURCES OF SNAKEBITE EPIDEMIOLOGY DATA

Snakebite epidemiology data is derived from three main sources:

1. Hospital statistics, which are gathered retrospectively or prospectively in order to determine number of patients, mortality, envenomings, quantity of ASV administered and treatment given [6-8].

2. Community surveys whereby the local population in a specific, normally high-incidence geographical area are surveyed to identify number of snakebites, envenomings and mortality [9].

3. Literature reviews of published papers [3,5].

LIMITATIONS OF DATA COLLECTION METHODS

Hospital Statistics

In the absence of an effective and consistent treatment protocol to diagnose snakebite itself and envenoming, these statistics can be highly misleading and overstated, as they can be complicated by the inclusion of patients with non-venomous bites, bites from venomous species that do not envenomate the victim, insect stings and simple misdiagnosis based on poor training [6-8,10].

Community Surveys

Community surveys rely on lay people being able to diagnose a snakebite and an

Table I. Snakebite mortality data by region estimated during the three global snakebite mortality reviews [1,3,5]

Source Data	Africa	Asia	Latin America	Total
Swaroop and Grab 1954	400-1,000	25,000-30,000	3,000-4,000	30,000-40,000
Chippaux 1998	20,000	100,000	5,000	125,000
Kasturiratne et al 2008	3,529-32,117	15,385-57,636	540-2,298	19,886-93,945

envenoming, when evidence demonstrates that doctors struggle to do so [10]. Deriving these figures from high incidence areas and factoring them across larger lower incidence areas compounds the potential for overstatement of the problem [3,9].

Literature Reviews

Authors acknowledge that these reviews are not comprehensive, are based on limited knowledge of geographical areas not within the author's range of experience and again rely on inconsistent data and assumptions [3,5].

PROBLEMS OF DATA TREATMENT/ HANDLING

In addition to the above limitations inherent in the data gathering process, which weaken the validity of the base numbers, once the figures have been compiled, they are then subject to further devices, pre and post publication which ensure that the highest number is always presented, due to the belief that bigger numbers justify more funding [2].

Pre publication devices include:

1. The 2008 W.H.O. study shows envenomings in Sri Lanka as 32,902 per annum in both the high and low estimate [5]. Yet, only three years previously, three of the same authors, two of whom were at the Melbourne meeting reported that 37,100 **cases** i.e. victims who reported to hospital with a snakebite, were reported in Sri Lanka in 2000 of which 14,375 required ASV [11]. Doubling the number of envenomings in a single country may make numbers more 'convincing' but is hardly credible.

For India, the country regarded as having the highest snakebite mortality, one of the key participants in the Melbourne meeting and the recent W.H.O. ASV exercise reported estimates of snakebite mortality varying from 15,000 to 100,000 per annum over a 15 year period, without carrying out any epidemiology work in India and stated in the Melbourne meeting "I haven't done the sort of careful analysis" [2,12-15].

Epidemiology carried out in India in 2007 suggests 11,000 is the most credible mortality figure although despite assurances not to range that number upwards, the latest exercise included earlier arbitrary 15,000 numbers as the high-end estimate [5,12].

2. The use of a multiplier for those victims who do not attend hospital but visit a traditional healer, despite the acknowledged principle that most victims of snakebite are not envenomed and even those who are envenomed and adopt traditional treatment as their first option, do eventually report to allopathic hospitals when the traditional healer realises they are dealing with a true envenomation [4,16].

3. Despite the failure of the most recent exercise to obtain numbers from some countries, any future numbers would need to be vetted by "a small committee of experts in this area to say this data is probably acceptable" [2]. Local experts must surely be better placed to estimate numbers of envenomings or deaths.

