FEATURES

A SECOND CHANCE

On a remote Melanesian island, a Spanish doctor has revived the 60-year-old quest to eradicate a disfiguring disease

By **Martin Enserink**, *on Lihir Island in Papua New Guinea; Photography by* **Brian Cassey**

In a small, poor village 15,000 kilometers from his home, Oriol Mitjà jumped out of a white van one early May afternoon and started to look at people's legs.

"Any children with ulcers here?" he asked in Tok Pisin, the lingua franca of Papua New Guinea (PNG). "Can we see them?" Soon, a young woman pushed a crying boy about 5 years old toward Mitjà. The boy was barefoot; he had a mop of blond curly hair, like most kids here, and was dressed only in dirty blue shorts. A group of villagers, mostly women and children, had gathered to watch. "What's his name?" Mitjà asked as he sat down on a low wooden bench, pulled on disposable gloves, and gestured to the sobbing kid to come sit on his right leg. "Jeremiah," his mother said.

Mitjà, 38, a physician-scientist from Spain with earnest eyes and a friendly smile, has a way of putting kids at ease. As Jeremiah calmed down and began to wipe the tears from his eyes, Mitjà took a close look at his legs. On each, the boy had a glistening pink ulcer the size of a coin, with slightly raised edges. Nearby were whitish, warty splotches. Mitjà also checked Jeremiah's arms, hands, and the soles of his feet; they looked fine.

Jeremiah's mother didn't seem overly concerned. The ulcers were common, and she said she hadn't taken the child to a clinic. "Does Jeremiah play with the other kids?" Mitjà asked. She nodded. "Does he go to school?" No, she said—not yet.

The ulcers and splotches, or papilloma, are symptoms of a tropical skin disease called yaws, Mitjà's professional and personal obsession. Yaws affects people in hot, humid areas in PNG and at least 13 other countries in the western Pacific Ocean, Southeast Asia, and Africa. The disease is caused by the bacterium *Treponema pallidum* subspecies *pertenue*, a close relative of the organism that causes syphilis, and it spreads primarily through skin contact, often between children. Yaws isn't fatal, but if left untreated it can disfigure the skin and bones, causing lifelong pain and disability.

When Mitjà arrived in PNG in 2010 to work at a local clinic, he had no idea what yaws was; the disease was so neglected that it didn't appear on many lists of neglected tropical diseases. And yet eradicating it was once a major global public health goal. In

PHOTOS: (LEFT TO RIGHT) WHO; BRIAN CASSEY

Yaws hangs on in Papua New Guinea decades after a global eradication effort (left). Oriol Mitjà, whose work has triggered a new effort, examines a young patient named Jeremiah, who has an active infection, but can be cured with a dose of azithromycin (right).

the first half of the 20th century, colonial health administrators recorded staggering numbers of cases—an estimated 50 million worldwide in 1952—in 90 countries girdling the equator (see map, p. 218). Then, in 1948, scientists discovered that a single injection of penicillin cured yaws, and in 1952, the World Health Organization (WHO) in Geneva, Switzerland—founded 4 years earlier and brimming with optimism—embarked on an audacious plan to wipe it out.

But the campaign fizzled out in the 1970s and '80s. Penicillin had its drawbacks. The injections—in the buttock, with a thick, hollow needle—are painful and can introduce bloodborne pathogens if not done safely; penicillin allergy is a problem as well. After cases had been slashed by some 95%, the campaign became a victim of its own success. Yaws faded from a global priority to a forgotten disease.

That is now changing, thanks largely to Mitjà, an assistant professor at the Barcelona Institute for Global Health (ISGlobal) in Spain. In 2012, he published a paper in *The Lancet* showing that yaws can be cured with a single dose of the oral antibiotic azithromycin. That much safer and easier treatment can be given not only to infected people, but also to entire at-risk populations. The study—"perhaps the most important [paper] on yaws in the past 50 years," as David Mabey of the London School of Hygiene & Tropical Medicine (LSHTM) wrote—revived the dream of eradication. WHO is now spearheading a new global attack plan. If it succeeds, it would be a major feat, because only one human disease has been eradicated: smallpox, in 1980. (Campaigns to end polio and Guinea worm disease are in their final stages.) Yaws would also be the first bacterial disease to be wiped out.

