Sociology and serotherapy – what are the global trends to control snake bite envenomation

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Abstract:

Approximately 5.4 million people are bitten by snakes each year, with over 2 million envenomation events occurring globally, leading to 400,000 amputations, and an estimated 100,000 fatalities. This review aims to highlight the most current advancements within human-snake conflict mitigation and co-existence, as well as the most up to date information on anti-venom development. The information for this review was taken from the most recent peer-reviewed studies on the topics of anti-venom development, human-wildlife coexistence, and holistic approaches to snakebite prevention. After investigating the literature, it is my belief that the use of herpetological data on snake behaviour, spatial ecology, and temporal activity patterns is the best option for society to control global trends in snake bite mitigation.

Introduction:

Since the dawn of human civilisation, many societies across the globe have lived in fear of snakes and the deadly repercussions that a bite from certain species can wield. This fear continues today within modern society as between 1.8-2.7 million envenomation events occur globally every year (Gutiérrez, et al., 2017), which result in over 400,000 amputations (WHO, 2013), and close to 100,000 deaths (Kasturiratne et al., 2008). India is the worst effected country by this tropical disease (Goswam et al., 2014), with over 50% of global snake bite deaths occurring on Indian soil alone (Suraweera et al., 2020). Venom in squamates is thought to have evolved once, approximately 60-80 million years ago at the base of the colubroid radiation event (Fry et al., 2005). Today the planet is home to 600 species of venomous snake, across the families *Viperidae* (vipers), *Elapidae* and *Hydrophiinae* (cobras and kraits), *Atract aspididae* (mole vipers), and some members of the family *Colubridae*, most notably the boomslang (Goswam et al., 2014). Snakes use their venom as a means of immobilising and killing their prey, as well as a defence mechanism (Jacobsen et al., 2014), with its composition being a complex conglomeration of proteins and enzymes such as phospholipase A2, small peptides called myotoxins, various proteolytic enzymes, and coagulant substances (Goswam et al., 2014). Venom is categorised into three main groups, divided up in respect to the effects it has on the target's body. Members of the family *Viperidae* primarily possess hemotoxic venom which attacks an individual's circulatory and cardiovascular system, while many members belonging to the *Elapidae* family wield neurotoxic venom which attacks an animal's nervous system, or cytotoxic venom which attacks specific cellular functions, depending on the species or geographical range (Goswam et al., 2014).

The highest percentage of fatalities from snakebite occur within rural communities across African, Latin American, Asian, and Oceanic countries, with individuals working in agriculture being the most effected (Gutiérrez, et al., 2017). Often areas suffering from the most fatalities from envenomation coincide with the most remote or impoverished communities, as there is a dearth of medical, educational, and protective infrastructure in place to deal with human-snake conflict (Gutiérrez, et al., 2017). In this review, I will examine all current practices and approaches that are employed by governing bodies and organisations to mitigate the global burden of snakebite across three main sectors. These will include medicinal development, increased herpetological knowledge, and holistic approaches. Although advancements in the field of anti-venom treatments will be diligently discussed, this review will strongly focus on techniques and strategies that aim to prevent humans and venomous snakes from interacting with each other and sharing the same space. Zero species of venomous snake regard human beings as prey items, meaning that envenomation events usually occur under accidental circumstances when someone steps on a camouflaged snake while working in an agricultural setting, or when a snake finds its way into a human dwelling in search of prey items or a place to hide (Gutiérrez, et al., 2017). Most of the resources and funding spent on this issue has been centred around the development of anti-venom to treat the effects of snakebite (Malhotra et al., 2021). Although important, other critical areas have been grossly underfunded, such as public education to people living and working near snakes, the supplying of protective clothing to people most at risk due to their occupation, as well as research into important aspects of snake biology such as spatial ecology, behaviour, temporal activity patterns, and population demography (Malhotra et al., 2021). This review will examine how these aspects of snake biology as well as other the factors mentioned above can be used to reduce the number of interactions between medically significant snakes and humans, thus reducing yearly envenomation rates.