Post publication devices include continually referring to the highest possible estimates. A number of members of the meeting, including the academic editor of the paper, along with a W.H.O. Director, were directly involved in producing the 2008 estimate of 20,000 deaths per annum which 'may' be as high as 94,000 [5]. However by April 2009 the editor and one of the contributors are conducting press interviews where 125,000 deaths per annum are again reported [17]. Permitting higher figures to be published, having contributed to reports of lower figures, only sensationalises the issue but does not add credibility.

CONCLUSION

In light of the weaknesses in the approach to estimating snakebite mortality and envenomings and the variability introduced by the pre and post publication devices, funding agencies are entitled to be highly dubious about 'snakebite epidemiology'.

Proposals to reduce the previous high estimates for India and Pakistan elicited the following response from a leading member of the Melbourne meeting and a contributor to the W.H.O. exercise: "From a scientific point of view, it would be good to get accurate figures, but politically, it would be best if these figures were not revised downwards too much just yet. Not having the data means we can quote this paper (Chippaux 1998) and maybe gain funding etc support. If a new figure way less is published, it reduces the argument for resource allocation, which focuses on deaths rather than misery" (Personal Communication J. White, Women's and Children's Hospital, Adelaide).

This is the central contradiction of the assumption that the prime function of epidemiology is to secure funding - the very experts who argue for bigger numbers to justify funding presumably have the least interest in reducing actual mortality and morbidity as it is perceived to weaken the case for funding [2].

It is essential that epidemiology is de-linked from funding and instead targeted at determining number of envenomings in order to effectively estimate ASV requirement then this can be addressed. There are studies with reliable protocols currently available that can be used to estimate ASV requirement, which is a key priority in reducing avoidable deaths. There is no need to spend further money and resources on epidemiology [6-8]. Estimates will not be exact but will enable major progress in sustainable ASV provision.

THE PROBLEM OF POLICY

The W.H.O. approach has failed to recognise that consistent failure to improve the snakebite problem is the result of significant flaws inherent in the policy approach [4,18,19].

Policy Approach: Sources and Limitations

W.H.O. consult the same experts and the same organisations in terms of ASV providers who, unsurprisingly, give consistently the same answers (Table II). One of the chief organisers of the new initiative and the driver of the strategy session stated, "I have spent the last 40 years being disappointed that people wouldn't take snakebite seriously" [2]. Perhaps it's not snakebite but the leadership, approach and lack of implementation that are not being taken seriously?

Table II. Summary of Recommendations Remaining Unresolved in W.H.O. Reports on Snakebite 1981-2007. [4,16,18]

Source Data	Develop Better Epidemiology Data	Develop Quality Standards for ASV	Improve Medical Training	Seek Charitable Funding
W.H.O 1981	X	X	X	
W.H.O. 2001	X	X	X	X
W.H.O. 2007	X	X	X	X

Policy Approach: Key Drivers to Reduce Mortality

There has been a focus for the last 30 years on the search for funds to work on the problem, which has prevented the application of imaginative and effective low cost solutions that are readily available [16]. For example, a major omission over the last 55 years has been the development of a single unified locally relevant treatment protocol to form the basis of medical education. The weakness of general western textbooks, so heavily used in developing world medical education has been well documented but not acted upon [10,20-21].

The decades old mantra of 'no funds, do little' needs to be replaced with 'no funds, think differently'!

POLICY APPROACH: PERIPHERAL FOCUS AND INCORRECT CORE GROUPS

Despite the request for more funding, when funds are made available they are poorly utilized. With an initiative starting in 2005, a

major meeting in Geneva in 2007 determined that "effective treatment, critically dependant on therapeutic antisera is often unavailable or unaffordable". [4] Notwithstanding this identified issue, W.H.O. instigated meetings in Addis Ababa and Jakarta in 2008 involving considerable expenditure of funds and time with numerous W.H.O. chosen attendees, mainly from ASV providers, poison centers, quality specialists and regulatory bodies, to address quality issues [19].

