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# The kissing bug disease and the woman who would stop it

*The WHO's pay-to-play regulatory system inhibits innovation, critics say, exposing fault lines in global public health*

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Mateo Pilar covers a house with Inesfly, her newly formulated insecticide paint, in Urundaiti, Bolivia, in 2012. The chemist first came to Bolivia in 1998 and was struck by the poverty and disease endemic in the Guarani regions of the country. She has returned dozens of times, often painting homes herself. Inesfly

UNRUNDAITI, Bolivia — Maria Teresa Segundo remembers thinking the deaths were normal. Her grandparents and older neighbors would suddenly see swelling in their knees or wrists. They'd be very tired. And then, one day, they'd be gone.

"We thought it was just age," says the 50-year-old woman from the Guarani ethnic group, who has the loose skin and shrinking body of someone decades older. Then, in the 1990s, the Bolivian government began reaching out to communities to explain that the deaths were being caused by a disease called Chagas, which is transmitted by a bug called the vinchuca. This pest, known in the U.S. as the "kissing bug," lives in the walls of mud huts in the eastern Bolivian region known as the Chaco and elsewhere. The beetlelike insect feeds off of the blood of animals and people.

Chagas is a disease that can lay dormant for years, eventually causing extreme fatigue and joint swelling; the lifetime risk of developing heart or other vital organ failure is about 30 percent. For decades Chagas has been endemic throughout South America. Several countries greatly reduced contagion through fumigation and by building homes of concrete, which the vinchuca can't penetrate, but approximately 8 million people in 18 countries (http://www.cdc.gov/parasites/chagas/gen_info/detailed.html) in the Americas still suffer from the disease.

After a visit to Segundo's village decades ago, local government officials sprayed people's homes with insecticides every few months, she says. She would get headaches from the smell, which lingered for days. The pests always returned.

The vinchuca or kissing bug is also known as barbeiro in Brazil, pito in Colombia, chinche in Central America and chipo in Venezuela. Rasbak via Wikipedia

But, she says, everything changed in 2002 when her house got a fresh coat of paint: a newly formulated insecticide paint, Inesfly, developed in 1995 by a Spanish chemist named Pilar Mateo. "We haven't seen a vinchuca in this village since," says Segundo.

The results were replicated elsewhere. Inesfly wiped out vinchuca infestation in small parts of the Chaco region, according to the head of Bolivia's regional Chagas program there. But the South American country still has the highest infection rate

in the world. One study in 2008 found that more than 57.7 percent of homes in the Bolivian Chaco were still infested.

“Everywhere we have painted, we have a zero reinfestation rate,” says Dr. Abraham Gemio, who used to head Bolivia’s national Chagas eradication program and now works for Inesfly Corp., Mateo’s company. He says that 10 years of monitoring — tracking vinchuca sightings and health or environmental complications in painted homes — have shown him that Inesfly works.

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> Inventor of Inesfly

What makes Inesfly effective, Gemio says, is not that it contains a powerful new chemical, but that it is a new vehicle for insecticide delivery: The paint’s base is embedded with microcapsules containing the chemical, and the formula can be adjusted, depending on which insect needs to be killed. The microcapsule is a nanotechnology version of a slow-release pill, and it increases the duration of the effect of the insecticide inside. It can also be embedded into other products, such as shampoo, clothes or sprays targeting agricultural pests. Mateo “has given us an important tool,” says Javier Lucientes, a parasitologist at the University of Zaragoza in Spain, who has been testing Mateo’s microcapsules in animal-disease prevention.

Despite its success and potential for adaptation, however, Inesfly is still not a widely used tool for combating the spread of Chagas. When Mateo began producing paint laden with microcapsules, her company comprised her, four employees and her husband, Eduardo Castell. (Today it has 17 employees.) Mateo decided not to partner with a large pharmaceutical company to bring Inesfly to market because, she says, “I didn’t want profit motives dictating how this important tool was brought to the world.” Her decision has forced her onto a difficult path that exposes critical fault lines in global public health: a pay-to-play regulatory system that critics say purports to encourage innovation but that can inhibit the development of promising new methods to prevent and fight disease. Rather than fostering new ways to rid the world of terrible diseases, our global health structure sometimes hinders it.

