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Strep A bacteria kill a half-million people a year. Why don't we have a vaccine?

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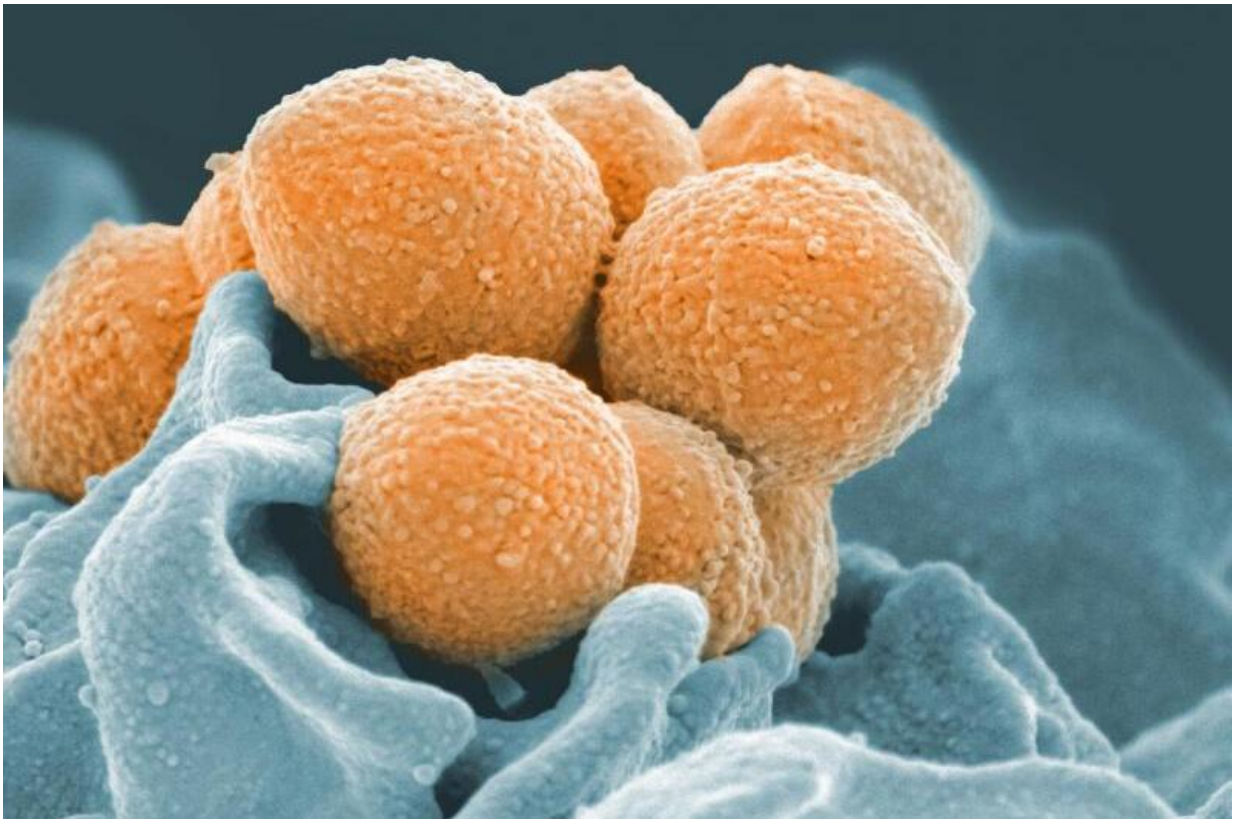

A scanning electron microscope image of Group A Streptococcus (orange) during phagocytic interaction with a human neutrophil (blue). Credit: NIAID

Looking back, Otto remembers struggling to breathe when he was as young as four. Exertion would make him cough, and the coughing fits

would go on and on. Growing up in a family of eight children in a village in northern Uganda, he would try to run and play with other kids. But usually he ended up collapsing or needing to rest.

At age ten, he passed out while riding a bus to a mill, where he was supposed to grind maize for his family. By the time he was a teenager, running 100 metres would wipe him out. His heart would race and he would sweat profusely. He was often dizzy.

