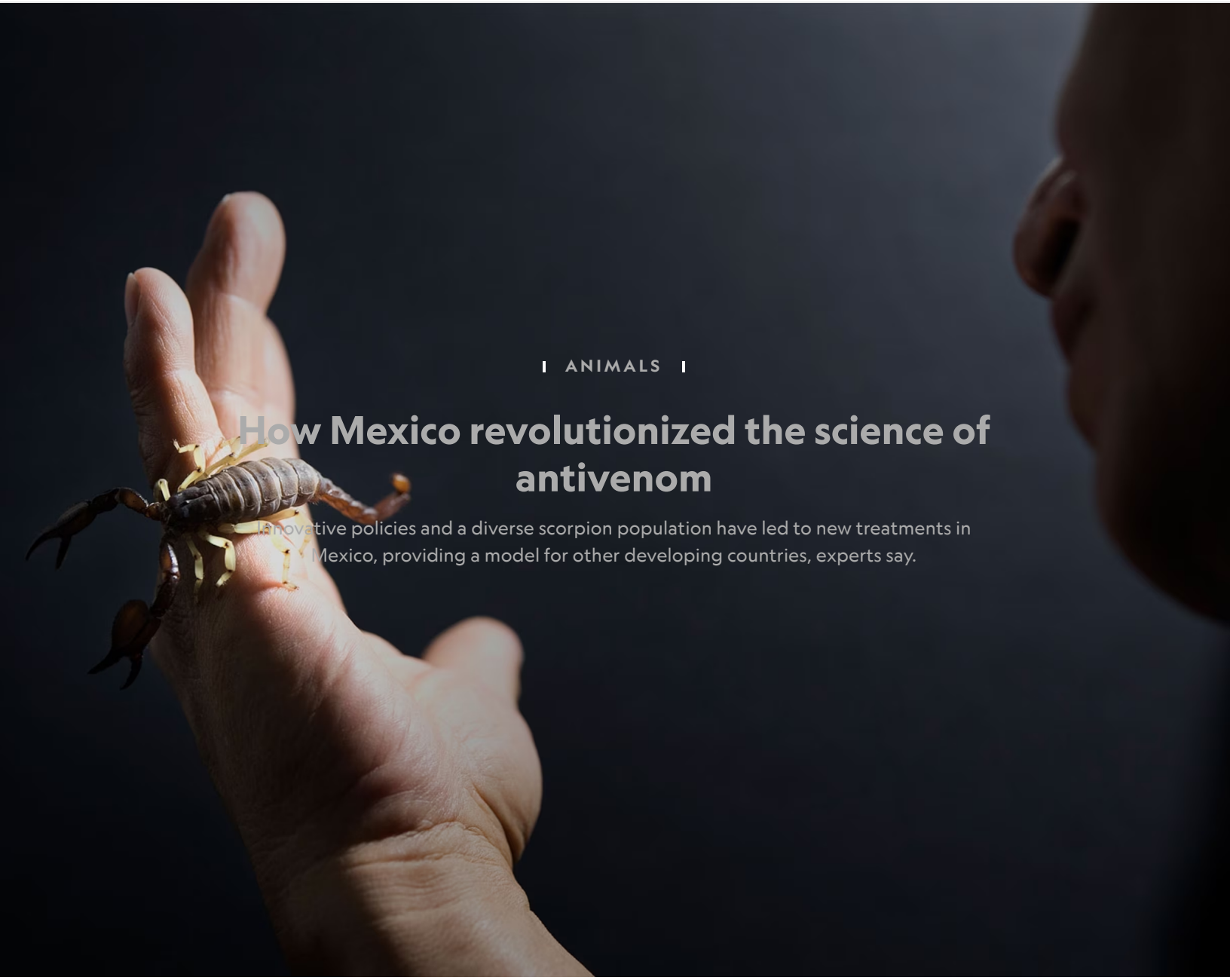

ANIMALS

# How Mexico revolutionized the science of antivenom

Innovative policies and a diverse scorpion population have led to new treatments in Mexico, providing a model for other developing countries, experts say.

Biologist Cipriano Balderas Altamirano holds a venomous species of burrowing scorpion native to Oaxaca.

BY **BRENT CRANE**

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**PUEBLA STATE, MEXICO** — Ojo de Agua Ranch, at the edge of the sleepy town of Agua Fria, is home to nine dogs, six geese, 12 canaries, 21 sheep, and 163 horses. The sprawling 400-acre oasis is the inheritance of five brothers, the eldest of which, Alejandro Alagón, bought the equines in 2008 with a specific purpose in mind: Creating antivenom.

