MATTIAS KLUM/NGS

The snakebite fight

Snakes kill tens of thousands of people each year. But experts can't agree on how best to overcome a desperate shortage of antivenom.

BY CARRIE ARNOLD

Abdulsalam Nasidi's phone rang shortly after midnight: Nigeria's health minister was on the line. Nasidi, who worked at the country's Federal Ministry of Health, learnt that he was needed urgently in the Benue valley to investigate a cluster of dying patients. People were bleeding out of their noses, their mouths, their eyes. Names of spine-chilling viruses such as Ebola, Lassa and Marburg raced through Nasidi's mind.

When he arrived in Benue, he found people splayed on the ground and tents serving as makeshift hospital wards and morgues. But Nasidi quickly realized that the cause of the mystery illness was millions of times larger than any virus. The onset of the rainy season had brought the start of spring planting for farmers in the valley, and flooding had disturbed the resident carpet vipers (*Echis ocellatus*). Many farmers were simply too poor to buy boots — and their exposed feet became targets for the highly venomous snakes.

Nasidi wanted to help, but he found himself with limited tools. He had only a small amount of antivenom with which to neutralize the toxin — and it quickly ran out. Once the hospital exhausted its supply, people stopped coming. No one knows how many people were killed. In an average year, hundreds of Nigerians die from snakebite, and that rainy season, which started in 2012, was far from average.

Snakebites are a growing public-health crisis. According to the World Health Organization, around 5 million people worldwide are bitten by snakes each year; more than 100,000 of them die and as many as 400,000 endure amputations

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Bites from venomous snakes such as the Jameson's mamba (*Dendroaspis jamesoni*) are a public-health crisis.

and permanent disfigurement. Some estimates point to a higher toll: one systematic survey concluded that in India alone, more than 45,000 people died in 2005 from snakebite[1] — around one-quarter the number that died from HIV/AIDS (see 'The toll of snakebite'). "It's the most neglected of the world's neglected tropical diseases," says David Williams, a toxinologist and herpetologist at the University of Melbourne, Australia, and chief executive of the non-profit organization Global Snakebite Initiative in Herston.

Many of those bites are treatable with existing antivenoms, but there are not enough to go around. This long-standing problem became international news in September 2015, when Médecins Sans Frontières (MSF, also known as Doctors Without Borders) announced that the last remaining vials of the antivenom Fav-Afrique, used to treat bites from several of Africa's deadliest snakes, were about to expire. The French pharma giant Sanofi Pasteur in Lyons had decided to cease production in 2014. MSF estimates that this could cause an extra 10,000 deaths in Africa each year — an "Ebola-scale disaster", according to Julien Potet, a policy adviser for MSF in Paris. Yet, because most of those affected by snakebites are in the poorest regions of the world, the issue has been largely ignored.

SPOTLIGHT ON SNAKES

In May, however, the crisis was discussed for the first time at the annual World Heath Assembly meeting in Geneva, Switzerland. The world's handful of snakebite specialists gathered in a small conference room in the Palais des Nations — although they shared concern over the problem, they were split about how to solve it. Many want to use synthetic biology and other high-tech tools to develop a new generation of broad-spectrum antivenoms. Others argue that existing antivenoms are safe, effective and low cost, and that the focus should be on improving their production, price and use. "From the physician perspective, patient care and public health comes before anything new," says Leslie Boyer, who directs an institute dedicated to antivenom study at the University of Arizona, Tucson.

The debate mirrors those around many other developing-world challenges, from improving agriculture to providing clean drinking water. Do people need high-tech solutions, or can cheaper, lower-tech remedies do the job? The answer is simple to Jean-Philippe Chippaux, a physician working on snakebite for the French Institute of Research for Development in Cotonou, Benin. "We have the ability to fix this problem now. We just lack the will to do it," he says.

Every December, Williams sees snakebite victims flood into the Port Moresby General Hospital in Papua New Guinea. Nearly all of them were bitten by the taipan (*Oxyuranus scutellatus*), one of the world's deadliest snakes, which emerges at the start of the rainy season. The venom stops a victim's blood from clotting, paralyses muscles and leads to a slow, agonizing death. It seems a far cry from Australia, where Williams is based. "There's this incredible suffering just 90 minutes away from the modern world," he says.

Yet Williams knows that these people are the lucky ones. The hospital ward, which might be treating as many as eight taipan victims at any time, is often the only place in the country with antivenom drugs. Without them, some 10–15% of all snakebite victims die; with them, just 0.5% do. The situation is reflected around the world. "Many countries don't want to admit that they have such a primeval-sounding problem," Chippaux says.

The method used to make antivenom has changed little since French physician Albert Calmette developed it in the 1890s. Researchers inject minuscule amounts of venom, milked from snakes, into animals such as horses or sheep to stimulate the production of antibodies that bind to the toxins and neutralize them. They gradually increase doses of venom until the animal is pumping out huge amounts of neutralizing antibodies, which are purified from the blood and administered to snakebite victims.

