Snakebites in Africa: Challenges and Solutions

Geneva, Switzerland, 13th December, 2016

Rationale for the meeting:

On 13th December 2016, the Kofi Annan Foundation convened a stakeholder meeting entitled, **"Snakebites in Africa: Challenges and Solutions**", to discuss one of today's most neglected global health problems: snakebite-induced death and disability in Sub-Saharan Africa. The issue was first brought to Mr. Annan's attention by Dr. Rath in the local context of Ghana. In Ghana and across Sub-Saharan Africa, snakebite is a disease which impacts the lives of thousands, mostly the rural poor, and contributes to multiple issues that challenge subsistence agriculture and the overall quality of life in many settings. In order to better understand this challenge and define interventions with short and longer term outputs, the Kofi Annan Foundation convened this meeting of representatives from the scientific community, public health organizations, civil society and philanthropic institutions in Geneva.

From these discussions, the Foundation has prepared this report, summarizing both the discussions held and its own perspective about taking forward solutions to address snakebite in an effective and concerted manner.

The Perspective of the Kofi Annan Foundation:

The guiding philosophy of the Kofi Annan Foundation is that the challenge preventing many of the world's most pressing problems from being solved is a lack of political will. The expertise exists to address these challenges, but there is often a lack of vision, of leadership and of the unbending resolve to fix things. The Foundation convenes other leading stakeholders, forge innovative partnerships, and mobilize the political will to tackle these critical issues.

Emerging out of the meeting convened by the Foundation in December 2016 was that the Foundation can give added value to the efforts to tackle this challenge. The large majority of the victims of snakebite are politically voiceless: subsistence farmers and the rural poor, displaced populations, and children. Mr. Kofi Annan has stated that it is up to the international community to be their voice. The Foundation is prepared to play a constructive and catalytic role to empower a process which will help solve this issue and ultimately save thousands of people in Sub-Saharan Africa and around the world from death or disfigurement.

Next Steps:

From the discussions and conclusions of the meeting, a number of potential actionable next steps were identified. The most important and pressing of these, from the view of the Foundation and its role, are:

The Need for a Focal Point:

The Foundation sees the most pressing obstacle at the moment as being the lack of a focal point to coordinate a global effort to address snakebite. We believe that this focal point would ideally be located within the World Health Organization (WHO), assisted by key stakeholders. It is apparent that snakebite requires a concerted effort and a fully resourced focal point dedicated to this topic. The initial step must therefore focus on mobilizing the resources necessary to establish such a focal point and coordination mechanism.

Once established, this focal point position can serve as a nexus which brings together stakeholders to craft a framework for moving forward, the roadmap for action.

A Roadmap for Action:

The December meeting has made it clear that there are a range of perspectives and solutions on snakebite. This needs to be consolidated into a clear and accessible roadmap which outlines solutions in both the short and long term, including time frames and budget requirements, and provides a clear product which can be used in advocacy. The roadmap should include inputs from the full range of stakeholders. This roadmap will empower a call to action.

The Foundation believes that this roadmap should be the first priority of the dedicated focal point on snakebite. We recognize that as efforts to pursue the roadmap progress, new challenges will emerge which will require flexibility. The roadmap will provide a needed framework to both leverage and maximize the international community's support for countries, communities, and people affected by snakebite.

Summary of the Meeting

Part I: Overview of the Challenge

Following Mr. Annan's introductory remarks, Dr Harrison presented the current state of the snakebite challenge in Africa. It was especially clear that snakebite primarily impacts upon rural communities and is linked to rural poverty. Accurate disease-burden data is lacking, and the widely used estimates of 32,000 deaths and 100,000 disabilities suffered by snakebite victims in sub-Saharan Africa (sSA) may in fact under-represent the scale of the problem.

Snakebite also poses significant socioeconomic problems, with an impact equal to and exceeding that of many other tropical diseases. Workers, particularly those in subsistence agriculture, are at greatest risk of snakebite when they are most economically productive and educationally vulnerable. Snakebite can also contribute to chronic anxiety, depression and post-traumatic stress disorder (PTSD). People who are bitten are often economically insecure and snakebites can push them over the edge into poverty.