Since then, these Criollo horses have likely saved thousands of human lives with their precious *sangre*, a crucial ingredient in making antidotes to

venomous snakebites and arthropod stings, says Alagón, a venomologist with the National Autonomous University of Mexico in Cuernavaca.

Nearly 140,000 people die from snakebites annually, many of which are treatable with antivenoms, according to the World Health Organization. Envenomations—the term for bites and stings caused by animals such as snakes and scorpions—are also a silent scourge: In 2017, WHO added snakebite envenomations to its list of neglected tropical diseases.

The horses at Ojo de Agua receive weekly showers, eat organic and vitamin-rich meals, and are monitored for disease.

That's why, throughout the 20th century, Mexican researchers improved and invented over a dozen antivenoms now used in the U.S. and elsewhere. Today, Mexican antivenoms are marketed through the country's three biggest antivenom firms, Instituto Bioclon, BIRMEX, and Inosan Biopharma, which supplies the U.S. military.

In Mexico, scientists "always had a huge incentive to make lower-cost, safer antivenoms, because they had hundreds of thousands of people per year that were going to use them if they were safe enough," says Leslie Boyer, a venomologist at the University of Arizona, the state with America's highest per capita rate of envenomations.

Alagón, who has worked extensively with Bioclon and Inosan, has invented or improved upon 16 antivenom products, two of which have been approved by the U.S. Food and Drug Administration.

**Left**: Scientists Vanessa Gomez Zarosa and Edgar Neri Castro hold a Veracruz neotropical rattlesnake at the Institute of Biotechnology.

**Right**: A snake's venom gland is located behind the eye. To milk the reptile, scientists force it to bite down on a hard object, releasing the venom into a receptacle.



"My research comes second only to my family, though I spend more hours in the lab than with my family. The fact is that, with antivenoms, lives are saved and suffering is diminished," Alagón says.

Worldwide, around 50 laboratories produce antivenoms, most of them government-funded programs in the Americas and Asia. Antivenoms, which constitute a growing, multibillion-dollar industry, generally target specific venomous species, including various types of cobras, pit vipers, or black widow spiders. They're typically administered to a patient intravenously.

Despite such progress, Mexico still has room to improve, Boyer says: Recognizing and treating envenomations, especially in rural areas, remains poor, with bites and stings significantly undercounted in medical data. *(Read about an antivenom that can treat 18 types of snakebites.)*

Photos of Alejandro Alagón and his family are on display at their home in Cuernavaca, Mexico.

Alagón, seen at his university's spider terrarium, has been stung by a bark scorpion twice—and was saved by his own antivenom.



But the country's inroads in drastically reducing envenomation deaths while building a world-leading antivenom industry offers lessons for other countries with high rates of snakebites and stings, she says.

## A momentous scorpion bite

One of the top places for antivenom research in Mexico is the Institute of Biotechnology at the National Autonomous University.

Their herpetarium boasts 61 endemic and foreign *serpientes*: among them the Nayarit coral snake, the Yucatán hognosed pitviper, and the Mexican green rattler. A smaller room contains scorpions living in boxes.

On a recent winter day, Cipriano Balderas Altermirano, the lab's scorpion biologist, demonstrates how the arachnids are "milked." He lifts up a squirming bark scorpion with tweezers, dipping it in water and shocking it with electrified copper coils to spasm its stinger, which then oozes a neurotoxic venom.

Samuel Cardoso Arenas, manager of the lab's spider terrarium, holds a red-tailed tarantula, which is native to Mexico and Central America.

This same species has stung Alagón twice: once in the lab and the garden. Both times, he was saved by his own antivenom. *(Read more about the search for a better antivenom.)*

A scorpion sting is also what transformed the Mexican antivenom industry into one of the world's most prodigious. After the son of then-President Ernesto Zedillo suffered a near-fatal scorpion sting in 1995, the traumatized politician mobilized the medical establishment. Nurses and doctors were trained in administering antivenom. Production was subsidized by the federal government. Rural communities were educated in treatment options. Zedillo's efforts paid off. From 1990 to 2007, snakebite mortality decreased by 66 percent, and scorpion mortality decreased by 83 percent, according to a 2020 study led by Alagón.

Even still, scientists possess only a modest understanding of how venoms work on a molecular level or how antibodies are formed within immunized animals.