Over time, Otto sought medical help, and he received treatment – for both bronchitis and malaria. But he never really got better. Then in March 2017, a doctor took ultrasound images of his heart and finally gave him a diagnosis that explained everything: he had rheumatic heart disease – an irreversible illness caused by group A Streptococcus bacteria. He was 22.

"All of those years, I suffered a lot of pain, stopping me from playing games, kicking the football, running and so on," says Otto, now a 24-year-old schoolteacher in the Ugandan city of Gulu. "The condition stopped me from playing like people play."

Group A strep, or strep A, ranks among the most destructive pathogens on Earth, rivalling malaria parasites, tuberculosis bacteria and HIV. In high-income countries, it's normally associated with the knife-swallowing pain of strep throat, a nuisance that is often cleared with antibiotics. But in lower-income countries, infection is more common and people are less likely to receive effective treatment. Repeated and untreated infections can then lead to rheumatic heart disease, which causes the heart valves to leak.

Rheumatic heart disease used to be a common cause of death in the West, often striking when people were in their early 20s. It has now been largely eradicated in Europe and North America, thanks in part to the

regular use of antibiotics. But the disease still hits hard elsewhere, affecting more than 33 million people globally and killing around 300,000 each year. Taking into account other, invasive conditions caused by strep A – such as streptococcal toxic shock syndrome, sepsis and 'flesh-eating' necrotising fasciitis – strep A's annual death toll stands at over half a million.

It's a public health catastrophe – and one that's crying out for a vaccine. Experts say making one is feasible – there have been some recent breakthroughs, and several vaccine candidates are in trials – but actually having a vaccine available has remained on a constantly retreating horizon for decades.

As the lab work goes on, some researchers have been looking for other ways to confront the ongoing crisis of rheumatic heart disease in low-income countries. Among them is Andrea Beaton, a 39-year-old paediatric cardiologist whose team is conducting an intensive trial with children in Uganda. They're looking to see whether the disease can be slowed, stopped or even reversed – before another generation becomes like Otto, threatened by heart failure in the prime of life.

On a hot Thursday afternoon in July, a white 10-passenger van pulls up to Gulu Prison Primary School, which is named after a prison down the road and enrols about 500 kids aged 5 to 13.

Now a bustling city with coffee shops, an Ethiopian restaurant and hotels with swimming pools, Gulu was until recently at the heart of an insurgency run by the Lord's Resistance Army (LRA), a rebel group that has waged a decades-long guerrilla campaign against the Ugandan government. Infamous for kidnapping children and turning them into soldiers and sex slaves, the LRA killed Otto's father in 2004, making him one of more than 100,000 casualties of the conflict. The group was mostly driven out of Uganda over a decade ago.

As the region has slowly recovered, Gulu has drawn increasing numbers of NGOs and other foreign organisations, including a team from the Children's National Health System in Washington, DC, led by Craig Sable. For years, Children's National has been helping facilitate surgeries for Ugandan children with congenital heart defects.

Andrea Beaton, until recently based at Children's National, first arrived in Gulu in 2013. Her initial plan was to focus on rheumatic heart disease, but she quickly realised that she needed to pay attention to strep throat too. Energetic and friendly, Beaton had visited schools with colleagues to ask children if they had sore throats. "Everyone threw their hands in the air," she says. "We were shocked. We thought, man, we have really been ignoring this."

A closer look showed just how common strep throat was in the community. In a pilot study, Beaton found strep A in the throats of 50 per cent of kids with sore throats and in 30 per cent of all kids, including those with no throat pain. She estimates the average Ugandan schoolkid has at least one and possibly as many as four cases of strep throat each year, compared with just 15 per cent of kids getting a strep infection each year in the US.

"It's a huge amount of strep compared to what we see in the US, and none of those kids are seeking treatment," Beaton says. "They're just hanging out in school."

Although the penicillin family of antibiotics is highly effective against strep A, many Ugandan families instead visit traditional healers, whose treatments include scraping tonsils with a spoon or a sharp piece of wood until they bleed. If parents do seek out antibiotics, they might just buy two pills of penicillin, not the full course necessary to clear an infection.