The invited consultation groups were unable to address the two key areas of availability and affordability and the resulting draft ASV document concluded with the following: "In addition to the need for appropriate antivenoms to be produced, other issues need to be addressed in ensuring both that antivenoms are appropriately used, and that outcomes for envenomed patients improve. These include availability of antivenoms and appropriate distribution policies, affordability of envenoming treatment and training of health workers to allow safe and effective use of antivenoms and effective management of snakebites envenoming. These important issues are outside the scope of this document and so will not be further addressed specifically herein" [19]. The offer to W.H.O. to provide analysis showing that ASV provision could be affordable and sustainable was rebuffed despite assurances that alternative views would be sought [19,22].

THE PROBLEM OF ASV SUPPLY, SUSTAINABILITY AND AFFORDABILITY

ASV Requirement and Supply

ASV supply remains a problem in terms of an adequate supply of affordable and sustainable products. A requirement of 10 million vials of AV has been estimated and current production levels are considerably below that level [4].

However, very little if any work has been carried out to:

1. Determine why this has occurred [19,21-23]. At the Melbourne meeting it was proposed in a separate document that the problem with ASV in Africa was insufficient demand, justified by an amount of unsold ASV! [24]. The fact that this ASV was unaffordable was addressed by a proposal to gain funding to subsidise costs and increase demand [24].

2. Determine why new entrants do not enter the market or to create the conditions whereby new entrants to the market could reduce or eliminate this shortfall [4,19].

ASV Quality and Affordability

The single approach to increasing supply from the W.H.O. and associated snakebite experts seems to be sourcing unnecessary funding by charitable donation and improving ASV quality with no regard to the costs associated with that effort [2.4].

The drive for quality improvements without regard for the economic consequences makes sense only if it is possible to separate ASV production from the financial realities of cost and sustainability. The approach envisioned by W.H.O. in their latest exercise appears to be just that; separate the cost and sustainability argument from the ASV debate by concentrating on current suppliers, supplying no useful data to help market entrants and convincing a donor to pick up the bill [4,19].

The constituency of many of these W.H.O. meetings focused on the attempt to increase supply includes large numbers of existing ASV suppliers, who it can be assumed have little incentive to increase the number of competitors [19]. The W.H.O. in 2007 stated that:

1. Some production facilities require extensive upgrading to meet quality standards

2. Those with more advanced methods need clearer definition of market size [4].

They further conclude, " Many manufacturers in the public sector operate on a small production scale…this highlights the need for substantial investment in equipment, infrastructure and training "[4]. This conclusion is focussed on current producers and sourcing funds to develop them and completely ignores consideration of new market entrants [4].

In May and July 2008, W.H.O. held two regional consultation meetings with a number of antivenom suppliers and other concerned parties to review a set of guidelines for antivenom production [19]. The W.H.O. stated objective was the "guidelines should include all aspects of antiserum manufacture and control" [4]. The guidelines were inadequate to enable new suppliers to enter the market and key details were absent, including the recommended method of production to ensure efficiency, detailed ASV specifications, adequate clinical trial designs and any economic analysis for suppliers [19].

Those who might have advocated fresh approaches to the problem, which did not require more funding, were not invited [19].

It makes little sense to concentrate on improving the quality of a product that is unavailable with little evidence that product quality is a key issue and yet this was the W.H.O. approach [4]. Developing more stringent standards without a risk benefit analysis will inevitably make an unaffordable product more expensive and is therefore counterproductive. Research has shown that it is entirely possible to produce a safe and affordable product and this should be the priority [25-27]. The last 30 years has seen an increased focus on product quality and a decline in availability, perhaps the two are not unconnected [16,18,19].

Following criticism of drafts of the new ASV production document, the W.H.O. representative finally admitted at the Melbourne meeting that "we have to put more information with regard to the distribution of venomous snakes…the antivenom, the information of anti venoms…we have to go as far as we can" [2].

THE SOLUTION

How then can the snakebite problem for both adults and children be significantly improved? Does this require major funding? The answer is a firm negative. The constant clamouring for funds to carry out more research and epidemiology is both unnecessary and no substitute for action. Significant improvements can be made without funding but with resolute actions.