But success isn't guaranteed. The scale of the challenge is uncertain because no one knows how many yaws cases remain—or just how many countries are still afflicted. Global health's usual benefactors, having

picked other priorities, have refused to open their wallets. And some scientists say Mitjà and WHO ignore an inconvenient fact: Unlike other agents marked for eradication, the yaws bacterium—or a close relative—also infects monkeys and apes, suggesting the disease could jump back into the human population at any time.

Those questions haven't deterred Mitjà, whose tireless campaign—mixing science, medicine, and advocacy—has made him a celebrity in Catalonia, his native region of Spain. This spring, together with PNG health officials and with modest funding from a group of donors, he launched the first of three mass treatments with azithromycin, each 6 months apart, to test the feasibility of eradication. Jeremiah's village on the island of New Ireland is part of the study area. "Tomorrow, a team will come with yaws medicine. Everybody will get the drug," Mitjà said after the boy, now smiling faintly, had hopped off his lap. "Jeremiah's ulcers will be gone within a few weeks," he promised the boy's mother.

IN 2010, A MEDICAL CENTER on Lihir, a very remote island, advertised a temporary position for a doctor. About one-third the size of New York City, Lihir has 18,000 inhabitants and one of the world's biggest gold mines, operated by an Australian company named Newcrest Mining Limited, which also supports the clinic. Mitjà, who had finished his residency and taken a course in tropical medicine at LSHTM, answered the ad.

Mitjà grew up in a small town 40 kilometers northeast of Barcelona. He loved travel and languages, and as a medical student at the University of Barcelona he spent 3 months at a rural clinic in the state of Punjab in India—a "life-changing experience" that strengthened his desire to work on tropical diseases and help the poor. Lihir had both, in abundance. The local population has not benefited much from the riches dug up here; few villages have electricity or running water, and living conditions are unhygienic. But Mitjà wanted to do science as well as practice medicine. "He came to me and said, 'Look, if I take this offer, do you think we could attach a research component to that?'" says Quique Bassat, Mitjà's Ph.D. supervisor and mentor at ISGlobal. "I said: 'Yeah, but I have no clue what you could do there.'"

Bacteria from yaws ulcers can infect another person when they enter through wounds or scratches.

Mitjà found his answer in yaws. "When I saw the first case, I asked the health workers whether they knew what it was. It was embarrassing because I was the expatriate doctor supposedly helping them," he says. But he was drawn by the idea of focusing on a forgotten disease—a PubMed search turned up mostly old studies—and he loved Lihir, with its lush vegetation, mountainous interior, and friendly people. "I was really moved by the conditions of the people here. I wanted to do something to help," he says.

Yaws often starts with a single ulcer, which can last for months if not treated; in the second stage, lesions can turn up elsewhere on the body, as they had in Jeremiah. In the long term, the bacterium can infect joints and the outer layer of bones, causing them to swell. It also can cause painful hardening of the skin on the palms and soles of the feet, as well as eruptions on the face.