Medical advancements in anti-venom production:

Although I believe that the best course of action to lower global envenomation rates is to focus on preventing bites before they occur, it would be foolish to assume that even the most diligent prevention methods would lead to all envenomation events to cease. The production of sustainable and widely available anti-venom is a key weapon in lowering the level of consequence attached to being bitten by a venomous snake. Recent advancements in the treatment of malaria (Feng et al., 2021) are showing that having widely available treatments for tropical diseases can help affected communities continue to live in high-risk areas without the consequence of infection being fatal. Anti-venom is traditionally produced by injecting large mammals (often horses) with the venom of the target species to allow the animal to produce anti-bodies as an immune response to the venom. Certain immunoglobins are then identified in the animal's blood and are harvested (Knudsen and Laustsen, 2018). Although technically effective, I believe they are many drawbacks to this traditional method. These include the need to harvest snakes from the wild, which is unsustainable and increases envenomation risk, and breeding the target species in captivity can be difficult, time consuming, and inefficient. Anti-venom being species specific (and sometimes specific to age class in species) is also another major drawback to the classical method (Knudsen and Laustsen, 2018). In this section I will review recent advancements in the areas of peptides and small molecule inhibitors (Knudsen and Laustsen, 2018), recombinant anti-venom developments such as oligonucleotides (El-Aziz et al., 2017) and novel "plantivenoms" (Julve Parreño et al., 2017), as well as research into proteomics and synthetic biology for anti-venom development (Arnold, 2016).

Varespladib is a small molecule snake venom inhibitor that has recently been identified by medicinal chemistry researchers as a possible multi-species anti-venom with muscle/tissue damage reducing properties (Lewin et al., 2016). Lewin and their team discovered that PLA^2 can be inhibited by picomolar and nanomolar amounts of varespladib. This is incredibly significant as PLA^2 is a common component of the venom of several medically significant snake species found across several continents (Lewin et al., 2016). This is a critical development as species within this toxin group often yield poor immune reactions from production mammals when attempting to create these anti-venoms (Laustsen et al., 2017). Further research has shown that varespladib's effectiveness on PLA^2 is dose dependant, with laboratory tests carried out on ten mice, showing a 43% survival rate when 4mg/kg of varespladib was administered to the mice shortly after they received a lethal dose of *Vipera berus* venom (Wang et al., 2018). When the amount of varespladib administered was increased to 8mg/kg, 100% of mice survived the lethal dose of venom (Wang et al., 2018). The effectiveness of varespladib was tested against other medically significant snake venoms containing PLA^2 with similar promising results. A group of rats were injected with a lethal dose of *M.fulvius* venom with varespladib administered 5 minutes after the envenomation event, the varespladib was able to stop the rise in PLA^2 activities and prevent haemolysis from occurring, leading to 100% of envenomated rats surviving (Wang et al., 2018). Varespladib not only seems to be a promising leap in the direction of an effective, sustainable, and efficient multi-species anti-venom, studies have also shown that it has the ability to reduce muscle and tissue damage, as well as the haemorrhagic plaques caused by many medically significant viper and pit viper species across Asia (e.g. *A. halys* and *D.Acutus)* (Wang et al., 2018). This is a step forward from many traditional anti-venom serums, as even though they can prevent fatality, many cannot prevent the lifelong tissue and muscle damage associated with envenomation events. Wang and their team have also concluded that varespladib appears to have a greater effect over the venom of viperid snakes rather than elapid species, with the scientists hypothesising this could be linked to differences in PlA^2 abundance or the presence of unknown subtypes (Wang et al., 2018). One of the most exciting aspects of varespladib is its ability to be synthesised into the orally taken methyl-varespladib. This is being trailed as a possible early treatment method that can be administered to victims immediately, giving them a better chance of surviving the journey to adequate medical facilities, that in some regions can be several hours away (Knudsen and Laustsen, 2018).