ACTION 1: PRIORITY TARGETS

A priority list of the most significant actions/items that would contribute the greatest reductions in snakebite mortality should be specified, costed and rapidly implemented by developing world experts. For example, Action 2 below would dramatically improve the effectiveness of treatment in developing countries [8,28,29]. Neurotoxic snakebite contributes a significant number of deaths and yet simple, practical measures for airway support in resource constrained environments have only recently been specified and are yet to be widely disseminated [28-30]. The list should include no more than 8-10 items to ensure that implementation is practical. Lengthy lists of non-prioritised options have been regularly specified but not implemented [16,18].

Some options may indeed cost little to achieve but deliver the greatest reductions in mortality. These items are where any available funds should be deployed immediately. Other, less relevant areas such as venom research should be de-prioritised until the key items are implemented.

ACTION 2: A SINGLE RELEVANT TREATMENT PROTOCOL

In the absence of a single source of effective snakebite treatment guidelines, some countries, for example India, have developed a National Snakebite Protocol [28]. Regional guidelines were sorely lacking in local relevance, contained no guidance as to ASV dosages, incorrect criteria for administering ASV and drugs that are not available locally [14]. In the area of paediatric snakebite management, there is no clear guidance of ASV dosage levels and confusion abounds across all the geographic areas with a serious snakebite problem. Trial data for the Indian Protocol has shown enormous improvements

in the effectiveness of treatment, reduced mortality, reduced patient time in hospital and crucially massive reductions in the use of ASV [8].

Ironically however much of snakebite treatment is non-specific to the relevant area [28-29]. For example, intra muscular adrenaline, in response to anaphylactoid reactions, should be used everywhere such reactions are encountered and is a cost effective alternative to additional funding to eliminate adverse reactions to ASV [31]. Unfortunately, even where a standard approach is applicable, in the absence of a single relevant protocol for treatment, this is not consistently carried out [10]. Consequently doctor confidence when dealing with snakebite is sub optimal and often results in referral of patients to other hospitals even when ASV is present [10].

In addition to the obvious improvement in treatment, there are other benefits that such a protocol would provide:

1. Maximising the effectiveness of current and future supplies of ASV [8].

2. Effective epidemiology data in terms of envenomings. Hospital cases are a useful place to start in identifying levels of envenoming but only if a reliable and universally accepted protocol is in place which definitively determines whether an actual envenomation is present [6-8,21].

The cost of producing such an authoritative, comprehensive developing world snakebite protocol, containing the common features of snakebite management common to all environments and specific regional variations; placing the PDF on the W.H.O. website to be downloaded and printed free of cost locally is minimal [28-29]. This should be done as a matter of priority and marketed by W.H.O., developed by experts in developing world government health systems, not western academics [10,14,21].

ACTION 3: ACTIVE FACILITATION OF NEW MARKET ENTRANTS TO INCREASE ASV SUPPLY

There are many medium/large sized pharmaceutical companies in developing countries looking for production opportunities rather than the normal import and resell option so prevalent in the developing world. What is essential is that these companies, typically with investor interest are presented with clear products, volumes to be delivered, the most efficient equipment arrays, and a clear understanding of an acceptable market return [21-22].

To achieve this, workshops should be held under the auspices of W.H.O. in Africa and Asia inviting pharmaceutical companies who might be interested in entering the market to provide additional ASV.

In order to finalise the most efficient production methods, the required venom supplies and the impact of regulatory or commercial aspects, which has not been achieved to date, the attendees for these initial workshops would also need to include:

1. Equipment suppliers that can provide technical guidance on the most efficient production arrays for manufacturers based on specific products and volume requirements, e.g. Millipore Corporation, Billerica MA, USA. Emphasis should be given to those suppliers that can provide significant portions of the equipment array, as this ensures the minimal number of suppliers providing support and training, vital to ensuring continuity of production in developing countries [21-22].