Mateo and Inesfly engineer Franz Espejo paint a house in Urundaiti in 2010. Despite impressive results, Inesfly has not been used in Bolivia's national Chagas prevention programs because the paint lacks clearance from WHOPES, the World Health Organization Pesticide Evaluation Scheme. Inesfly

As far back as she can remember, Pilar Mateo was always inventing something. The 55-year-old chemist dreamed of being a pianist or an artist, but says she found "a natural connection between creativity and the sciences." She opted for chemistry in order to support the family business, a paint company.

In 1989, a few years after finishing her graduate work on anti-rusting varnishes, she had a lightbulb moment: While reading about the closing of a local hospital due to a bug infestation, she thought, 'If walls are homes for many common pests, couldn't there be a better way to attack them at the source?' Her first attempt at creating insecticide paint

— crudely mixing chemicals into the base — was disastrous. Toxins leached out, and the active ingredients degraded so quickly that within a few days, the paint couldn't kill an ant walking along the surface.

It took her six years to hit upon microencapsulation and, with it, something close to the holy grail of the pesticide industry: ensuring that a pesticide-sprayed surface remains an anathema to insects long after application, while also remaining relatively safe for the environment and people's health. Traditional fumigation typically loses its kill power after anywhere from a few weeks to six months. Almost always, massive amounts of time and money are then spent on reapplication. Inesfly, depending on the surface and formulation, has proved effective for two years. Scientists say Inesfly is also promising because of its ability to limit the development of resistance. Mateo found a way to include Insect Growth Regulators, which attack unborn or young insects that traditional pesticide chemicals can't kill, in her microcapsules and in the paint.

"The probability of resistance is dramatically lowered because you are leaving fewer of the bugs alive," says Jorge Mendéz Galván, former head of Mexico's vector-control program, who has used Inesfly to reduce dengue in Mexico.

A number of labs in Latin America and Spain have shown the paint is safe, and there have been no reports of environmental or health problems. As a safety mechanism, the paint includes a substance that, if ingested, will induce immediate vomiting.

Mateo visits Urundaiti, an indigenous Guarani community that is the worst affected by Chagas, in 2007. Chagas disease can be fatal and has no cure. Bolivian healthy officials estimate that nearly a quarter of the country's population is infected. Inesfly

When Mateo realized what she'd done, "The first thing I did was call my father and say, 'We're going to make millions!'" she says. "I figured I'd sell it to wealthy people to rid their homes of cockroaches and flies."

That changed when a man named Cleto Cáceres showed up on Mateo's doorstep. A Bolivian doctor from the Chaco, Cáceres happened to be in Spain when news of her invention hit newspapers. He told her about how his fellow Guarani were being ravaged by Chagas and asked her to come to Bolivia to see if her paint could help.

"I could barely locate Bolivia on a map," Mateo recalls. But she went.

Once she began traveling the countryside, sleeping in huts, she quickly realized that she wanted to use her paint to combat the spread of disease. For the first few years, all went well. With the help of Cáceres, a prominent figure in the Bolivian public health system, Mateo began securing small grants from nonprofit organizations to paint huts in Chaco villages. She worked with local health officials to monitor the paint's efficacy and safety by revisiting and testing painted homes at determined intervals; she did toxicity testing in highly reputable labs.


Mateo and Dr. Patience Mama Yeboah at the Inesfly paint manufacturing facility in Accra, Ghana. Completed in July 2014, the factory has 75 employees and is expected to produce approximately 1.5 million liters of insecticide paint in 2015. Inesfly

But when she tried to expand her operation — which for most disease-prevention tools in the developing world means getting government health officials to use it in their nationwide programs — she faced a seemingly insurmountable problem. “There is no way we could use the paint before it gained clearance from WHOPES,” Max Enriquez, then head of Bolivia’s National Chagas Program, told Al Jazeera in an interview in 2012.

Many nations’ health and nutrition sectors are regulated by a governmental body akin to the U.S. Food and Drug Administration. But, in 1960, out of growing concern about possible health and environmental problems with pesticides, including DDT, which was being widely used against malaria at the time, the World Health Organization decided to create a program, which came to be called the World Health Organization Pesticide Evaluation Scheme, or WHOPES (http://www.who.int/whopes/en), to oversee pesticide development and usage.