Although promising, varespladib has a few negative limitations attached to it that are important to address. Firstly, not all medically significant snake venoms rely on PLA^2, for example the *Dendroaspis* genus, which contains the green and black mambas, are devoid of PLA^2 meaning that varespladib will likely have little effect (Ainsworth et al., 2018). Another downside of varespladib is its lack of clinical testing. This drug was first proposed as a treatment for acute coronary artery syndrome but failed to meet the medical and commercial requirements (Mostafa et al., 2018). After reviewing the literature on the subject, I believe this drug is a promising novel development due to its multi-species effectiveness and methyl-varespladib's ability to be orally taken as a first line of defence after envenomation, but further clinical trials are needed to test the validity of varespladib's effectiveness on a broader scale.

Although varespladib seems to be the front runner in recent anti-venom developments, scientists have also made significant strides with oligonucleotides and other recombinant anti-venom strategies. Scientists have been able to use oligonucleotide-based aptamers to create novel compounds for snakebite envenomation therapy (Sharma et al., 2017). The original study was carried out examining cone snail venom not snakes, but researchers quickly realised that these oligonucleotide-based aptamers could also be applied to snake venom (Sharma et al., 2017). Oligonucleotides when applied to anti-venom development seem to have far less negative production issues when compared to traditional immunisation methods (El-Aziz et al., 2017). The benefits of this method include longer shelf life, no need for refrigeration, shorter production time, more cost effective, and better immunogenicity of smaller toxins (El-Aziz et al., 2017). The low cost of its small-scale synthesis for research and development is of particular interest as it allows scientists to investigate many molecules at a limited cost (Ascoët and De Waard, 2020). El-Aziz and their team succeeded in identifying oligonucleotides that have the capability of inhibiting the toxin *Conus parius* found in cone snails, and although this study was not focused on snake venom, it is incredibly promising considering they found full protection against the toxin in both vivo and vitro tests using oligonucleotides.

I believe that the use of Oligonucleotides within anti-venom development is extremely promising. The longer shelf life, shorter production time, low production cost, and it not needing constant refrigeration means it can be stored easier in developing countries and rural settings that often don't have the consistent electricity or the facilities in general to store large amounts of traditional anti-venoms. Unfortunately, I believe that the dearth of research specifically looking at snake venoms and oligonucleotides, leaves us quite far from a widespread acceptance and use of this anti-venom production technique.