Across much of Latin America, government-funded labs typically produce antivenoms and distribute them free of charge. But in other areas, especially sub-Saharan Africa, these life-saving medications are too often out of reach. Many governments lack the infrastructure or political will to purchase and distribute antivenom. Bribery and corruption often jack up the price of an otherwise inexpensive drug from a typical wholesale cost of US$18 to $200 per vial to a retail cost between $40 and $24,000 for a complete treatment, according to a 2012 analysis[2]. Not all hospitals and clinics can afford the antivenom, and some won't risk buying it because their patients either can't pay for it or won't, because they doubt that it really works.

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With no reliable market for the medicines, some pharmaceutical companies have halted production. Sanofi Pasteur stopped making Fav-Afrique because, at an average retail price of around $120 per vial, it just couldn't sell enough to make production worthwhile. A total of 35 government or commercial manufacturers produce antivenom for distribution around the world, but only 5 now make the drugs for sub-Saharan Africa. In the absence of medicines, snakebite victims have been known to drink petrol, electrocute themselves or apply a poultice of cow dung and water to the bite, says Tim Reed, executive director of Health Action International in Amsterdam.

But there are also problems with the drugs themselves, says Robert Harrison, head of the Alistair Reid Venom Research Unit at the Liverpool School of Tropical Medicine, UK. They often have a limited shelf life and require continuous refrigeration, which is a problem in remote areas without electricity. And many are effective against just one species of snake, so clinics need an array of medicines constantly on hand. (A few, such as Fav-Afrique, combine antibodies to create a broad-spectrum product.)

Venoms from spiders and scorpions typically have only one or two toxic proteins; snake venoms can have more than ten times that amount. They are a "pandemonium of molecules", says Alejandro Alagón, a toxinologist at the National Autonomous University of Mexico in Mexico City. Researchers do not always know which proteins in this toxic soup are the damaging ones — which is why some think that smarter biology could help.

OLD PROBLEM, NEW SOLUTION

Ten years ago, teams led by Harrison and José María Gutiérrez, a toxinologist at the University of Costa Rica in San José, began parallel efforts to create a universal antivenom for sub-Saharan Africa using 'venomics' and 'antivenomics'. The aim is to identify destructive proteins in venoms using an array of techniques, ranging from genome sequencing to mass spectrometry, and then find the specific parts, known as epitopes, that provoke an immunological response and are neutralized by the antibodies in antivenom drugs. The ultimate goal is to use the epitopes to produce antibodies synthetically, using cells rather than animals, and develop antivenoms that are effective against a wide range of snake species in one part of the world.

The scientists have made slow but steady progress. Last year, Gutiérrez and his colleagues separated and identified the most toxic proteins from a family of venomous snakes known as elapids (Elapidae). By combining information about the abundance of each protein and how lethal it is to mice, the team created a toxicity score to indicate how important it was to neutralize a protein with antivenom, a first step towards making the treatment[3].

In March this year, a Brazilian team reported that they had gone further, designing short pieces of DNA that encode key toxic epitopes

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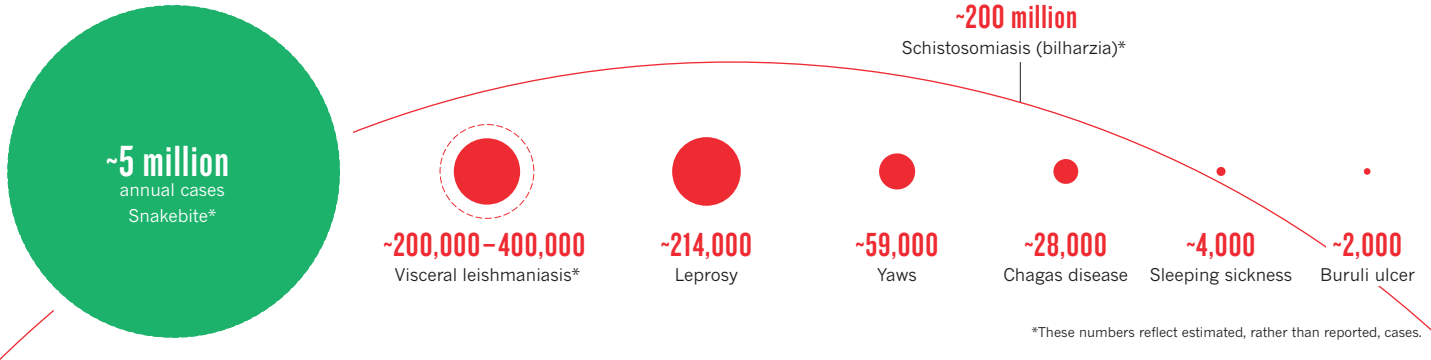
THE TOLL OF SNAKEBITE

Snakebite affects more people each year than many other neglected tropical diseases, and often causes death, disability or disfigurement. The issue receives little attention: data are scarce and the condition mostly strikes the world's poorest regions.



