World Health Organization

EXECUTIVE BOARD **EB142/17**
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Provisional agenda item 4.1

Global snakebite burden

Report by the Director-General

1. An item on global snakebite burden was proposed for inclusion at the 140th session of the Board in January 2017: before that session, the Officers of the Board agreed to defer consideration of the item to the Board's session in January 2018.[1]

2. Snakebite envenoming is a potentially life-threatening disease that typically results from the injection of a mixture of different toxins ("venom") following the bite of a venomous snake. Envenoming can also be caused by venom being sprayed into a person's eyes by certain species of snakes that have the ability to spit venom as a defence measure. Not all snakebites result in envenoming: some snakes are non-venomous and venomous snakes do not always inject venom during a bite. About 50–55% of all snakebites result in envenoming. Snake venoms are complex mixtures of protein and peptide toxins, varying from one species to another, and even within species. The toxins in snake venoms are evolutionarily adapted to interact with a large variety of cellular targets in the organisms exposed to them. In humans and animals, snakebite envenoming affects multiple organ systems (depending on the particular species of snake and the classes of toxins present in the venom) and can cause, among other things: haemorrhage and prolonged disruption of haemostasis, neuromuscular paralysis, tissue necrosis, myolysis (muscle degeneration), cardiotoxicity, acute kidney injury, thrombosis and hypovolaemic shock.

MORBIDITY, DISABILITY AND MORTALITY DUE TO SNAKEBITE ENVENOMING

3. As for other neglected tropical diseases, estimation of global morbidity, disability and mortality due to snakebite envenoming is problematic. The reasons for this include: the prevalence of the disease among individuals in impoverished agricultural and herding communities in low- and middle-income countries who have limited options to seek health care and may have poor health-seeking behaviour; and a lack of systematic data collection on snakebite envenoming by health ministries. An early attempt by WHO to quantify global mortality due to snakebite envenoming in 1954 was hampered by poor-quality data, yet arrived at an estimate of 30 000 to 40 000 deaths per year. More recent attempts using data of improved quality (albeit incomplete) provide a broad global estimate of 81 000 to 138 000 deaths resulting from 1.8 million to 2.7 million cases of snakebite envenoming, and 4.5 to 5.4 million bites from venomous and non-venomous snakes.[2] The recently released Global Burden of Disease 2016 study was more conservative and estimated there was a total of 79 000 deaths

[1] See document EB140/1 (annotated).

[2] Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017;3:17063. doi: 10.1038/nrdp.2017.63.3.

caused by venomous animals in 2016, with an uncertainty range of 56 800 to 89 400.[1] This would indicate an upper limit for deaths due to snakebites similar to the lower limit reported in the other recent study.[2] An estimated 400 000 people a year face permanent disabilities, including blindness, extensive scarring and contractures, restricted mobility and amputation following snakebite envenoming.[3] The psychological effects of snakebite envenoming are underrecognized. There is evidence from Sri Lanka that snakebite envenoming causes long-term psychological sequelae, and that the prevalence of post-traumatic stress disorder in people who had had systemic envenoming following a snakebite was comparable to the levels of post-traumatic stress disorder observed following the tsunami that affected Sri Lanka in 2004 or after major road-traffic crashes.[4]

4. Snakebite envenoming affects people in predominantly poor, rural communities in tropical and subtropical countries throughout the world. There is a large body of literature demonstrating a strong association between low socioeconomic status or poverty and a high incidence of, and mortality due to, snakebite envenoming. Rural hunter–gatherers, agricultural workers, working children (10–14 years of age), families living in poorly constructed housing, and people with limited access to education and health care are all particularly vulnerable.[5,6,7,8] The prevalence of snakebite envenoming is inversely proportional to the level of country income: the prevalence is highest in low- and middle-income countries, and lowest in high-income countries. In West Africa there are 16 low- and middle-income countries with at least 3500 to 5350 deaths annually due to snakebite envenoming, equivalent to 1.2 deaths per 100 000 population (95% confidence interval: 0.9–1.4 per 100 000) per year.[9] In just one Nigerian hospital 5367 people were treated for snakebite envenoming over two years (2009–2010) with 82 deaths recorded,[10] and in Burkina Faso 114 126 snakebites were reported over five years

[1] Global Burden of Disease Collaborative Network. Global Burden of Disease study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation; 2017 (http://ghdx.healthdata.org/gbd-results-tool, accessed 28 November 2017).