“A key rationale for WHOPES is the concern that developing countries often lack any registration for insecticides used in public health, and if there are national schemes, implementation is a problem,” says Peter Hough, a principal lecturer in international politics at Middlesex University in London who has studied the global pesticide market and regulatory field.

WHOPES, with its capacity to streamline and safeguard the testing of all new agricultural or public health chemicals, as well as any new chemical delivery mechanism, emerged as the de facto gatekeeper for pesticide use in the developing world. This, says Hough, works in favor of Big Pharma, which has the resources to submit to years of WHOPES testing, which in turn can deter smaller companies.

WHOPES is not a regulatory agency (technically, it does not approve products for use, but rather issues “recommendations”). Legally, any country can stock its disease-fighting arsenal with any product or chemical it wants. However, governments generally use the products that the international agency recommends, avoiding those that haven’t passed WHOPES’ trials.

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on BASF’s global public health team

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The WHOPES-as-gold-standard approach has clear benefits, including confidence that a product used in countrywide public health initiatives has been through the ringer. But there are also drawbacks. WHOPES isn’t a testing center itself. Rather, the organization outlines stringent testing procedures that have come to be known as the WHOPES trials: four stages from lab to field that must be carried out in exact accordance to complex guidelines, by WHO experts, with material tested only in WHO-approved labs. After a product has been tested using WHOPES’ strict guidelines, it can then be submitted for review by the WHOPES Working Group. It is a labyrinthine structure that requires knowing the system and its players. Product manufacturers must find the independent experts to lead the trials and

manufacturers foot the bill because WHOPES itself does not provide financing for testing. In fact, the organization that's entrusted with safeguarding our public health disease control system is a tiny part of the World Health Organization. WHOPES is under the Vector and Ecology Management unit within the Department of Control of Neglected Tropical Diseases and has only four employees.

In the early 2000s, Mateo had never heard of WHOPES. Inesfly had long been tested for safety and efficacy in WHO labs, but this alone was not sufficient to satisfy WHOPES protocol.

"Larger companies have whole legal departments, and if they have decided they want to promote a product, they have substantial finances to do it," says Chris Schofield, who recently retired from the London School of Hygiene and Tropical Medicine and is familiar with Inesfly. Egon Weinmueller, on the global public health team of BASF, a chemical company, agrees: "There's no shortage of great scientific discoveries out there that the public will never see," he says, because WHOPES' structure is difficult to navigate and painfully slow. Testing timelines can span decades. University scientists "just don't have the know-how or name power or knowledge of the systems or the funding to get it out there."

Funding was a challenge for Mateo too. She cobbled together some foundation and university grants, but it was slow going. A WHOPES spokesman says the institution is "absolutely" an equal-opportunity player and, in 2012, said that an estimated cost of trials for a product like indoor residual spraying is $350,000. But according to scientists familiar with the WHOPES process, real trial costs can range from $300,000 to tens of millions; Schofield says companies undertake the expensive endeavor, which he says can include "the funding of trials and tests that may not even be necessary," because a green light from WHOPES "can boost sales significantly." He believes WHOPES is a vital instrument for safety but adds that it's a bit of a paradox: "On the one hand, WHO argues we need new products in public health. On the other hand, it produces a system that does not exactly accelerate the development of such products."

WHO recently recognized that WHOPES needed some reform. In 2013, WHOPES launched the Vector Control Advisory Group, which assesses new inventions and approaches to disease control. Steve Lindsay, a professor in the School of Biological and Biomedical Sciences at Durham University in England and a member of VCAG, says the

group was created because WHO and others in the field "r[ed] that thi[s] is too slow and painful and needs to speed up."