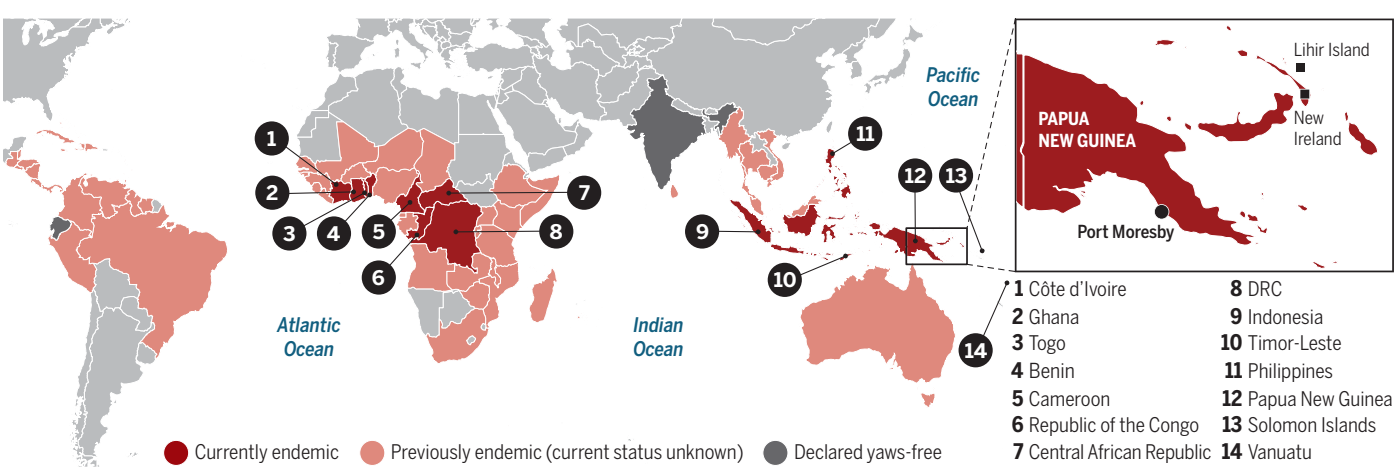
One afternoon in May, Mitjà went to see a 15-year-old Lihir boy named Stanis Malom, who had suffered long-term damage from yaws. The bacterium had caused a symptom sometimes called saber shin, in which the shinbone curves forward. This had likely made the leg prone to tearing of the skin, Mitjà said, and caused a permanent open wound the diameter of a teacup, which he covered with a bandage.

Stanis had stopped going to school because of the pain, his father said, and was now helping him grow vegetables. (Mitjà believed the stigma of disease may also have played a role.) Stanis had been treated with antibiotics and no longer had yaws, but the damage had been done; the open wound made him vulnerable to all sorts of infections. In a richer country, an orthopedic surgeon might be able to repair the leg—"You'd have to break the bone and put it back together in a better position," Mitjà said—but that option did not exist here. "The bottom line is, he's not going to have a happy life."

IN THE LATE 1940s, when antibiotics were new, public health experts began to think big. At the First International Symposium on Yaws Control, in Bangkok in 1952, they discussed how to set up a massive, modern campaign to fight the disease across the tropics. "This symposium marks the coming of age of yaws and the passing of its con-

Unfinished business

Sixty years ago, yaws affected a broad belt of countries around the equator. An early eradication effort sputtered out, and the disease persists in at least 14 countries. It may be present in others; so far only Ecuador and India have been declared yaws-free.



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trol from the enthusiastic amateur to the professional slayer of dragons," one scientist gushed in *The British Medical Journal*. "The purpose of the campaign will be the eradication of yaws from the community, not merely its reduction to some ill-defined low endemic level," another wrote.

Their optimism was understandable. One shot of benzathine benzylpenicillin effects a seemingly miraculous cure, especially in children. "The ulcers just melt away—it has always fascinated me," says Donald Hopkins, a former director of health programs at The Carter Center in Atlanta, who saw lots of yaws cases in Sierra Leone in the 1970s.

Between 1952 and 1964, a campaign supported by WHO and the United Nations Children's Fund screened more than 300 million people in 46 countries, treated more than 50 million, and slashed the number of cases by an estimated 95%. But efforts in the 1960s and '70s to integrate the military-style program into developing countries' own fledgling health systems failed. Even as cases of yaws dwindled, other, deadlier diseases, including HIV/AIDS in the 1980s, were becoming more urgent. The campaign also had an inbuilt flaw. Most countries treated only patients with visible symptoms, along with their contacts. But for every active case, five or six latent carriers may exist whose disease can reactivate, sometimes many years later, and infect others.