[2] Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017;3:17063. doi: 10.1038/nrdp.2017.63.

[3] Peden M, Oyegbite K, Ozanne-Smith J, Hyder AA, Branche C, Fazlur Rahman AKM, et al., editors. World report on child injury prevention. Geneva: World Health Organization; 2008 (Box 6.1; http://whqlibdoc.who.int/publications/2008/9789241563574_eng.pdf, accessed 6 November 2017).

[4] Williams SS, Wijesinghe CA, Jayamanne SF, Buckley NA, Dawson AH, Lalloo DG, et al. Delayed psychological morbidity associated with snakebite envenoming. PLoS Negl Trop Dis. 2011;5(8):e1255. doi: 10.1371/journal.pntd.0001255.

[5] Bochner R, Struchiner CJ. [Exploratory analysis of environmental and socioeconomic factors related to snakebite incidence in Rio de Janeiro from 1990 to 1996]. Cad Saude Publica. 2004;20(4): 976-85 (in Portuguese).

[6] Chaves LF, Chuang TW, Sasa M, Gutiérrez JM. Snakebites are associated with poverty, weather fluctuations, and El Niño. Sci Adv. 2015; 1(8):e1500249. doi: 10.1126/sciadv.1500249.

[7] Harrison RA, Hargreaves A, Wagstaff SC, Faragher B, Lalloo DG. Snake envenoming: a disease of poverty. PLoS Negl Trop Dis. 2009;3(12):e569. doi: 10.1371/journal.pntd.0000569.

[8] Bertolozzi MR, Scatena CM, França FO. Vulnerabilities in snakebites in Sao Paulo, Brazil. 2015. Rev Saude Publica. 49. pii: S0034-89102015000100264. doi: 10.1590/S0034-8910.2015049005839.

[9] Habib AG, Kuznik A, Hamza M, Abdullahi MI, Chedi BA, Chippaux JP, et al. Snakebite is under appreciated: appraisal of burden from West Africa. PLoS Negl Trop Dis. 2015;9(9):e0004088. doi: 10.1371/journal.pntd.0004088.

[10] Ademola-Majekodunmi FO, Oyediran FO, Abubakar SB. Incidence of snakebites in Kaltungo, Gombe State and the efficacy of a new highly purified monovalent antivenom in treating snakebite patients from January 2009 to December 2010. Bull Soc Pathol Exot. 2012;105(3):175-8. doi: 10.1007/s13149-012-0232-2.

(2010–2014).[1] Although the data are incomplete, estimated mortality due to snakebite envenoming across sub-Saharan Africa between 1970 and 2010 was between 20 000 and 32 000 cases per year.[2] A landmark study conducted from 2001 to 2003 estimated that 1.4 million to 2.8 million snakebites a year occurred in India, resulting in at least 46 000 fatalities.[3] In neighbouring Bangladesh a national study in 2009 estimated that there were 589 919 snake bites resulting in 6041 deaths annually.[4] Snakebite envenoming results in large numbers of disability-adjusted life years in Africa, influenced by factors such as the size and density of human and snake populations, environmental factors, and the effectiveness of health systems (for example, the annual numbers of disability-adjusted life years due to snakebite envenoming in Guinea-Bissau and Nigeria were 1550 and 124 484, respectively). Based on an analysis of data published between 1976 and 2010, there are an estimated 319 874 disability-adjusted life years due to snakebite envenoming annually in West Africa.[5] The Global Burden of Disease 2016 study estimate of overall disability-adjusted life years due to venomous animal attacks in West Africa in 2016 is quite similar, at 330 000 (uncertainty range: 247 000–398 000).[6]