2. Venom suppliers able to supply the required venoms for use in the two regions or to source currently unavailable but medically significant venoms. Examples include Latoxan, Valence, France [21-22].

3. Health and Commerce officials from key countries such as Angola that have shown a positive approach to commerce and creating innovative technical employment opportunities to advise on regulatory and commercials aspects of the ASV operation [22].

The workshop agenda would be:

1. Basic background to the problem of snakebite and the importance of anti snake venom

2. A detailed explanation of the caprylic acid fractionation method as the preferred method of production in terms of efficiency i.e. double the antibody yield and economic return [22,25-27].

3. An explanation of the similar safety profile of whole IgG and F(ab)2 ASVs and the simple methods available to deal with adverse reactions [25-27]. Whole IgG ASVs are simpler to produce, safe and present opportunities to develop a cheaper product which enables adequate financial returns to be achieved for suppliers who will fund the development [21-22]. There is thus no issue of poor quality products being advocated for developing countries. The testing regimen will ensure that any ASV meets the pharmacopoeia of the relevant country.

4. The plan of the ideal facility to produce ASV, including building outlines, dimensions, power supply, means of achieving Class 100 areas, a Class 100 room in itself or by the use of laminar flow hoods and workspaces, which will provide cheaper alternatives [22].

5. A detailed list of target ASVs to produce including specific detail of species to be contained within each ASV: one will be shortly available for Africa [32].

6. Venom sources and inoculation schedules for each specified ASV and likely costs of venom supplied by venom providers.

7. Volume requirements for each ASV in terms of annual numbers of vials required [32].

8. Quality testing methods and the possibilities of pre qualification support from W.H.O. nominated and independent laboratories.

9. Details of the basic clinical trial method for each ASV. The methodology proposed needs to be simple and preferably rated against an existing ASV to reduce the required sample size which should be specified during the meeting and speed ASVs to market. Non-specific requests for 'trials' help nobody [19].

10. A detailed profit and loss account and balance sheet for the new operation including the level of shareholder return measured in terms of ROA [21-22].

PATH FORWARD

Despite a snakebite death toll of 125,000 being actively promulgated for years, snakebite is still regarded as 'neglected' [4-5]. After fifty years the numbers are still "unreliable" and there is no reason to suspect that this will change in the near term. Whatever the final exact figures turn out to be, snakebite will remain a low priority when expressed in terms of deaths, particularly when compared to other medical problems e.g. tuberculosis, diarrhoea etc [33]. Indeed the W.H.O. representative at the Melbourne meeting confirmed that the Gates Foundation had not considered snakebite a key priority for funds utilisation [2].

However, snakebite can be effectively addressed but requires a paradigm shift and new leadership if we are to avoid continued failure. An objective and inclusivere-evaluation is needed which includes all opinions even if contrary to current thinking, particularly those that show that practical , low cost solutions are available that do not require major funding to implement [8,10, 21-23,32,33-35]. This should follow the example of Bjorn Lomborg's approach to global warming; many of his key principles are applicable and we can borrow heavily from them: [36]

1. Snakebite "is real "[36]

2. The "strong, ominous and immediate consequences of" snakebite "are often wildly exaggerated" [36]

3. "We need simpler, smarter and more efficient solutions", not more funding [36]

4. "Many other issues are more important" and we should be happy if funds are committed in these areas [36]

5. "Our ultimate goal… is to improve the quality of life" for the maximum number of patients, not solely snakebite victims and this may impact snakebite funding [36]

The best battle cry for snakebite is not 'we need more epidemiology to drive funding' but rather 'we can fix this problem with some simple actions and minimal financial support'. Instead of trying to intimidate health officials and donors with unreliable numbers which has not proved successful to date, we should provide pragmatic success and then ask them to help close the remaining gap. It would certainly have the element of surprise!