If strep throat is left untreated, it can lead to an overactive immune

response, sparking an illness called acute rheumatic fever, where antibodies damage the heart valves. Once a child's body overreacts once, it will overreact to every subsequent infection. Rheumatic heart disease is the end result.

"You can have extremely severe heart involvement the first time you get rheumatic fever, but the most common presentation is that you get little bits of heart damage over time," Beaton says, which means there's a silent period between when heart damage begins and when symptoms appear. "By the time you are in your teenage years, you walk in with heart failure and advanced heart disease."

The problem is widespread in Uganda. In the capital, Kampala, Beaton's team documented rates of rheumatic heart disease totalling about 1.5 per cent of the population. When they screened kids in Gulu, they found rates twice as high. In low-income countries like Uganda, across the population the likelihood of dying from the disease is around four to five times higher than in high-income countries.

Beaton and her colleagues have launched a trial to try to disrupt the progression from strep infection to heart disease. They also want to figure out how to intervene earlier – at the beginning of that silent period when heart damage starts to accumulate. By the time people in Uganda get a diagnosis of rheumatic heart disease, Beaton says, 85 per cent are in a severe condition.

To begin with, the team needed to find children with the earliest stages of heart disease. So, from last June, they began visiting as many as seven schools a day.

When the team's van arrives at Gulu Prison Primary School, students in maroon uniforms fill the courtyard, enjoying the end of their lunch break. Half a dozen American and Ugandan nurses, project coordinators

and doctors file out and into a classroom, where they move benches to make room for padded exam tables and a mat on the floor. The screeners, mostly doctors volunteering for a week from the US, sit at stations with portable echocardiogram devices, each with a white wand connected to an iPad-sized screen. The devices, Beaton and colleagues found in a 2015 study, are over four times better than stethoscopes at detecting early-stage heart damage.

As rhythmic sounds of drums and xylophones waft through the schoolyard, three or four students at a time lie on their left sides, heads on elbows, while screeners squirt gel onto their chests, press the wands over their hearts and pull up grainy grey images that show their valves opening and shutting. Some kids crane their heads to see the splotches of red and blue that indicate the direction of blood flow. Each screening takes about a minute.

About 15 minutes into the session, a lean and muscular 16-year-old boy in maroon shorts and brown boots stretches out on a table in front of Marco Costa, a gregarious cardiologist based at Case Western Reserve University in Cleveland, Ohio. Costa finishes the scan and sends the boy off, saying, "Go play soccer!" Then he points at a splotch of blue pixels on the screen: blood leaking through the valve in the wrong direction.

"The valve is opening, and the objective of the valve is to close," Costa says. "He doesn't have disease yet, but if we don't treat it, he will in five to ten years."

Costa checks the "abnormal" box on a piece of paper, which will then go to the boy's parents, encouraging them to come to the project's clinic in Gulu for a follow-up screening with better equipment. Thanks to years of trust-building work in the region, parents welcome the care. If the diagnosis is confirmed in the clinic, the family will then have the option of enrolling their son in the next stage of the trial.

By 4.30pm, the team have screened 401 kids and flagged 13 with potential rheumatic heart disease. Overall, the trial has screened the hearts of more than 102,000 schoolchildren, reaching its goal of finding 916 kids with early-stage rheumatic heart disease who can be enrolled into the next stage, being randomly assigned into one of two groups.

Half will get monthly shots of penicillin, which is standard treatment for patients in advanced stages of the disease but which has never been tested during early phases, when heart damage has begun but symptoms of it have yet to appear. The other group will get education and healthcare but not antibiotics. "Every kid in that trial will show up one Saturday a month," Beaton says. "In two years, we should know if penicillin makes a difference in those children."

It's a complicated endeavour. Families in Gulu often can't afford the costs of travelling to clinics. Many don't have mobile phones. And many kids diagnosed are ineligible to take part because their disease is too advanced or they are already taking daily antibiotics for HIV/AIDS, among other disqualifications. "We are finding a ton of kids with disease that is too severe," Beaton says. "It's really depressing."

Should the treatment work – slowing, stopping or even reversing the progression of rheumatic heart disease by preventing further strep A infections and allowing the heart to heal – it will offer powerful justification for investing in screening programmes and distributing penicillin injections. If the treatment doesn't help, it might make sense instead to scrap the screening efforts and find new strategies for battling the disease.