Dr Harrison outlined some possible reasons for the gap between the severity of the problem and the lack of engagement and data. These include:

- Most victims reside in remote, rural, impoverished areas with little political representation
- Poor road and ambulance infrastructures lead to delays in treatment
- Rural hospitals are often inadequately equipped to effectively manage snakebite patients
- Deficient training of physicians and nurses in the diagnosis and management of snakebite envenomings
- Antivenom market failure problems:
    - Low demand for antivenoms by governments who assign snakebite as a low priority
    - Cheaper but ineffective antivenom (AV) crowding the market
    - Lack of quality control and regulation of AV.

Dr Harrison mooted that the low public health priority snakebite in Africa is also due the lack of accurate disease-burden data and to the fact that snakebite (i) is not eradicable, (ii) treatment is expensive and complex, and (iii), in the context of resource-limited budgets, has a lower priority than other tropical diseases that are cheaper to treat and benefit from more effective advocacy.

Ambassador Whyte Gomez from Costa Rica expressed her support for the work of the meeting and affirmed that Costa Rica views snakebite as a serious public health concern.

Part II: Identifying Interventions

This discussion focused on identifying interventions for tackling the challenge of snakebite. The participants agreed that any strategy needs to be a holistic system and incorporate multiple interventions and stakeholders with both short and long term outcomes to reduce disease burden. The following are the key issues discussed in thematic order rather than chronological and where possible delineates both short and long term interventions.

1. Affected Populations

It was noted that considerations of affected populations should also include displaced people. Conflict and snakebite vulnerability are linked.

2. Systems to reduce bites

Short term: Public health education campaigns would be effective in advising people to sleep under bed-nets, use sticks and torches, and use other inexpensive 'bite-prevention' measures. This has been done, for example, in the Indian state of Bihar. Short advocacy messages can be distributed on national TV, radio stations, and mobile phones informing and educating people about simple steps to avoid snakebite. Messages should adapt to particular cultural contexts and should involve the local communities in their design and implementation.

Long term: Incorporate inexpensive 'snake proofing' into the design of rural homes and change housing patterns such as getting people to move away from their granaries. Corporations can also be encouraged to adopt safety practices such as mandatory wearing of anti-snake boots. Advocacy messages targeting companies (particularly agricultural businesses) may help to incorporate these recommendation into the corporate ethos.

3. Country Champions

The meeting repeatedly raised the possibility of working with a select number of so-called champion countries in Africa. These states could be the first to engage and take ownership of the roadmap. Ghana should be included and those African countries that joined with Costa Rica at the WHA should be approached.

It was noted that Ministries of Health will be key participants in the initiatives to reduce the impact of snakebites. Permanent programs on snakebite should eventually be established at the ministerial level, so that coordinated activities can be developed.

4. Snakebite Intervention and Research Centres (SIRCs)

Dr Harrison shared his proposal for the establishment of a SIRC network designed to (i) provide accurate disease burden data, (ii) establish preclinical antivenom efficacy-testing facilities, (ii) establish national clinical guidelines for the effective management of snakebite before, during and after hospital admission, (iii) instigate an ambulance system to improve access to treatment (iv) establish student/scholar exchange programs and (v) develop effective advocacy. The participants noted and expressed approval of this type of initiative, which provides a good model for intervention and has a lot of synergy with many of the issues discussed at the meeting. The importance of inexpensive 'first aid' transport was especially highlighted. It was also noted that the SIRC network is designed to integrate into, and add capacity to existing public health efforts of local Ministries of Health.

5. Antivenom (AV) Supply to sub-Saharan Africa

5.1 Presentation by Médecins Sans Frontières (MSF)

Dr Alcoba presented MSF's work in four sSA countries. MSF sees snakebite as an indicator of poverty. MSF is currently using 2 AVs which hopefully will be included in the assessment by the WHO with positive outcomes.