Funding: None.

Conflicts of interest: None declared.

Ethical approval: Not required.

ACKNOWLEDGEMENT

Authors Contribution: IDS and IMJ conceived and planned the review. IDS, carried out the article preparation, IMJ performed the article review. IDS is the guarantor of the paper.

REFERENCES

1. Swaroop S, Grabb B. Snakebite mortality in the world. Bull WHO, 1954; 10:35–76.
2. Global Snakebite Initiative. Open discussion of the global snakebite initiative concept., Melbourne, (2008) Available from: http://www.snakebiteinitiative.org/files/GICT%20Conference%202008/Audio/Session%2016%20audio/Session%2016%20Open%20Discussion.mp3 [Accessed 11th April 2009].
3. Chippaux JP. Snakebites: appraisal of the global situation. Bull. World Health Org, 1998; 76: 515-24.
4. World Health Organisation. Rabies and envenomings: a neglected public health issue. Geneva, World Health Organisation, 2007.
5. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna, R et al. Estimating the global burden of snakebite: A literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med 2008, 5: e218. doi:10.1371/journal.pmed.0050218.
6. Blaylock R. Epidemiology of snakebite in Eshowe, KwaZulu-Natal, South Africa. Toxicon. , 2004; 43: 159-66.
7. Blaylock RSM. Snake bites at Triangle Hospital January 1975 to June 1981. Centr Afr J Med, 1982; 28: 1-11.
8. Ghosh S, Maisnam I, Murmu BK, Mitra PK, Roy A, Simpson ID. A locally developed snakebite management protocol significantly reduces overall anti snake venom utilization in West Bengal, India. Wilderness Environ Med, 2008; 19: 267-74.
9. Hati AK, Mandal M, Mukherjee H, Hati RN. Epidemiology of snake bite in the district of Burdwan, West Bengal. J. Indian. Med. Assoc, 1992; 90: 145-7.
10. Simpson ID. A study of the current knowledge base in treating snakebite amongst doctors in the high risk countries of India and Pakistan – does snakebite treatment training reflect the local requirement? Trans Roy Soc Trop Med Hyg, 2008, 102: 1108-14.
11. Kasturiratne A, Pathmeswaran A, Fonseka, MMD, Lalloo, DG, Brooker, S, de Silva, HJ. Estimates of disease burden due to land-snake bite in Sri Lankan hospitals. Southeast Asian J Trop Med Public Health, 2005; 36: 733-40.
12. Warrell D.A. Tropical Health: Venomous bites and stings in the tropical world. Med J. Aust, 1993; 159: 773-779.
13. Warrell, D.A., 1995. Snake bites in Europe, Africa, Asia and Oceania. in: White, J.(Ed), Clinical toxicology short course 2005 handbook. Women's and Children's Hospital, Adelaide, 2005; 259-85.
14. Warrell DA. WHO/SEARO Guidelines for the clinical management of snakebite in the Southeast Asian Region. SE Asian J. Trop. Med. Pub. Hlth, 1999; 1: 1-85.
15. Warrell DA. Bites by venomous snakes outside the Americas. In: Auerbach PS, ed. Wilderness Medicine. St. Louis, MO: Moseby, 2007; 1086-1123.
16. World Health Organisation. Progress in the characterization of venoms and standardization of antivenoms W.H.O. Offset Publ, 1981; 58: 1-44.
17. Watson J. The Global Snakebite Initiative is working to improve treatment for victims Press; 2009 [Cited 2009 Apr 22] Available from: http://www.voanews.com/specialenglish/2009-04-22-voa1.cfm?renderforprint=1 [Accessed 10th May 2009].