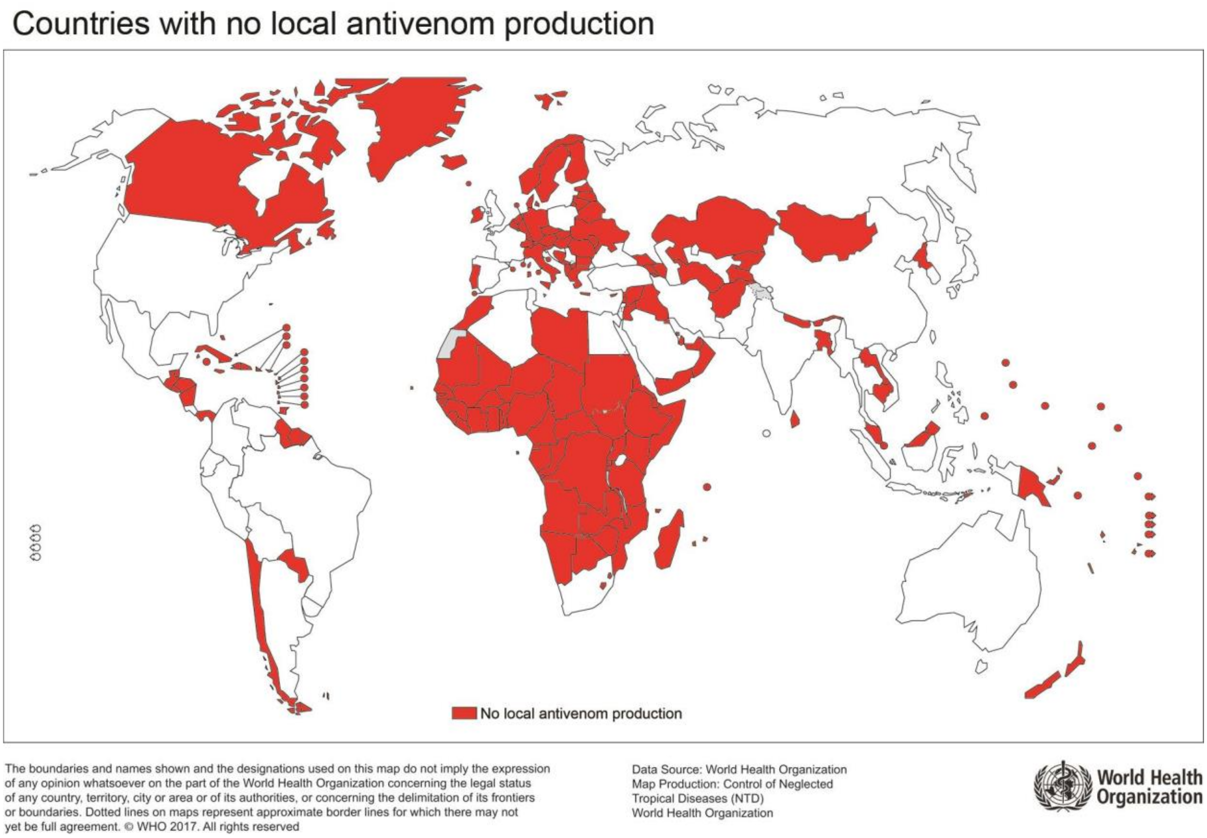
Recent developments in using plants in the production of recombinant antivenoms have emerged. Developers of these novel "Plantivenoms" aim to increase the production rather than the stability of anti-venoms (Julve Parreño et al., 2017). Polyclonal antibodies were derived from VhH sequences of camels immunised with venom from snake species including *B.asper*, *C.scutulatus*, and *C.simus* (Julve Parreño et al., 2017). Researchers achieved this by inserting Arabian camel VhV sequences into a vector genetically modified from tobacco mosaic virus. Antibody production was stimulated and the "plantibodies" produced could bind the venom of all snake species previously mentioned above, with a 100% survival rate of mice when treated with 61.24mg per mg of venom from *B. asper* in clinical studies (Julve Parreño et al., 2017). I believe this to be quite significant as *B.asper* (The fer-de-lance snake) is the most medically important venomous snake species throughout all of Latin and South America.

Although holding many positives, after extensive research on the topic I believe that "Plantivenoms" still need vast amounts of continued research and development before being thought of as a global solution. These problems include a lack of comprehensive facts supporting their claims of being more cost effective then current anti-venom producers, plant expression systems leading to problems such as non-human glycosylation patterns and significantly lower protein yields, and when "plantivenom's" performance was compared to the traditional horse derived Fer de Lance anti-venom control, it was out preformed and was not successful in the invitro coagulant activity (Laustsen et al., 2018). It also proved ineffective against several species in the *Naja* genus, which are incredibly medically significant across many continents (Laustsen et al., 2018).

The final development in global anti-venom production I will touch on will be the use of proteomics and synthetic biology (Arnold, 2016). This is the most underdeveloped method that will be discussed in this review, but I believe its future potential is worth examining. Scientists working in Brazil have used proteomics to engineer short strands of DNA capable of triggering anti-body response against coral snake venom (Arnold, 2016). Small segments of DNA from a coral snake that coded for venom toxins were injected into mice to attempt to prime their immune systems. After several attempts and methodology changes only 60% of mice injected with a lethal dose of venom survived (Arnold, 2016). This result leads me to believe that this field of anti-venom development is only in its infancy.