5. Snakebite envenoming has a multitude of consequences for the individuals affected and their families. In many cases it pushes poor people further into poverty by virtue of high treatment costs, loss of income and enforced borrowing. In sub-Saharan Africa in 2010 and 2011 the direct cost of antivenom alone ranged from US$ 55 to US$ 640 for an effective treatment, using recommended doses, with the average cost being US$ 124.[7] In India the cost of initial treatment in 2010 was reported to be as high as US$ 5150, with an additional US$ 5890 in long-term costs.[8] Some individuals with snakebite envenoming faced financial losses equivalent to 3.6 years' income, and others sold land worth up to 14 years' income. Some families were forced to remove children from education because of lost income following snakebite envenoming, and there were cases of children being forced to leave school to work in order to assist with family living costs, or to care for a person with a disability due to snakebite envenoming. A study in Zimbabwe found that from 1980 to 1989 the average cost of just caring for a snakebite-envenomed patient in hospital was US$ 225 per day, before any treatment was

[1] Gampini S, Nassouri S, Chippaux JP, Semde R. Retrospective study on the incidence of envenomation and accessibility to antivenom in Burkina Faso. J Venom Anim Toxins Incl Trop Dis. 2016;22:10. doi: 10.1186/s40409-016-0066-7.

[2] Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017;3:17063. doi: 10.1038/nrdp.2017.63.3.

[3] Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM, et al. Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis. 2011;5(4):e1018. doi: 10.1371/journal.pntd.0001018.

[4] Rahman R, Faiz MA, Selim S, Rahman B, Basher A, Jones A, et al. Annual incidence of snake bite in rural Bangladesh. PLoS Negl Trop Dis. 2010;4(10):e860. doi: 10.1371/journal.pntd.0000860.

[5] Habib AG, Kuznik A, Hamza M, Abdullahi MI, Chedi BA, Chippaux JP, et al. Snakebite is under appreciated: appraisal of burden from West Africa. PLoS Negl Trop Dis. 2015;9(9):e0004088. doi: 10.1371/journal.pntd.0004088.

[6] Global Burden of Disease Collaborative Network. Global Burden of Disease study 2016 (GBD 2016) results. Seattle, WA: Institute for Health Metrics and Evaluation; 2017 (http://ghdx.healthdata.org/gbd-results-tool, accessed 28 November 2017).

[7] Brown NI. Consequences of neglect: analysis of the sub-Saharan African snake antivenom market and the global context. PLoS Negl Trop Dis. 2012;6(6): e1670. doi: 10.1371/journal.pntd.0001670.

[8] Vaiyapuri S, Vaiyapuri R, Ashokan R, Ramasamy K, Nattamaisundar K, Jeyaraj A, et al. Snakebite and its socio-economic impact on the rural population of Tamil Nadu, India. PLoS One. 2013;8(11):e80090. doi: 10.1371/journal.pone.0080090.

given.[1] In Bangladesh nearly 75% of snakebite-envenomed individuals in a 2006 study spent their savings on treatment, with over 60% of these borrowing to meet the costs.[2]

TREATMENT AND REHABILITATION FOR SNAKEBITE ENVENOMING

6. Immunotherapy with animal-derived antivenom preparations containing either immunoglobulin G or its derivative fractionation products ($F(ab')_2$ or Fab), has been the main treatment for snakebite envenoming for over 120 years. When antivenoms are manufactured in compliance with current good manufacturing practices, and subjected to rigorous preclinical and clinical evaluation before registration, they are very effective products, especially if administered as soon as possible in an adequate dose after a snakebite.[3] Currently many regions experience poor availability and accessibility of appropriately manufactured and quality-assured products; poor control and regulation of snake antivenom preparations is partly responsible for this situation.[4] In many settings there are no minimum product specifications for the potency, effectiveness, dose or safety profiles of antivenom products. Weak health systems and weak regulatory frameworks create environments in which unsafe and ineffective products enter markets with no preclinical or clinical evaluation before registration.[5,6] One of the consequences of these fragile systems is that inferior products have become pervasive, particularly in sub-Saharan Africa and Asia, forcing competitors in well- regulated environments to abandon production.[7] Market weakness also hinders investment in research and development, particularly in relation to improving current treatments and developing the next generation of biotherapeutics with the aim of reducing cost, improving safety and increasing effectiveness.