On Lihir, Mitjà set out to find a better and easier cure. Azithromycin, an antibiotic not available in the 1950s, was a logical candidate. Most antibiotics destroy bacteria only when they multiply; because *Treponema* divides slowly, once every 30 hours or so, a single-dose antibiotic can work only if it has a long half-life, as intramuscular penicillin does. Azithromycin fits the bill, and in a trial with 250 children, Mitjà showed that a dose of 30 milligram per kilogram of body weight works just as well as the painful penicillin shot.

Mitjà told WHO about his findings before *The Lancet* published them. "We were very thrilled," says Kingsley Asiedu, a medical officer responsible for yaws in the agency's department of control of neglected tropical diseases. The finding promised to revolutionize yaws control, Asiedu says: "A single dose, no more injections—that means you can treat populations very quickly." And that would help get rid of the latent cases.

WHO had never officially called off the eradication campaign—that would have been admitting defeat—but for all practical purposes it had stopped. After hearing about the findings from Lihir, the agency included new, bold targets in its 2012 global road map for neglected tropical diseases: Countries in Asia and the western Pacific Ocean could get rid of yaws by 2015, and those in Africa by 2020. Asiedu also invited Mitjà, Mabey, and other experts, as well as health officials from affected countries, to discuss a new plan to reach those goals. (It was named the Morges Strategy, after the medieval town on Lake Geneva in Switzerland where they met.) Optimism was back.

Pilot projects got underway in several countries. Researchers from the U.S. Centers for Disease Control and Prevention and Ghanaian health officials set up a mass treatment study in Ghana—Asiedu's home country, heavily affected by yaws. In the Solomon Islands, mass administration of azithromycin was already planned for another disease, trachoma; LSHTM researchers decided to track how the drug affected yaws. And Mitjà turned Lihir into a giant lab by setting up an island-wide mass treatment program. In April 2013, teams of health officials and volunteers swarmed out to all 28 villages to give azithromycin tablets to the entire population. The effort treated 83% of the population. After 12 months, the number of active cases had dropped from 323 to 33, the team reported in 2015 in *The New England Journal of Medicine*—an almost 90% reduction. The outcome was good, if not stellar.

That result also led to a research revival. Mitjà recruited new collaborators, including Sheila Lukehart, a syphilis expert at the University of Washington in Seattle, and Michael Marks, a young scientist at LSHTM who had worked in the Solomon Islands. The scientists studied diagnostic tests, epidemiology, and the feasibility of eradication. In PNG, Mitjà's work was welcomed, says Wendy Houinei, a health extension officer with the PNG Department of Health in Port Moresby, the capital. "Yaws is an important public health problem, and he made it a priority," she says. Houinei says she especially appreciates Mitjà's efforts to help build up local research capacity and clinical expertise. "He's also very easy to get along with," she says.

Stanis Malom's (center) untreated infection caused an open wound on his shin. He no longer attends school.

PHOTO: BRIAN CASSEY

But the work took a personal toll. Getting anything done in PNG can be exhausting, he says, and being away from his partner, Sergi Gavilán, for 8 months a year made it harder. "I missed him and my family so much that at one point I was very close to leaving Lihir." In 2015, the University of Barcelona agreed to give Gavilán a position as an administrator to help with the project. "Now, I don't think about going back to Spain," Mitjà says.

Meanwhile, his work attracted attention back home. A 2015 documentary about Mitjà stole many hearts—especially in Catalonia, a fiercely independent-minded region that loves its heroes, Bassat says. "People saw a sweet, young guy, very hardworking, ready to sacrifice himself by going and living in this crazy faraway place." The documentary also helped Mitjà raise donations, from both charities and private citizens, some as small as €20.

Children in Papua New Guinea are at high risk of yaws. The earlier eradication effort failed to treat kids with symptomless infections, who could later spread the disease.

PHOTO: BRIAN CASSEY

Some news stories in Spain cast Mitjà as a lone hero who would singlehandedly eradicate yaws within a few years. "This is a very dangerous thing," Bassat says. "I told him, 'You need to be careful with these headlines because it's going to bounce back if you don't succeed.'"