After reviewing the literature on current trends in anti-venom production, I believe that the above-mentioned techniques, while not perfect, provide the best blueprint for future sustainable production. I believe that it is key that this future production must take place in-situ within the worst effected countries. The map below shows how currently most of the worst effected countries of this tropical disease do not have in-country anti-venom production.

Image source: credited to the World Health Organisation



An increased herpetological knowledge of medically significant species.

Venomous snakes have had the ability to captivate, interest, and inspire biologists to investigate their phylogeny, ecology, biology, and behaviour for centuries, allowing famous herpetologists to present the wonders of these creatures to the wider public. But the use of herpetological data has been grossly overlooked regarding snake bite mitigation and the reduction of human-snake conflict. Understanding where medically significant snakes are abundant, why they prefer certain locations, and when they are most active, are ways we can ensure humans and snakes avoid each other (Malhotra et al., 2021). The World Health Organisation has said it aims to reduce global fatality and disability due to snake envenomation by 50% before 2030 (WHO, 2017). For the World Health organisation to achieve this goal more resources must be channelled toward preventing humans and potentially dangerous snakes from crossing paths, rather than treating the problem once bites have occurred. WHO outlined "four key objectives" to obtaining this goal which included "empower and engage communities, ensure safe, effective treatment, strengthen health systems, increase partnerships, and coordination and resources" (WHO, 2017). Unfortunately, these vague objectives have no direct mention of using herpetological knowledge to decrease human-snake interactions. This section of the review will focus on how scientific data on snake population demography, behaviour, spatial ecology, and variations in temporal activity patterns can help prevent negative human-snake interactions from occurring.

Understanding spatial ecology and resource requirements of venomous species:

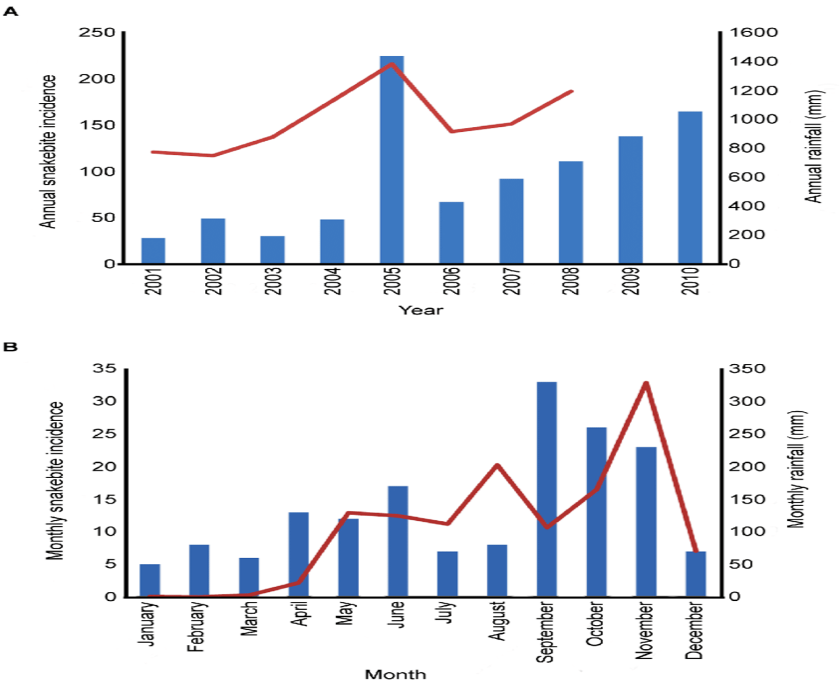
Radio telemetry is a method of tracking animals and understanding their movement patterns throughout a period of time. Radio telemetry systems rely on detecting radio signals given off by the radio transmitter worn by the animal, and read by the radio receiver (Kennedy et al., 2018). This method of data collection allows biologists to better understand the resource requirements, spatial ecology, and population dynamics of venomous species (Lomas et al., 2019) (Malhotra et al., 2021). Understanding the resource requirements of a species is essential to mitigating human-snake interactions (Ward et al., 2017). This data can allow biologists to advise members of an affected community on how best to make their living environment as unappealing to snakes as possible. Snakes are attracted to areas with piles of debris or clutter in which they can hide under, sitting water sources, agricultural practices (leading to a rodent population), small free ranging livestock, or damage to buildings that may provide a dark hiding place for them (Ochoa et al., 2021). Many snake bites occur when venomous species enter human habitations in search of rodents or other prey items and cannot find their way out, this causes the snake to feel trapped and threated leading to defensive behaviour. Many agricultural practices in Asian countries involve the use of shallow waterways as a means of irrigation for farming crops. Unfortunately, many medically significant species in the *Naja* genus also use these waterways as highways to move to different areas of their territory or to search for food in this artificially created prey rich environment (Shipley et al., 2013). If species specific resource requirements can be gathered using radio telemetry, then local communities can make simple changes to their environment that would deter venomous snakes from entering their community.