18. Theakston RDG, Warrell DA, Griffiths. Report of a W.H.O. workshop on the standardization and control of antivenoms. Toxicon, 2003; 41: 541-557.
19. World Health Organisation. Proposed WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins. Geneva, World Health Organisation WHO/BS/08.2088, 2008
20. Auerbach P.S., Norris R.L. Disorders caused by reptile bites and marine animal exposures. In: Kaspar D.L., Fauci A.S., Longo D.L., Braunwald E., Hauser S.L., Jameson J.L., ed. Harrison's Principles of Internal Medicine 16th Ed. New York. McGraw-Hill, 2005; 2593-2600.
21. Simpson ID, Norris RL. The global snakebite crisis-A public health issue misunderstood, not neglected. Wilderness and Environmental Medicine, 2009; 20: 43-56.
22. Simpson ID, Jacobsen IM. Anti snake venom production crisis – Who told us it was uneconomic and unsustainable? Wilderness Environ Med, 2009; 20: 144-55.
23. Simpson ID. Time for an alternative perspective: The eternal problem of supply and quality of anti snake venom in the developing world - 'It's the economy stupid' Wilderness Environ Med, 2008; 19: 186-94.
24. Brown N. Analysis of the antivenom market in Sub-Saharan Africa: A commercial explanation of antivenom shortages and possible solutions Melbourne, (2008) Available at: http://www.snakebiteinitiative.org/files/GICT%20Conference%202008/Session%203/Dr/%20Nick%20Brown.ppt [Accessed 18th May 2008].
25. Rojas G, Jiménez JM, Gutiérrez J.M. Caprylic acid fractionation of hyperimmune horse plasma: description of a simple procedure for antivenom production. Toxicon 1994;2:351-363.
26. Otero-Patiño R, Cardoso JL, Higashi HG, Nunez V, Diaz A, Toro MF, et al. A randomized, blinded, comparative trial of one pepsin-digested and two whole IgG antivenoms for bothrops snake bites in Uraba, Colombia. Am. J. Trop. Med. Hyg, 1998; 58: 183-9.
27. Otero R, Gutiérrez J.M, Rojas G, Núñez V, Díaz A, Miranda E , et al. A randomized blinded clinical trial of two antivenoms, prepared by caprylic acid or ammonium sulphate fractionation of IgG, in bothrops and porthidium snake bites in Colombia: correlation between safety and biochemical characteristics of antivenoms. Toxicon, 1999; 37: 895-908.
28. Government of India. National snakebite protocol. New Delhi: Health & Family Welfare Department, 2007.
29. Simpson ID , Quraishi NA, Qureshi HI,. Snakebite management in Pakistan – A guide to the latest methods of treatment. Pakistan Medical Research Council. Islamabad, 2008.
30. Simpson ID, Jacobsen IM. Understanding and Treatment of Neurotoxic Snakebite in the Developing World: Air Today or Gone Tomorrow! Indian Journal of Emergency Pediatrics, 2009; 1: 15-24.
31. McLean-Tooke APC, Bethune CA, Fay AC, Spickett GP. Adrenaline in the treatment of anaphylaxis: what is the evidence? BMJ, 2003; 327:1332–1335.
32. Simpson ID, Blaylock RS. The anti snake venom crisis in Africa: A suggested manufacturers product guide. Wilderness and Environmental Medicine 2009;20:275-82
33. Editorial. Snake bite: time to stop the neglect. The Lancet, 2010; 375: 2.
34. Williams DJ, Gutierrez JM, Harrison R, Warrell DA, Winkel KD, Gopalakrishnakone P. The global snake bite initiative: an antidote for snakebite. The lancet, 2010; 375: 89-91.
35. Warrell DA. Snake bite. The Lancet; 375: 77-88.
36. Lomborg B. Cool it: The sceptical environmentalists guide to global warming. Alfred K Knopf, New York, United States, 2007.

Editors' note:

We have initiated the new series on management of neonatal emergencies based on Cochrane/other systematic reviews. The first of the series is a common situation in neonatal emergency care. Such discussions will follow on pediatric emergencies as well in forthcoming issues. It would be meaningful and effective to have data from various centers on these common problems.