NOBODY BELIEVES WHO'S 2020 target is feasible—"I always thought it seemed rather ambitious, to say the least," Mabey says. (Asiedu says WHO may soon set a new deadline.) Adding to the concerns, the Lihir experience showed that one massive round of azithromycin isn't enough because too many people are missed. That's why Mitjà's team is now trying three rounds of mass drug administration (MDA) at 6-month intervals in a district on New Ireland that's home to some 60,000 people.

The team is finding that mass treatment in a poor country takes persistence. New Ireland sits about 80 kilometers from Lihir; a speedboat covers the distance in 2 hours. Mitjà, suffering from seasickness, sat on the deck with his eyes closed almost that entire time, his head propped up on a folded mosquito net. Gavilán sat next to him, but the roar of the engine made talking almost impossible. Accompanying them was a Spanish Ph.D. student from the University of Lisbon, Camila González-Beiras, who had spent several weeks training 20 teams of local health workers and volunteers—some 100 people altogether—to administer the drug. The next day, a driver took González-Beiras and Mitjà to the outskirts of a town named Namatanai, to see one of the teams in action on its first day.

Things weren't going well. Only three people from what was supposed to be a five-member team had shown up at the site, a small field surrounded by a few simple homes. Just two dozen people had gathered, waiting for the distribution to begin. Mitjà looked alarmed. "There should have been hundreds of people here already," he says. The team leader, a PNG scientist named Michael Soi, said the group had problems getting organized and people weren't very motivated to come. The island had also recently seen a mass treatment campaign against lymphatic filariasis, and a certain fatigue had set in. Mitjà wasn't buying it. "We need 100% coverage," he exhorted, "otherwise, we will not have eradication."

"We will try," Soi said, "but this is Papua New Guinea."

At last, an older woman began to dispense azithromycin tablets from a big jar, noting each person treated. To determine the success of the operation, recording the number of yaws cases at the start was vital. So whenever the team found someone with an active ulcer, Helen Soi, a nurse and Michael's wife, did a diagnostic test that took about 20 minutes. It required a series of steps she hadn't fully mastered; Mitjà had to walk her through the entire procedure as more ulcer patients were lining up behind her.

After a while, dozens more people started to arrive—"This is beginning to look more like an MDA," Mitjà said—but the scene also became more chaotic. Mitjà tried to get the newcomers to line up and asked Michael Soi to help. "Michael, you support your team now? Because they are stressed out," he said. "You organize it."

"I'm glad you got to see that," Mitjà said later, in the van heading back to the village. "This is also part of an eradication. It's not always easy." "It was a disaster," González-Beiras said at dinner the next evening.

But later she and Mitjà sounded a more positive note. It was only the first day of the 2-week program, Mitjà said; González-Beiras added that teams elsewhere on the island had run a very smooth operation. Her draft report about the mass treatment effort, finished in July, said almost 80% of the target population had been treated in the first round. Asiedu says he expects the second and third rounds, 6 and 12 months later, to do better.

THE MICROBE ITSELF could introduce new obstacles. In a follow-up analysis of the Lihir mass treatment program, published last February, Mitjà and colleagues showed that resistance to azithromycin had developed in five patients. They were all in one village, suggesting that the bacteria in one patient developed resistance, which then spread to others. The finding will complicate eradication plans and make them more expensive. After doling out the pills, teams will have to follow up on every patient to check whether their ulcers have healed. If not, a traditional penicillin shot is in order.

Meanwhile, Sascha Knauf of the German Primate Center in Göttingen has questioned whether eradication is even possible—at least in the traditional sense. According to the International Task Force for Disease Eradication (ITFDE), a respected think tank at The Carter Center, a disease isn't "eradicable" if it occurs not only in humans but also in animals; in such cases, the best achievable result is "elimination as a human health problem" or some such. Old studies, as well as recent ones by Knauf, show that the same subspecies of *T. pallidum* also infects chimpanzees, gorillas, and smaller primates in Africa. The bacterium might be able to jump to humans—for instance, when somebody slaughters an infected monkey. In a study published in 1971—and now considered unethical—researchers inoculated people with *Treponema* bacteria from West African baboons and found they could cause an infection. Yaws eradication planners "are not thinking about this from a one-health approach," Knauf says, referring to the notion that animal and human health are inextricably linked.