Understanding behaviour and temporal activity patterns:

Another advantage of employing radio telemetry for snakebite mitigation, is that it can allow us to better understand the behaviour (Clark, 2005) and temporal activity patterns (Whitaker and Shine, 2002) of medically significant snakes. Researchers in Australia have used radio telemetry to gather data on *Pseudonaia textilis* (Eastern brown snake) to help local communities understand what time of year and during what weather events are they most likely to encounter this highly venomous snake (Whitaker and Shine, 2002). The data collected allowed these scientists to conclude that people were most likely to encounter this species in late spring, and then again in late summer (Whitaker and Shine, 2002). Whitaker and Shine inserted radio transmitters into 40 individual Eastern brown snakes and were able to learn that this species actively prefer a body temperature of 31 degrees Celsius, with external weather conditions dictating whether they were above ground gaining heat, or below ground in their burrows thermoregulating (Whitaker and Shine, 2002). In a separate earlier study, Whitaker and Shine were able to successfully use radio telemetry to locate Eastern brown snakes and assess their behaviour when approached by humans (Whitaker and Shine, 1999). Their study birthed extremely interesting results, finding that Eastern brown snakes were able to perceive and evade humans quicker and more effectively when the researchers were wearing dark clothing that contrasted the lighter surroundings (Whitaker and Shine, 1999). Construction and agricultural workers in these areas should be advised to wear darker clothing during the months of highest *Pseudonaia textilis* activity, or when working in *Pseudonaia textilis* preferred habitat such as messy building sites or farm sheds (Shelton et al., 2020).

Although radio telemetry can supply critical biological and ecological data to improve human-snake relations, there are still some major draw backs to this method of attempted co-existence. Field studies that investigate temporal activity patterns, space use, or behaviour can vary greatly depending on the season, the sex ratio of the population, or the geographical location, meaning that these studies can be long, complex, costly, and can take a long time to reach a clear conclusion (Malhotra et al., 2021). I found that these studies often failed to address how people could remove potentially dangerous snakes if a population is already established within their community. Studies have shown that removing a snake from its natural range can cause a decrease in fitness, higher mortality, and less mating success for the individual (Devan-Song et al., 2016), a later study highlighted that although snakes removed from urban areas and relocated within their natural range did not loss any fitness, these individuals were likely to be attracted back to the same human populated area, or possibly a new nearby village or town (Wolfe et al., 2018).