MSF views the snakebite challenge as an antivenom demand and supply crisis with five causes:

1. Neglect of victims
2. Poor understanding of the cost-effectiveness of AV
3. Unstable demand
4. Inadequate quality control
5. Equine polyclonal antivenoms considered outdated

These are invisible victims afflicted by an invisible disease trapped in a vicious cycle which urgently requires donor investment. MSF then outlined some potential interventions:

1. WHO Assessment of AV
2. A joint AV stockpile with negotiated prices
3. More work on the epidemiology of snakebite
4. Preclinical studies to compare African AV
5. Technology transfers
6. A new WHO position on snakebite, it should be labelled an NTD and have a coordinator

MSF sees these as long terms solutions:

1. Cost effectiveness studies
2. WHO Prequalification program for AV in place
3. Support only pre-qualified AV to block cheap ineffective alternatives

5.2 Presentation by the World Health Organization (WHO)

Dr Wood presented WHO's perspective on the snakebite issue in sub-Saharan Africa and described that WHO seeks opportunities and resources to expand their efforts. WHO is currently engaged with:

- A Prequalification team assessing product dossiers submitted by manufacturers of sSA AVs
- The NTD department seeks to return snakebite on the priority NTD list but faces serious logistical challenges to achieve this
- WHO has been in contact with UN Procurement who have the expertise in supply chains and can help with end-to-end health system solutions for AV

WHO sees a need for:

- Implementation for early case management
- Tools and training for personnel
- Solutions and campaigns for snakebite prevention
- Research on snakes, snake venom, and diagnostics
- Synergies with existing public health programs

- A policy framework on procurement
- Holistic solutions with local ownership

The participants agreed that there is currently a lack of demand for a variety of reasons, two important ones are that the poor cannot afford AV and that the current market in Africa is being crowded by cheap, unreliable products.

WHO noted that the situation is similar to that of vaccines, where initial high prices were reduced and markets stabilized by quality controls and WHO-led efforts to improve demand. WHO action can help create healthy markets for AV which then enables prices to decline.

WHO also informed participants that an agenda item on prevention and control of snakebites will be discussed at the 142nd Meeting of the Executive Board in January 2018. If the Board agrees, a proposed resolution will then be submitted to the May 2018 World Health Assembly.

5.3 AV Assessment

It was discussed that a major barrier to ensuring the accessibility and availability of AV is the lack of approved AV products. WHO reported that it initiated a process to identify existing safe and effective AV products targeted for sSA in 2016, and that the list of products assessed by WHO with positive outcome will be released in the first half of 2017. In total, eight dossiers were submitted to WHO. Five products were identified suitable for the next phase which is their testing for venom binding capacity by an experienced laboratory. The importance of future regional venom standards was mentioned. Some of the AV manufacturers will also be inspected by WHO, dependant on their current inspection status. It was agreed that this is a very important progression, as it will identify which AVs can be used and provide manufacturers of respective products with greater confidence for future investment. MSF noted the importance of this for its own work; it does not want to purchase AV until they have been assessed by the WHO.

5.4 Procurement of AV by sub-Saharan African governments

It was agreed that advocacy is required to persuade sSA governments to increase the prioritization of (i) snakebite on their health agendas and (ii) AV procurement. Advocacy at senior, policy-making decision levels is required throughout the political infrastructure of sub-Saharan Africa.

5.5 AV Delivery to sub-Saharan Africa

The participants discussed that once the WHO Prequalification program has been extended to AV, manufacturers will need to be encouraged to produce AV, presumably by fiscal support that secures their investment. WHO raised the possibility of applying their existing rotating vaccine stockpile framework for snakebite, as a means of setting up a system of efficient and adequate production and regulation of AV.

MSF noted that the AV EchiTAb PLUS ICP was seeing promising results. MSF is using this in some countries for specific snakebites, but without WHO approval this is not possible across the continent. Sanofi Pasteur's FAV Afrique was valuable because, despite a comparatively high retail cost, it possessed multi-snake species efficacy (a polyvalent AV) and was manufactured within a strong EU regulatory framework. It was noted that the costs of existing AV, such as those manufactured in South Africa, rise exponentially if purchased outside South Africa or its neighbours. Thus, the

effective polyvalent antivenom is $75/vial within the Southern African economic community but rises to an unaffordable $300/vial outside this political boundary.