7. Although immunotherapy is central to treatment for snakebite envenoming, patients typically require a range of health services. Antivenom neutralizes accessible venom components, but does not reverse the damage to organ systems as a result of exposure to these toxins. Once some toxins are sequestered inside cells they become inaccessible to antivenom immunoglobulins. Effective treatment involves antivenom administration plus supplementary medical interventions such as: cardiorespiratory and/or fluid resuscitation; airway intubation; mechanical ventilation; haemodialysis; wound debridement and reconstructive surgery; physiotherapy; and other rehabilitation services. Improving patient outcomes and reaching effective control targets to reduce the incidence of and

[1] Kasilo OM, Nhachi CF.A retrospective study of poisoning due to snake venom in Zimbabwe. Hum Exp Toxicol. 1993;12(1):15-8.

[2] Hasan SM, Basher A, Molla AA, Sultana NK, Faiz MA. The impact of snake bite on household economy in Bangladesh. Trop Doct. 2012;42(1):41-3. doi: 10.1258/td.2011.110137.

[3] Gutiérrez JM, Burnouf T, Harrison RA, Calvete JJ, Kuch U, et al. A multicomponent strategy to improve the availability of antivenom for treating snakebite envenoming. Bull World Health Organ. 2014;92(7): 526-32. doi: 10.2471/BLT.13.132431.

[4] WHO Expert Committee on Biological Standardization: fifty-ninth report. Geneva: World Health Organization; 2012. (WHO Technical Report Series, No. 964; http://apps.who.int/iris/bitstream/10665/75167/1/WHO_TRS_964.pdf, accessed 6 November 2017).

[5] Visser LE, Kyei-Faried S, Belcher DW, Geelhoed DW, van Leeuwen JS, van Roosmalen J. Failure of a new antivenom to treat Echis ocellatus snake bite in rural Ghana: the importance of quality surveillance. Trans R Soc Trop Med Hyg. 2008;102(5):445-50. doi: 10.1016/j.trstmh.2007.11.006.

[6] Warrell DA. Unscrupulous marketing of snake bite antivenoms in Africa and Papua New Guinea: choosing the right product – "what's in a name?". Trans R Soc Trop Med Hyg. 2008;102(5): 397-9. doi: 10.1016/j.trstmh.2007.12.005.

[7] Williams DJ. Snake bite: a global failure to act costs thousands of lives each year. BMJ. 2015;351:h5378. doi: 10.1136/bmj.h5378.

mortality associated with snakebite envenoming requires: strengthening of health systems; improved access to essential medicines such as antivenoms; efforts to eliminate substandard antivenoms and other substandard medicines; commitments to strengthen health workers' knowledge of diagnosis and treatment of snakebite envenoming; improved capacity to regulate antivenom products; effective distribution of antivenoms; and monitoring of their use and safety.

WHO'S RESPONSE TO SNAKEBITE ENVENOMING

8. In March 2017, a subcommittee of the WHO Strategic Technical Advisory Group for Neglected Tropical Diseases at its 10th meeting recommended that snakebite envenoming should be included in the WHO neglected tropical diseases portfolio as a Category A neglected tropical disease.[1] The Director-General endorsed this recommendation in May 2017 and WHO included snakebite envenoming in the list of neglected tropical diseases in June 2017.