This makes constructing effective antivenoms all the more difficult, which is why Alagón's lab focuses mostly on the nitty-gritty of creating antivenoms uniquely tailored to individual species.

The sun rises over a paddock at the Ojo de Agua ranch, founded by Alagón's maternal grandfather.

Criollo horses eat their breakfast at dawn. Native to South America, the breed is known for its hardiness and endurance.

## From horse blood to antivenom

The horse has been the industry's chief blood source since 1895, when antivenom was invented in France. Other mammals could do the job, but horses are docile, in addition to having bountiful blood and antibodies. Over a period of six months, a horse is injected with a small but increasing amount of venom until it is immunized against the toxin. Then, the animal's antibodies are extracted and sent to a lab.



In the early morning darkness on the Oja de Agua Ranch, dozens of horses trot into the ranch's feeding area, eager for breakfast.

Rancheros in cowboy hats direct the animals into spotless stables, where they're tied to posts and munch at piles of grain. Great-tailed grackles swarm the troughs, which are backdropped by mahogany trees, royal palms, and low hills. After sunrise, the bloodletting will begin.

Ranch manager Jesus Pulido Hernández oversees the bloodletting process, inserting the needle into each horse's jugular. Hernández has worked at the ranch for more than 25 years.

Gravity separates the plasma, the antibody-rich part of blood, which collects at the bottom of the bag in a maroon stripe.

A horse named Californiano is led into the *area de sangria,* or the bleeding area. A technician in a white hazmat suit spreads buttery iodine on a shaved patch of skin along the gelding's jugular, then tightens a rope around its neck to expose a vein. Enclosed in a tight pen, Californiano flinches as the needle enters, then stills as his blood flows through a tube into a hanging bag. Five liters takes 10 minutes. Gravity separates the plasma, the antibody-rich part of blood, which collects at the top of the bag in a maroon stripe. *(Read how harnessing the power of venom could lead to new medicines.)*

In an hour, the plasma-less blood will be returned to Californiano. By the end of next week, the plasma in the vials will become antivenom. For scorpion antivenom, the yield is high: one horse's output can produce 2,000 vials. For African snakes, 200. Taken together, Alagón's 163 horses produce 350,000 vials a year.

Alagón says his horses—all neutered males—are treated well. They receive weekly showers, eat organic and vitamin-rich meals, and are monitored for disease.

Though the horses may feel minimal pain at first, they quickly shake it off, Alagón says. "There is no alternative. When an alternative appears, we will stop using horses. But we are saving lives."

Jessica Stark, director of communications and public affairs from the U.K.-based nonprofit World Horse Welfare, says "there is no doubt antivenom is of huge benefit to society."


Inoserp, an antivenom made with horse blood from Ojo de Agua Ranch, is used to treat snakebites in sub-Saharan Africa.



"But even under the best conditions, the horse's welfare will be compromised by repeated injections of a noxious substance. We encourage a move to synthetic alternatives as soon as possible."

Molecular biology might help advance antivenom production beyond horses. In 2020, scientists in the Netherlands found a way to produce cape coral snake venom using stem cells. Indian scientists also recently sequenced the full genome of the cobra, the most comprehensive snake genome ever assembled. Such developments may bring scientists closer to synthesizing antivenoms in a lab, rather than on a ranch.

## A model for the world

Envenomations are most common in rural areas, particularly in Africa and southern Asia, where people have less access to medical care.

India, with a rate of 58,000 deaths a year, has the world's highest rates of snakebites, followed by sub-Saharan Africa, with around 30,000 annual deaths. Scientists believe that increasing human migration, coupled with environmental and climatic changes, is bringing more people into contact with venomous creatures. *(Read more about Africa's forgotten snakebite crisis.)*

Julian Hernández Villegas, Moisés Pelcaste Peñafiel, Jesus Pulido Hernández, Alberto Mohedano Ocaña, Benito alba Flores, Ezaquiel Pedro Rivera, Eulalio Amaya Pulido (left to right) care for the ranch's horses, particularly during the blood-collecting process.



Jean-Philippe Chippaux, a French venomologist, first began using the term "vicious cycle" to describe the socioeconomic process by which developing countries become trapped in a state of high envenomation and low antivenom accessibility.

Mexico broke that cycle by marshaling several public and private resources in what Boyer calls a "big blitz": ample funding for antivenom research and manufacturing, nationwide education programs, investment in modern technologies, and skilled scientists.