DISCOVER — ENGAGE — IMPACT

ANTIVENOM'S FATAL FLAW

A UQ researcher is working to change a toxic attitude towards antivenom manufacturing, which adds to a mounting death toll and plunges communities into poverty.

In sub-Saharan regions of Africa, Asia and the Middle East, farmers are risking their lives and their families' livelihoods every time they walk into a field or step out their front door.

Because in those fields, under rocks and among homes, lurks a creature deadlier than lions, crocodiles and hippopotamuses combined.

It's a snake known as Echis, or the saw-scaled viper, and the species kills more humans each year than almost any other snake.

Even if victims don't suffer a long and agonising death, the injuries and illnesses resulting from bites often last a lifetime, resulting in loss of income and further poverty.

Yet these deaths and injuries could be easily avoided and, according to Associate Professor Bryan Fry from UQ's School of Biological Sciences, cheap and ineffective antivenoms are to blame.

A study led by Dr Fry has found that antivenoms produced using snakes from one region may perform poorly or fail completely against the same species of snakes from other regions.

Researchers tested the effectiveness of two African and two Indian saw-scaled viper antivenoms against saw-scaled vipers from 10 regions.

The results showed that the two African antivenoms were only effective against snakes from restricted ranges.

One antivenom performed well against West African saw-scaled vipers and the other performed best against the East African saw-scaled vipers. The Indian antivenom only worked against saw-scaled vipers from the region where the antidote was produced and failed against toxins from other Indian regions. It failed completely against African saw-scaled vipers.

"These antivenoms are being sold and used interchangeably to treat all saw-scaled viper bites, and in many cases they are not working," Dr Fry says.

"In Kenya, snakebite deaths have increased dramatically after hospitals switched supplies of a very effective African antivenom with a cheaper Indian variety."

"This creates a knock-on effect in these communities. It's hard enough to convince people living in these regions not to go to traditional healers to treat snakebite. And if someone does seek proper medical care but dies because of ineffective antivenom, it will be even harder to convince the next victim to seek out antivenom."

It is estimated that snakebite affects up to 5 million people globally and accounts for almost 100,000 deaths annually. Of the millions of people affected, hundreds of thousands of those suffer from permanent injuries ranging from amputation to kidney failure.

"These numbers are well recognised as being gross underestimations due to the poor record keeping in the most affected rural regions in the developing world."

Dr Fry believes snakebite is the most neglected tropical disease, yet antivenom production is decreasing in favour of more profitable projects.

"The health systems in places like Africa and India are so over-burdened across the board, from HIV through to malaria, and this means snakebite treatment is neglected by foreign aid," he says.

"Snakebite is an extremely socially destabilising force, not only directly due to deaths of primary bread-winners in farming communities, but also due to the severe permanent injuries to survivors. Entire family groups may be plunged into poverty."

Most of the antivenom in Africa and India is stored in the big cities, so it might take a rural snakebite victim a day or two to get there. But by then, Dr Fry says a lot of tissue injuries have already set in and the only treatment left is to prevent further spreading.

"If you get in early with the proper antivenom, the odds of a contracting a permanent disability plummets."

MAKING THEMSELVES AT HOME

Saw-scaled vipers are native to arid regions of Africa, Asia and the Middle East, and are often found hiding under loose rocks. Their diet includes rodents, lizards and insects.

"When you modify a habitat for a rural farming environment, you're going to create a 'snake Hilton' for one particular species or another – usually a generalist who likes to eat rodents," Dr Fry says.

"That means the density of snakes found on farms can be much greater than in the wild.

"In rocky farming areas of Nigeria, it's not uncommon to find at least one saw-scaled viper under most large rocks.

"And in India, the development of rice paddies was the best thing that ever happened to a species known as the Russell's viper. They thrive in slightly flooded, grassy areas, and rice farmers have perfectly recreated their preferred habitat."

Socio-economic factors have also led to an increased number of snakes living among human communities.

Dr Fry says inadequate indoor sanitation and plumbing means people in rural areas are forced to defecate outside – and many (women particularly) will hold on until after dark, which is when snakes such as saw-scaled vipers are most active.

But snakebite isn't just a threat confined to rural areas.

"In India, we can catch two or three cobras if we go to the forests during the day. If we go to some of India's larger city slums at night, we can catch almost 20 in a couple of hours due to the density of prey, such as rats and mice."

VIPER VENOM'S LETHAL EVOLUTION

It's the variety of the saw-scaled viper's prey, from rodents to insects, that researchers say could be the reason why antivenom from one region might not work in another.

"Antivenom is effective and reliable when venom composition does not vary greatly between individual snakes," UQ PhD candidate in Toxinology Bianca op den Brouw wrote in an article for The Conversation.

"Unfortunately, the venom composition from saw-scaled vipers varies between populations and is thought to be partly due to an evolutionary adaptation linked to their diet.

"Different saw-scaled viper populations feed on different prey. The physiology of these prey animals differs, and this dictates what makes a toxin effective.

"From a medical perspective, this means that the antibodies in an antivenom may not be able to adequately recognise and fight all the harmful toxins in the venom."

Saw-scaled viper venom targets the blood to induce clotting. This causes a potentially lethal condition called 'venom-induced consumption coagulopathy' (VICC), which can result in severe internal bleeding.