The issue has led to fierce arguments. Asiedu is so annoyed by Knauf's papers that he prefers not even to discuss them. No evidence exists of yaws jumping from primates to humans in nature, he says. "As long as they haven't shown that, it's a distraction," he says—one that could sap enthusiasm for eradication. Knauf, who calls the debate "very political," says finding watertight evidence for species crossover is going to be hard because such events are probably rare—but that doesn't mean they don't happen. Hopkins, a member of ITFDE, says he too has "worries" about the natural reservoir.

Money is another concern. Some countries may be able to finance eradication themselves—Indonesia already did one mass treatment—but many others would need help. A 2015 cost-effectiveness study by WHO health economist Christopher Fitzpatrick put the cost of eradication somewhere between $75 million and $1 billion; given the disease burden, "that's within the ballpark of the best buys in global health," he says. And raising money and awareness "should not be that hard," says Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston, Texas, a successful campaigner for other neglected tropical diseases himself.

The new eradication effort is based on mass drug administration. Volunteers dole out antibiotic tablets to everyone, regardless of whether they show symptoms.

PHOTO: BRIAN CASSEY

But that isn't the experience Mitjà and WHO have had. "We've knocked on everybody's door," Mitjà says. The Bill & Melinda Gates Foundation has declined: It's sticking to a list of 10 diseases included in a 2012 agreement called the London Declaration on Neglected Tropical Diseases, a spokesperson says. The Carter Center, which is underwriting the fight against Guinea worm disease, needs to finish that job, Hopkins says. "An enlightened philanthropist could singlehandedly fund the eradication," Fitzpatrick says. "It has been a surprise that there hasn't been a taker." On the upside, a big Brazilian pharmaceutical company named EMS last year pledged to donate 153 million tablets of azithromycin.

FOUR WEEKS AFTER the start of the New Ireland study, Mitjà and Gavilán were back in Barcelona. On a Tuesday evening in late May, they strode into Catalonia's National Theater for a gala. Mitjà wore a yellow ribbon signaling solidarity with Catalan politicians in prison or exile after last year's constitutional crisis. The newspaper *El Periódico* was about to announce its Catalan of the Year 2016 award. (The event was supposed to be held in 2017, but was postponed because of a strike.) Mitjà was one of three finalists, competing against a cartoonist and a priest known for his social work.

Just 4 days earlier, Mitjà had bagged a Medicines & Solidarity Award from a health insurance company, in the presence of former Spanish Queen Sofía. Tonight's event had plenty of VIPs as well. Catalonia's new president, Quim Torra, gave a speech. Thunderous applause erupted when the evening's emcees tore open an envelope and announced that Mitjà, seated in row 7 with his family, had won. Mitjà's face turned red, and he cried as he made his way to the stage.

In his acceptance speech, he recalled police violence against Catalans during the 2017 referendum on independence before he addressed inequities in global health. And he made a plea for money: "It is within our reach: Catalonia can become an even stronger force for solidarity," he said. "And if we achieve our goals … we will have eradicated the second disease in history." Afterward, at a reception, people approached Mitjà to take selfies; women he didn't know hugged and kissed him.

The contrast was striking. At home, his fight against yaws had made Mitjà a star and turned *pian*, Catalan for yaws, into a household word. But in the wider world, the disease remained almost as unknown as it was 8 years ago. Mitjà's hopes that the 2015 documentary would trigger an international breakout had not come true; its producers have been unable to sell an English version outside of Spain. "Making people aware of this disease, not only in Barcelona but also in the rest of the world," he said, "that would be my dream." ■

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A second chance

Martin Enserink

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