9. WHO has included snakebite envenoming as part of the Organization's wider efforts to overcome the global impact of neglected tropical diseases, a diverse group of communicable and zoonotic diseases that prevail mainly under tropical and subtropical conditions. Although the importance of these diseases differs at the national, regional and global levels, their common characteristic is that they affect poor and difficult-to-reach populations. In 2005, the Secretariat established a dedicated technical response capacity for the control of neglected tropical diseases. Since then, the operational focus has shifted from individual diseases to interventions. Action against a specific disease using the most appropriate set of interventions in any given setting is guided by adequate knowledge of the disease's epidemiology and the availability of appropriate prevention, detection and control measures that can be successfully implemented, especially in low-resource settings.

10. WHO recognizes the need to improve the quality, safety and regulation of snake antivenom immunoglobulin preparations that are used in the treatment of snakebite envenoming. In 2007 the Secretariat recognised the need to develop specific guidance on this subject, resulting in the 2010 publication of technical guidelines, which were subsequently revised and updated in 2017[2] and the creation of an online tool to assist with appropriate antivenom selection based on the distribution of venomous snakes.[3] In 2015 the Secretariat established a technical assessment process for antivenom products marketed in sub-Saharan Africa, in order to be able to provide evidence-based recommendations to Member States.

11. WHO recognizes that a number of tropical and subtropical, poverty-related diseases including snakebite envenoming, remain neglected. Opportunities exist to advance knowledge of such diseases in order to: facilitate advocacy in support of awareness; stimulate the generation of further knowledge; and encourage the development of appropriate control tools and strategies for inclusion in the WHO

[1] Report of the tenth meeting of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases, 29–30 March 2017, WHO Geneva. Geneva: World Health Organization; 2017 (http://www.who.int/neglected_diseases/NTD_STAG_report_2017.pdf?ua=1, accessed 15 November 2017).

[2] Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Annex 5. Replacement of Annex 2 of WHO Technical Report Series, No. 964. Geneva: World Health Organization; 2017. (http://www.who.int/entity/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf?ua=1, accessed 15 November 2017).

[3] Venomous snakes distribution and species risk categories. Snake and antivenoms database. Geneva: World Health Organization (http://apps.who.int/bloodproducts/snakeantivenoms/database/, accessed 15 November 2017).

portfolio of neglected tropical diseases. In support of this effort, the Secretariat has established a working group on snakebite envenoming to assist in the development of a strategic plan for the disease. This plan will identify the key areas in which support and assistance is necessary for effective reduction and control of snakebite envenoming, and will assist the Secretariat in identifying and mobilizing resources to initiate, undertake and evaluate specific interventions.

12. Elaborating a public health strategy for the prevention and control of snakebite envenoming will require significant investment in a multifocal reduction and control strategy, so that cost-effective prevention, diagnosis, early treatment and case management can be practised in low-resource settings. It will be essential to mobilize additional resources in order to facilitate the inclusion of public health interventions against snakebite envenoming among those advocated by WHO against other neglected tropical diseases. Early diagnosis, treatment and rehabilitation using available tools is the most appropriate approach for lessening the disease burden imposed by snakebite envenoming. Increasing community-based efforts to promote prevention, first aid and improved health-seeking behaviours, coupled with health systems strengthening, will further reduce the incidence of snakebite envenoming and increase access to effective treatment. Tackling the issue of limited investment in innovative approaches to diagnosis, treatment and control of snakebite envenoming also requires the mobilization of resources from diverse sources and the establishment of priorities and special focus areas.

13. The Secretariat, in headquarters and in the regional offices, will intensify efforts to advocate for improved surveillance and control of snakebite envenoming. It will continue to solicit focused support from international donors and partners and provide technical assistance to health ministries of affected Member States. This should allow knowledge of the disease to advance sufficiently to permit the development of control strategies and tools that are suitable for implementation in all circumstances, including in low-resource settings. This will build on experience gained in advancing the agenda of other tropical and subtropical, poverty-related diseases that currently remain neglected, and will increase the capacity to tackle them through innovative, intensified disease-management programmes, whereby all aspects of these diseases, including their ecology are dealt with in an integrated manner to reduce morbidity, disability and mortality.

ACTION BY THE EXECUTIVE BOARD

14. The Board is invited to note the report and provide further guidance on the Organization's response to the global snakebite burden.

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