Haemorrhage, stroke, and shock are typically the cause of death. Antivenom is the only effective antidote and it is needed within hours of the bite for survival.

Making antivenom is not a complicated process. It is developed by injecting a small amount of venom into a host animal, usually a horse because of its size and amount of blood in its body.

The animal's immune system responds by producing antibodies that fight venom toxins. These antibodies are extracted and purified.

It's the restricted shelf life, high cost to consumers and limited market that makes effective antivenom production difficult to justify for drug manufacturers.

Ms op den Brouw says the increasing death rate from snakebite in Africa can be linked to the discontinuation of a key antivenom known as Fav-Afrique.

"Some clinics reported a 100 per cent success rate when using this antivenom. But the antivenom's manufacturers, Sanofi-Pasteur, stopped production after claiming they were priced out of the market," she says.

"Parts of Africa have now seen an increase in the use of cheaper, Indian-produced antivenoms – many of which appear to be largely ineffective against African snakes."

STUDYING SNAKES TO SAVE LIVES

UQ's School of Biological Sciences is home to the Venom Evolution Laboratory, where researchers are using venom to further their understanding of pain and create life-saving medications and antivenom.

By studying which antivenoms work against certain species, researchers can provide doctors with a better guide for antivenoms that will work with critically ill snakebite patients.

The Venom Evolution Laboratory has collected and categorised a variety of blood and venom samples in one central bank for research. This resource will allow scientists to test the reaction of venom with blood.

Dr Fry says the project has spanned several decades and involves collaboration with a large network of international researchers.

"We have been collaborating with the South African Institute for Medical Research, testing their antivenoms against the venomous snakes of Africa. This has already had an impact by showing a geographically wider neutralisation ability of their saw-scaled antivenom than was anticipated."

Dr Fry and his team have also collaborated with international researchers such as Dr Nick Casewell, a Senior Lecturer at Liverpool School of Tropical Medicine, and Dr Kevin Arbuckle, a biosciences lecturer at Swansea University.

"We're studying snakes globally, using venoms we've collected over the last 20 years of fieldwork from the Amazon to Pakistan and into parts of Asia. We're testing a wide range of antivenoms against this incredibly broad suite.

"We have been fortunate to set up our blood laboratory with the help of a major equipment infrastructure grant in 2016 and, thanks to a research agreement with the Australian Red Cross, we now have an unparalleled ability to specifically test the effects of venom on blood.

"This is an area that has been neglected in venom research in the past."

Dr Fry hopes the research conducted at UQ can convince governments and pharmaceutical companies to improve antivenom development and policies in regions where thousands of people continue to die from snakebite.

"It amazes me that antivenoms continue to be sold in regions where it has been proved they don't work," he says.

"It is our hope that our research will not only have direct impact by providing crucial information necessary for clinical management strategies, but that we help raise broader public awareness of this grossly neglected tropical disease.

"Snakebite is not just a medical problem but a socioeconomic problem, too. Thus our strategy is not just about engaging with clinicians but also with economists and sociologists as well. This will allow us to present a complete case to aid agencies to raise the profile of antivenom provision.

"For value for money, no other foreign aid measure could have such immediate medical implications while also helping to promote stable, peaceful communities."

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(Image credit: Tom Charlton)

Contact details:

Associate Professor Bryan Fry
School of Biological Sciences
Faculty of Science
Email: bgfry@uq.edu.au
Phone: +61 7 3365 8515
Web: biology.uq..edu.au,
venomdoc.com/research

The adventure so far:

April 2016: The Venom Evolution Laboratory is successful in its application for a major equipment and infrastructure grant to establish the UQ Integrative Blood Coagulation Research Core Facility. The leading-edge technology established in the testing array includes a Stago STA-R Max coagulation analysing robot, the only one in Queensland, one of only six in Australia, and the only one in Australia used in a research laboratory.

September 2016: Dr Fry's team at the Venom Evolution Laboratory publishes its first paper in the journal Comparative Biochemistry and Physiology, documenting the changes in brown snake venom from neurotoxic, reptile-feeding babies to coagulotoxic, mammal-feeding adults. The radical shift in venom is what makes brown snakes so dangerous, with the effects on the blood being the fastest acting of any snake in the world.

May 2017: Dr Fry's team publishes its second paper in the journal Toxins, examining the effect of the antivenom made against an African snake known as the boomslang (Dispholidus typus, as well as the equally lethal relative the twig snake (Thelatornis mossambicanus). The boomslang antivenom was extremely efficient in neutralising the effects on the blood by boomslang venom, but performed extremely poorly against the blood-effects by twig snake venom. The paper shows that there are very poor management options for twig snake bites, based on current available antivenoms.

July 2017: Dr Fry's team publishes a paper on Australian snakes in the journal Comparative Biochemistry and Physiology, showing that tiger snakes and their relatives share an extremely conserved mode of action due to the extreme conservation of their target in the blood. This has resulted in an extraordinary conservation of antivenom efficacy.

August 2017: Dr Fry's team shows for the first time that anguimorph lizards, including the iconic komodo dragon, have a potent anticoagulant effect similar to that of some snakes.

August 2017: Dr Fry's team publishes a paper on the ineffectiveness of saw-scaled viper venoms in the Toxicology Letters journal. Dr Fry says this is the most important paper of his career from a medical perspective.