A house painted with Inesfly in Entre Rios, Bolivia, in 2009. With stalled progress at WHOPES in Bolivia, Mateo has recently focused her attention on Africa, testing and producing a version of the paint that attacks the malaria-carrying anopheles mosquito. Inesfly

VCAG is an important step forward, say public health experts. In Mateo's case, it could be helpful in the future because WHOPES doesn't have a protocol to evaluate paint and the new advisory group was set up specifically to smooth the review process for this kind of outside-the-box intervention. But VCAG is not a fix-all. Lindsay says that while product manufacturers can theoretically reach out to VCAG any time they wish, "in reality this means after they have tested the intervention in the laboratory and in small-scale field trials." Mateo's Chagas-related paint is barely at that point in its WHOPES testing process, which means that all the hurdles she has encountered thus far have not been minimized by the creation of this new committee.

On World Malaria Day in 2012, Abdel Kader Agne, the director of Bestnet's Niger office, distributed free mosquito nets to high-risk children and pregnant women in Balleyra, a community 100 kilometers north of the capital city of Niamey. With him were the First Lady of Niger and local officials. Bestnet

Mateo's paint isn't the only time WHOPES has thrown up troubling obstacles to disease prevention. Take, for example, the fight against malaria.

In the early 2000s, two companies, Sumitomo Chemical and Vestergaard-Frandsen, whose products were WHOPES-recommended, comprised 98 percent of the bed-net industry. According to Jasson Urbach of the nonprofit Africa Fighting Malaria, "these companies and many others, including bed-net procurers, put forward the idea of a WHOPES 'gold standard,' which implies other existing bed nets were possibly of lower quality." There is a strong bias in organizations combating malaria to only buy recommended nets; according to a representative from a main funder of anti-malaria campaigns, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the group only buys nets that have a WHOPES recommendation.

Also, the WHOPES process isn't infallible from a scientific perspective.

In 2013, Netprotect, a long-lasting insecticide net produced by a Danish company named BestNet, was rejected at the final stage of its WHOPES review. Torben Larsen, who was the company's director and co-owner until April 2015, when it folded, says that Netprotect's testing, carried out by WHO experts, was based on a report that he says contained serious flaws.

WHOPES guidelines include a minimum and maximum dosing for nets and evaluate all nets in a group based on the average dosing. Larsen says that Netprotect failed to gain a recommendation in part because of a 2010 field test in malaria-ridden Cambodia in which 45 percent of Netprotect nets were underdosed with insecticide. Correspondence from 2013 between BestNet scientists running the trials and a WHO representative, which was shown to Al Jazeera, indicates that the labs and scientists registered the problem of lower-dosed nets in 2010. However, WHOPES said the average dosing on the nets fell within its lower limits and therefore it did not request new nets.

Larsen says the company did not realize such a large number of nets were underdosed until the official WHOPES evaluation three years later, when Netprotect got rejected by the WHOPES committee. Larsen believes the company should have been allowed to send a properly dosed batch.

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> Middlesex University in London

It’s likely that the challenges posed by WHOPES have resulted in limiting the options for fighting malaria. There is little more than bed nets and indoor residual spraying when it comes to malaria prevention. “We are short of tools for a whole series of reasons,” says Lindsay of Durham University. Historically, he says, “there hasn’t been the money in R&D [research and development].”

It is a familiar refrain. The complaint that pharmaceutical companies put significantly fewer resources into preventing diseases that mainly affect the poor, or where they don’t stand to make large profits, isn’t new. Even GlaxoSmithKline’s much-lauded malaria vaccine needed a helping hand (http://fortune.com/2015/07/24/worlds-first-malaria-vaccine-wins-recommendation). The company has spent more than $350 million in development — and expects to throw in another $260 million before it’s done. But Glaxo took on the challenge not for African children — 305,000 of whom have died of malaria before their fifth birthday in 2015 — but for Western travelers and the military, who can afford to pay for a vaccine. According to a New York Times editorial from 2013, Glaxo was hesitant to even finance pediatric trials. So the Bill and Melinda Gates Foundation stepped in with $200 million (http://www.nytimes.com/2013/10/14/opinion/hope-for-a-malaria-vaccine.html).

In fact, developing chemicals for public health use has never been a stand-alone business. Experts say nearly all of the insecticides the world uses to fight diseases that afflict humans were once agricultural pesticides; they are not developed to target human health because of the high cost involved and the lack of potential profit on the other end.