Figure 1: shows snake bite occurrence in relation to rainfall: (Vaiyapuri et al., 2013)



Using population demographics and compartmental modelling to better understand snake bite incident rates:

The abundance of venomous snakes in human inhabited areas directly influences the probability of being bit (Fry, 2018). Cross examining snake population dynamics with proven correlates of snakebite such as human density, agricultural practices, and poverty rates allow for the implementation of location specific anti-snake bite mechanisms such as PPE gear for agricultural workers, education on identifying and avoiding local venomous species, as well as assisting local people in making their homes as “anti-snake” as possible (Malhotra et al., 2021). Compartmental modelling has recently been used to model incidence of snake bite (Bravo-vega et al., 2019). This method of modelling has been used in the past to deal with different infectious diseases and has seemed successful (Siettos and Russo 2013). This model was tested in Costa Rica, with the encounter rate of medically significant species found in the field used against estimates of local human population (Bravo-vega et al., 2019). This study was able to identify good variation within incidence and has shown positive potential as snakebite estimator tool (Bravo-vega et al., 2019). Under reporting can also be derived from this model as estimates can be compared with official snake bite records (Tchoffo et al., 2019).

Holistic approaches to lower envenomation rates:

When creating any ecological study or conservation plan it is of utmost importance that communication and collaboration with local communities is intrinsically linked with everything the researchers do (Zimmermann and Stevens, 2021). Lack of collaboration with indigenous communities will have significant long term negative effects for all parties involved, especially the wildlife (Stoldt et al., 2020). Respect and acknowledgement of local cultures, beliefs, and customs is essential for long term success in managing human-wildlife conflicts (Zimmermann and Stevens, 2021). Collaboration with local communities is not only important for conflict mitigation, but scientists can learn valuable lessons about the ecology, biology, and behaviour of the animal, which can help make a more specifically tailored strategy to avoid human-wildlife conflict (Jacobsen, 2014). Close collaboration with the Irula tribe in India allowed researchers to drastically improve human-snake relations within the area, as well as support the local community (Jacobsen, 2014). Before the collaboration villagers would routinely destroy entire dwellings in attempts to remove any snake that was discovered inside. Jacobsen and her team were able to stop this damage to property with simple education on how to identify venomous species apart from harmless rodent eating constrictors (Jacobsen, 2014). The villagers were taught that rodents can cause up to 100% of their crops to be soiled (Parshad, 1999), as well as carry deadly diseases such as hantavirus (Min et al., 2020).

The Irula tribe are historically expert snake catchers and, in the past, would catch snakes for use in traditional medicine (Jacobsen, 2014). After the Indian wildlife protection act was created in 1972 their traditional way of life seemed to be becoming impossible, but collaboration between the leaders of the tribe and famous herpetologists Romulus Whitaker and Revathy Mukherji allowed members of the tribe to be employed as snake catchers for anti-venom production (Jacobsen, 2014). This holistic approach to dealing with human-snake conflict should be the global standard, as the villagers, victims of snakebite, researchers, and most importantly the snakes all benefited from this collaborative project.

Conclusion:

I hope this review has shed light on the current most effective methods in mitigating snakebite occurrence, as well as the latest developments in anti-venom production. Although anti-venom is critical in treating the problem once it has occurred (Chippaux, 2017), I believe that stopping the negative interactions between humans and potentially dangerous snakes before they occur, using scientific data, education, and community engagement is of utmost importance. As our global population soars toward 8 billion individuals (Adam, 2021) humans and snakes are going to continue to be forced to share space. Snakes are fantastic candidates for coexistence with humans, due to their size, prey choice, cryptic and shy behaviour, along with their relatively low population densities (Goldstein et al., 2021) (Ediriweera et al., 2018).

Murray et al., (2020), discussed the disconnect in science today with understanding snakes and their ecology to the prevention of bites quite eloquently by stating "**This imbalance is akin to trying to combat malaria while overlooking mosquitoes**". This quote perfectly encapsulates the problem with the current solutions to this neglected tropical disease today.

Image below: A member of the Irula snake catching tribe extracting venom from a cobra for anti-venom research. **Credit;** The daily mail UK online forum.

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