A vaccine would be one such strategy. Preventing kids' immune systems from having to fight off strep A again and again would save health workers the trouble of scouring schools, educating families and keeping track of children who need shots, month after month, for years.

"Teaching children to treat sore throats will help, but if you could prevent the body from ever seeing strep, that's how you actually get rid of disease," Beaton says.

"If a vaccine was widely used and highly effective, we wouldn't be doing any of this."

The hunt for a strep A vaccine began nearly a century ago, at a time when the bacteria were wreaking havoc without discrimination across the world. In the late 1930s, evidence of rheumatic heart disease showed up in 8 per cent of autopsies at New York's Presbyterian Hospital.

Faced with a major public health problem, US scientists began conducting studies for a strep A vaccine. But by the 1940s, despite some alarming outbreaks of rheumatic fever among US troops, improvements in sanitation and housing meant rheumatic heart disease was starting to decline.

Widespread distribution of penicillin pushed numbers down even more. By the late 20th century, even as rheumatic heart disease continued to flourish in low- and middle-income countries, rates of rheumatic fever in the US had dropped to around 5 cases per 100,000 children.

But some US researchers never lost interest in developing a vaccine, says James Dale, chief of the Division of Infectious Disease at the University of Tennessee Health Science Center in Memphis, whose own quest for a strep A vaccine began in the 1980s.

Back then vaccine development was reeling from a major setback. In 1968, a vaccine candidate had supposedly caused acute rheumatic fever in at least two kids enrolled in a trial to test it. It wasn't clear whether the vaccine was actually responsible, but onlookers were spooked, and in 1979 the US Food and Drug Administration (FDA) banned human

testing of strep A vaccines – a ban that lasted nearly 30 years, stalling momentum everywhere.

"There are lots of questions about that trial," says Andrew Steer, a paediatric infectious diseases physician at the Royal Children's Hospital in Melbourne, Australia. But, he says, its consequences were clear: "An FDA restriction's effects are felt widely."

By the time the FDA lifted the ban in 2006, rheumatic heart disease had mostly been forgotten by the public – though the US National Institutes of Health has been unwaveringly supportive of work like his, Dale says.

What's missing is pharmaceutical investment. Drug companies have been unwilling to take financial risks when they can't be sure there'll be a market for a strep A vaccine in wealthy countries, where people know they can turn to antibiotics.

"If we were still having cases of acute rheumatic fever and rheumatic heart disease that were as rampant as they were in the Forties and Fifties, there would be more clamouring for a vaccine," Dale says. "But since that doesn't happen, nobody now gives one hoot about acute rheumatic fever in the United States – or, for that matter, other high-income countries."

But there is a scenario that might ignite that investment: a single vaccine that would work around the world, fighting off the many illnesses strep A causes and at all socioeconomic levels. If it could simultaneously prevent rampant skin infections in Fiji, sore throats in American schoolchildren and the cascade to rheumatic heart disease across low-income countries, it might be put on the list of recommended childhood vaccines – offering drug companies a reason to dole out the money needed.

"The pharmaceutical industry wants only one vaccine – a single silver-bullet antigen that would cover all strep A," says Dale. And it's a puzzle, he believes, that scientists are getting closer to solving. After decades of advances and setbacks, the vaccine search is gaining speed.

Partly this is because rheumatic heart disease is attracting fresh attention. There has been renewed effort to study the burden of the disease, while the World Health Organization, the World Heart Federation and the African Union have made fresh commitments to controlling it, as has the government of Australia, where the indigenous population suffers disproportionately.

At the same time, technological advances have helped a small, dedicated and close-knit group of researchers make new progress against a complicated enemy. Dale's team are leading the way.

One of the biggest challenges in developing a universal strep A vaccine is the bacteria's diversity. There are over 200 known types of strep A, distinguished by their unique M proteins – structures that sit on the bacterial cell wall like fuzz on a tennis ball. Our immune systems have to respond to the different M proteins, or M-types, by producing different antibodies.