*These numbers reflect estimated, rather than reported, cases.

SOURCE: WORLD HEALTH ORGANIZATION

in the venom of the coral snake (*Micrurus corallinus*), a member of the elapid family[4]. Mice were injected with the DNA using a technique that enabled some to generate antibodies against coral-snake venom, and the group enhanced the mice's immune responses by injecting them with synthetic antibodies manufactured in bacterial cells. These and other advances led Harrison to estimate that the first trials of new antivenoms in humans could be just three or four years away. But with so few researchers working on the problem, a paucity of funding and the biological complexity of snake venoms, he and others admit that this is an optimistic prediction.

Despite the growing literature on antivenomics, Alagón and Chippaux aren't convinced that the approach will help. Alagón estimates that newly developed antivenoms would need to be priced at tens of thousands of dollars per dose to be financially viable to produce, and that no biotech or pharma company would manufacture one without substantial government subsidies. Compare that, he says, to the rock-bottom price of many existing antivenoms. "You can't get cheaper than that," he says. "We can make an entire lot of antivenoms in one day using technology that's been available for 80 years."

Finding someone to produce new medications might be a greater challenge than actually developing them, Williams acknowledges: governments or non-governmental organizations (NGOs) will almost certainly have to step in to help to defray the development costs. But he argues that now is the time to research alternative approaches. These could "revolutionize the treatment of snakebite envenoming in the next 10–15 years", Williams says.

THE ROOM WHERE IT HAPPENED

All these tensions, brewing for nearly a decade, came to a head at the Geneva meeting in May. Around 75 scientists, public-health experts and health-assembly delegates crowded around three long tables in a third-floor conference room at the United Nations Headquarters. Spring rain pelted the tall windows.

Lights were dimmed, and then the screams of a toddler filled the room. A short documentary co-produced by the Global Snakebite Initiative told the story of a girl bitten by a cobra whose parents carried her for days over rocky roads in Africa to find antivenom. They arrived in time — the girl survived — but she lost the use of her arm. Her sister had already died after a bite from the same snake.

Convincing attendees of the scale of the problem was the meeting's primary goal; how to solve it came next. For 90 minutes, scientists and NGOs made short, impassioned speeches laying out the scope of the issue and the variety of problems that they faced. At the centre of each presentation was the same message: we need more antivenom.

But the meeting was strained. Chippaux and representatives of the African Society of Venomology were disappointed and angry that so few Africans had been invited to speak, even though the continent is where antivenom shortages are most acute. "Our voice, our issues, were completely overlooked," Chippaux says. Seated at the front of the room, group members whispered and gestured frantically to each other, and Chippaux barely managed to keep them from storming out.

They argue that the current antivenom shortage stems from Africa's reliance on foreign companies and governments for its drugs, and that the only solution lies in building up infrastructure in Africa to produce its own high-quality antivenom. Alagón views antivenomics as a dangerous diversion. "It's distracting many brilliant minds and resources from improving antivenoms using existing technology," he says. "Perhaps by 2050 this will be the standard technique, but the problem is now."

Williams and Gutiérrez take a middle ground. They feel that the problem requires attacks on all fronts. As well as innovation, Gutiérrez calls for existing manufacturers to step up the production of current drugs.

There are signs of this happening already. Latin America has a long history of producing antivenoms both for its own needs and for those of countries around the world, and even before Sanofi Pasteur announced that it would cease production of Fav-Afrique, Costa Rica, Brazil and Mexico were testing antivenoms for different parts of Africa. One product, EchiTAb-Plus-ICB, is produced by Costa Rica and effective against a range of African viper species; it completed clinical trials in 2014 and is now available for use. Several other antivenoms are expected to be ready in the next two years. The drugs should be affordable: government labs in Costa Rica have already indicated that they will not seek to make money from the antivenoms, just recoup their expenditures.

But beyond that, the way forward remains murky. Williams knows that the World Heath Assembly meeting was just a start. Inevitably, more meetings will be needed to produce a concrete action plan. But the discussion still gave him and some others a renewed sense of hope that the international community is beginning to take snakebite seriously — momentum they hope to build on by banging away at the topic at conferences and in the media.

Boyer says that whatever solution the snakebite field decides on, the most important thing is to "break the cycle of antivenom failure in Africa". Doing that requires building trust from governments, health-care workers and the public that the drugs are safe and effective, that clinics will have antivenom on hand, and that people will be able to afford treatment. "Without that, you've got nothing," Boyer says. Educating local clinics on how to care for snakebite victims and administer treatments in a timely manner would also go a long way towards preventing deaths.

Speaking of the devastation he saw in Benue, Nasidi says that something as simple as providing boots for poor farmers would have helped to prevent much of the suffering and death that he witnessed. It's perhaps the ultimate in low-tech methods in snakebite protection: shielding vulnerable human skin. ■

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