5.6 Local vs. International Production of AV

A discussion was held on the benefits of local versus international AV production. Currently, only South Africa manufactures AV. Local and international manufacturers should be given technical support from the expert community. However, it was recommended that having a diverse number of AV sources, manufactured both within Africa and internationally, might be best to ensure availability – whilst accepting some level of redundancy. The goal is to ensure that there is always a steady supply for treating patients. In this context, caution was recommended because while more local production is important, it was noted that local production of pharmaceutical products has often driven up prices because states prioritize these outputs for export rather than local consumption. In the short term, the participants suggested it may be prudent to prioritise increasing the manufacture and delivery of WHO-approved AVs.

5.7 The Potential of innovative Research to deliver improved Snakebite Therapy

Professor Schellekens presented his proposal for using monoclonal antibodies to manufacture AV. Adopting this technology for snakebite therapeutics should reduce production costs, side-effects and provide a more reliable source of antisera without the waste products inherent to the animal based methods currently used. It can also be done with much more compact technology. Professor Schellekens presented a 5 year business plan indicating that this could also be profitable, while noting that regulation will pose a significant challenge. The participants agreed that defining the target specificity of the monoclonal antibodies will be a key scientific challenge. The meeting also briefly touched on potential innovations in inhibitor technology and the need for rapid and affordable diagnostics.

Dr. Rath presented his initiative to produce higher quality AV manufactured internationally to treat snakebite in sSA, currently supported by Mr. Wientjes. He noted that he is pursuing the creation of both monovalent and polyvalent AV for use in the region. In the future he seeks the support of Prof. Schellekens to develop AV through the use of monoclonal antibodies. Dr. Rath requested guidance and input from the diverse stakeholders present for such an initiative.

5.8 Recommendations for improving antivenom supply to sub-Saharan Africa:

Short term:

- The WHO AV assessment needs to be completed. Then, organizations such as MSF and also African governments, can start to use the recommended AV. The program can signal to African governments that AV is available and that they should begin procurement. Manufacturers should be encouraged through investment to ramp up production
- The snakebite community needs to engage more effectively with sSA countries through their representatives in Geneva and domestically at the Ministries of Health to improve recognition of snakebite as a public health concern
- Provide technical assistance to manufacturers; focus upon prequalifying existing international AV.

Long term:

- Further research into manufacturing systems should be encouraged
- The regulatory capacity in Africa should be improved so that governments and local health agencies can assess AV effectiveness themselves
- WHO can provide regulatory bodies with expertise to improve capacity, following the model of vaccine registration

6. Disease-burden Data Collection

It was noted that the 2008 data on the global burden of snakebite will shortly be updated to provide more accurate data. MSF expressed the need for more epidemiological studies and noted that the value of these would be increased by provision of improved snake venom diagnostics – an urgently required output from research community.

It was agreed that although data is very scarce, the process of selling AV will generate data itself. For example, MSF noted that Ethiopia illustrates the links between AV supply provision and data, when their AV supplies ran out people stopped coming to the hospitals and data dried up. Taking AV to market will create the needed data; the goal should be for a plentiful supply of AV to be introduced to the market. After 3 years, a much clearer assessment of demand would emerge from sales.

6.1 Classification of Snakebite

Discussion arose about whether snakebite can be listed as a notifiable disease. For WHO this process would take time and may need to wait until (i) the 2018 World Health Assembly and (ii) snakebite is returned to the WHO's list of priority Neglected Tropical Diseases. Professor de Silva reported that the WHO regional office in South East Asia (SEARO) has made a strong recommendation that snakebite be made a specific notifiable disease in all countries of the region. Advocacy could be effective in persuading the WHO regional office in sSA to adopt the same prioritisation of snakebite.

The Global Snakebite Initiative (GSI) reported that it has already started processes to convince governments to make snakebite part of their formal health reporting.

7. Snakebite Guidelines for sub-Saharan Africa

It was agreed that national guidelines on snakebite prevention and treatment are needed. Complex and comprehensive frameworks can be adopted by countries and then transformed into simple guidelines for use in hospitals. Updating the WHO Guidelines (after the results of the WHO AV-