M-types explain why kids can get strep throat over and over: they may encounter new types they haven't previously battled. By adulthood, though, strep A infections become less common, suggesting that some immunity develops with age and that a vaccine could be feasible.

In low-income countries, a larger variety of types circulate. Types also vary from region to region, and even from one neighbourhood to another: a 2010 study in the Brazilian city of Salvador found a different distribution in slums than in wealthy areas.

Around the same time, a research group started to collect M-types from across the world in order to work out which types circulate where and which are most responsible for infections, says Dale. The group's discoveries have changed the way his team is approaching the problem.

It now appears that 117 M-types cause about 90 per cent of strep A infections, Dale says, and that they fall into about nine clusters. Immunity to one type offers immunity to others in the same cluster. Historically, attempts to develop a vaccine have focused on getting the body to produce antibodies to one M-type at a time. But the realisation that strep A can be grouped has opened up exciting possibilities.

"We've started an entirely new approach to vaccine development, looking at structure based on similarities rather than differences. We can pick M proteins that will most likely generate the broadest protection," Dale says. "We could finally have a vaccine for the world."

Using modern sequencing and computational techniques, Dale and his colleagues have developed a vaccine candidate that incorporates genes from 30 strains. These account for 98 per cent of all cases of strep throat in Canada and the US, along with 90 per cent of cases of invasive strep A in the US and 78 per cent of invasive cases in Europe. Invasive conditions can strike anyone at any time, regardless of socioeconomics.

In rabbits, the vaccine, called StreptAnova, has provoked the intended immune response. And in lab dishes, it's been effective at killing more than 80 per cent of strains tested, including ones it wasn't designed for. Analyses now suggest that StreptAnova could be up to 84 per cent effective in Mali's capital, Bamako, and 90 per cent effective in Cape Town, South Africa – supporting the idea that a universal vaccine is possible.

Dale's group recently wrapped up early-stage safety trials of StreptAnova

in Canada. He now hopes to move on to testing the vaccine in its target population: adolescents, and then younger children.

The group's M-type lumping strategy isn't the only approach. Elsewhere, researchers are trying to circumvent strep A's confounding diversity by targeting regions of the bacteria that are more consistent from strain to strain. None are as far along in development as Dale's team, though.

The history of rheumatic heart disease's virtual disappearance in the US and other places shows that experts know how to eliminate it, says Mark Engel, an epidemiologist at the University of Cape Town. And yet, decades later, it persists in poor countries. That failure to stop a preventable disease reinforces the need for a new approach. "That's why we need the vaccine," Engel says. "The feeling among many of us is that we just need to get on with it."

The biggest obstacle, according to researchers and campaigners, is the lack of money – a problem caused both by strep A's complexities and by its inequalities. Its health impacts don't fit neatly into a single disease category that can be claimed by a single medical community. Strep A affects children, but it doesn't contribute to under-five mortality – a target category that tends to boost funding for research – while it also affects adults and pregnant mothers. It is infectious, but also chronic and complex, and develops over a long period of time.

Strep A infections take their biggest toll on vulnerable populations: young people, women and those living in poverty. "They are the three groups of people who don't have much of a voice in the global health scene," says Andrew Steer. "It has been left off the agenda."

That agenda, though, is finally set for an overhaul. The WHO is releasing a roadmap for getting a safe, affordable and globally effective strep A vaccine developed and delivered. Researchers are also putting together a

consortium to identify what needs to happen to push for aggressive vaccine development, Steer says. Having a plan after years of neglect means there's now a glimmer of hope for eliminating rheumatic heart disease.

"It's great that we have vaccine candidates, but we don't have very many. As a pipeline, it's pretty thin, unfortunately," Steer says. "What we do have now is some genuine momentum at the global health level. That's a major step forward."

As the vaccine quest continues, Andrea Beaton's battle against strep A involves the routine obstacles of running a trial in Gulu, where, on a quiet Friday afternoon in July, a seven-year-old boy named Steven walks into her team's headquarters. Steven was flagged at a school screening and has come for a follow-up check. It isn't a scheduled clinic day, when Beaton and her team normally do echocardiograms on 100 kids or more. But sometimes, kids come on the wrong day, and the team always welcome them in.