The idea that WHOPES has been a barrier to innovation, especially for small companies, doesn’t surprise Peter Hough of Middlesex University. He says WHOPES gained strength in the 1990s out of what he calls an “unholy alliance” between big pharmaceutical companies and their critics. “Rules emerged largely as a result of campaigning by those who were horrified by the sector and by companies who decided that global regulation suits them,” he says. Firms decided to throw their weight behind global regulation via

WHOPES because they were worried about the possibility of even stronger restrictions being imposed from domestic legislation in the aftermath of the Bhopal industrial disaster in India (/external/2014/12/bhopal-tragedy-liveson.html).

The added benefit for large companies in deferring to WHOPES, Hough explains, is that they would have known that the expensive and lengthy regulatory process would cut down on competition. “The only people who can really do it are Big Pharma,” he says. “And it strikes me that is to some extent deliberate.”

A Bestnet Netprotect net in Kenya. Bestnet

Despite the setbacks in Bolivia, Mateo pushed ahead a continent away. In 2011, she launched Inesfly Africa, a partnership between her company, Inesfly Corp., and two private investors, which put up $10 million to build a paint factory in Ghana. Their plan is to produce a formula that specifically targets the anopheles mosquito and sell it retail across Africa. At the time of publication, the company was on track to produce 1.5 million liters in 2015; it plans to double production in 2016. Its factory has an annual capacity of 30 million liters.

Mateo is also making some progress with WHOPES trials on the malaria formulation of the paint. Several years ago, some top malaria experts noticed the potential of Inesfly and were able to provide the know-how for testing the paint. Also, since there is more

funding for malaria as compared with Chagas, she has been able to find financing for tests. Still, it's been more than a decade since they began and they are still only three-quarters of the way through.

"The results so far are promising," says Beatriz Mosqueira, an associate researcher at the University of Valencia in Spain, who's one of the WHO scientists testing the paint in the field. "What we have shown is that the paint kills a lot of mosquitos," she says. The next, and last, step is tests to determine whether the killing of mosquitos translates into reduced malarial incidence in areas with painted houses.

Inesfly Africa has had some success selling its paint on the retail and wholesale market. The company says its cost of production varies between $1.50 and $3.80 per liter, and it is aiming to sell the paint for 4.5 euros per liter. But until the WHOPES process is complete — likely still a few years out — the paint will probably not be used in national governmental eradication programs. Meanwhile, countries — especially those in sub-Saharan Africa — rely heavily on the big nonprofits, which decide what products are purchased for large-scale government-run disease programs.

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"We are forced into using what the funders say is acceptable," says a source close to the Ministry of Health in Uganda, another country with high malaria infection rates. And the biggest of those funders are clear: "We won't fund anything that hasn't been recommended by WHOPES," says Christoph Benn of the Global Fund, the single largest funder of malaria control programs in countries where the disease is endemic.

There is now money flowing specifically for R&D in the public health world from the Gates Foundation, which experts say is filling a critical void. Still, there are some, like Mateo, who wonder whether it's the best idea for the fate of the world's most pernicious disease to rest in the hands of one philanthropic couple. "There has to be some way for other inventors like me to get our products to market without having to be dependent on Gates or waiting 20 years," she says.

It's been almost two decades since the Guarani doctor Cleto Cáceres knocked on Mateo's door to ask her to help his ailing people. Chagas still rages in Bolivia and throughout the Americas, including new incidence in the United States (http://www.newyorker.com/tech/elements/americas-war-on-the-kissing-bug-and-chagas-disease).

There are no reliable stats on how many people a year are now dying of Chagas, but the Bolivian government still considers it a serious and growing health problem. Last year, the Ministry of Health estimated that over 3 million Bolivians — out of a total population of 11 million — live with the disease (http://www.eldiario.net/noticias/2014/2014_05/nt140522/agraria.php?n=23&-el-chagas-en-bolivia-afecta-a-3-millones-de-personas-de-bajos-recurso). The Guarani in the Chaco remain deeply affected.

Mateo says she understands the importance of a world body that can rigorously safeguard human and environmental health. But she doesn't understand why it had to feel like an insider's game with a price tag potentially in the millions. "I remember thinking, 'I've discovered this great thing that saves lives!'" she says. "I was so sure everyone would embrace it. And I was so wrong."

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