In a cool, quiet room at the back of the single-storey building, Beaton checks Steven's heart with a bigger machine than the ones used for school screenings. Then she wipes the gel off his chest and tells him to sit in a chair next to his mum. Crouching in front of them, she delivers the news: Steven has signs of early rheumatic heart disease.

"It is a very common problem in the community, and the screening programme in the schools was to find kids like Steven before they have a symptom of the problem," she says in English. A nurse named Pam translates her words into the Luo dialect that the family speak.

"It's good you're here today," Beaton says.

The next morning, around 9.30am on Saturday, Steven arrives at a

primary school about 30 minutes' drive from the centre of Gulu. Today is the first day of the next stage of the trial, where the enrolled kids come for three-hour playgroups to receive their treatment, which will happen monthly. The morning is reserved for those getting antibiotic injections, with those in the control group coming in the afternoon. Staff members have brought frisbees, colouring pages, a parachute and other supplies for games that will take place over the course of each session.

Things don't go to plan. Some parents bring neighbours' children along with their own, even if they've been assigned to different groups. Some show up hours early. Others arrive right at the end of their assigned session, even though the kids need to wait around for an hour after getting their shots. No matter when they arrive, Beaton greets the families with a smile.

"Good morning! Thank you for being here."

On name tags, she writes the children's names and whether they should get shots or not. Then she sends them off for games. Inside one of two classrooms, just swept of red dirt and set up for giving injections, she reminds nurses about the emergency protocol if any kids have an allergic reaction to the medication. Then she encourages them to be positive.

"A little energy here, you guys," she says. "Let's see some smiles!"

Making the experience positive for everyone is important: the children need to be injected every month for the next two years to make the trial viable. And Beaton will be back in the US for most of the sessions, so it has to sustain itself.

When it's Steven's turn to get his shot, he lies on his stomach on a padded table and fiddles with a fidget cube, his orange shorts pulled down to expose the flesh on his bottom. When the needle goes in, he

squeezes his eyes, clenches his teeth, and lets out muffled cries. Afterwards, with tears streaming down his cheeks, he says the fear was worse than the pain and that he won't be scared next time. Someday, Steven says, he wants to be a doctor.

Beaton's hope is that Steven and the rest of his cohort will be able to do whatever they want when they grow up – and that they can avoid the pain that Otto has had to endure.

At a follow-up appointment after his initial diagnosis, Otto learned that his only hope would be to have surgery within the year to replace two heart valves. The procedure would cost over 30 million Ugandan shillings (more than US$8,000). His teaching salary paid 150,000 Ugandan shillings (US$40) a month. He didn't know how he would ever pay for the operation. For months, he worried.

Then, about six months after his diagnosis, Otto got what seemed to be a gift from God: news that he had been selected to have surgery for free. Children's National had received grant money to cover a series of valve-replacement surgeries at the Uganda Heart Institute, located at Mulago Hospital in Kampala. Otto was one of seven patients from Gulu picked for the programme.

In November 2017, all seven rode in a bus together on the five-hour drive along a newly paved road from Gulu to Kampala. Otto was the oldest of the crew, and he looked after the others.

In Kampala, the bus stopped at the Mulago Hospital complex, which sprawls up a steep hill just outside of the city's centre. Once admitted, patients and their companions must feed themselves and do their own laundry. Colourful fabrics, draped to dry, cover most of the bushes and fences around the complex.

Otto's surgery took place at 3pm on a Thursday afternoon. It began with an incision in his chest to expose his heart, which was then stopped for more than four hours while his blood flowed through a heart-lung machine and surgeons replaced his mitral and aortic valves with mechanical versions. Otto was out of the operating room at 10.15pm, and after ten days in hospital, he was on his way home.

Although feeling much better since recovering from surgery, Otto still feels limited. He would like to get a better-paying job but is not sure if his heart will allow him to farm or work as a driver. For now, he continues to teach. A vaccine wouldn't make a difference for him. But, Otto says, it would be a huge help for Uganda.

"I can see a great number of people in this country – they are suffering," he says. "If we can be assisted by making that vaccine for us, it would be a good plan."

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