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THE CHASE

How fast can we roll out a Zika vaccine?

BY SIDDHARTHA MUKHERJEE

On a saturday morning in April of 2014, Nenad Macesic, a thirty-one-year-old doctor-in-training, received an urgent phone call from the emergency room of Austin Hospital, just outside Melbourne, Australia. Lean and taut, with a swirl of dark hair, Macesic resembles an aspiring urban d.j. In fact, by night he spun electronica in clubs around Melbourne; by day he was a fellow in infectious diseases. The call concerned a woman in her late forties who had come to the hospital complaining of a fever, headaches, and an unusual rash.

Travel-related illnesses may be an Australian obsession: foreign contagions brought into the country can spread like, well, rabbits. The woman in the E.R. had just returned from the Cook Islands, an isolated spray of atolls in the South Pacific, where she and her husband had been attending a family funeral. Other people at the funeral had been sick with mysterious fevers, but she hadn't made much of it. Now that she was home, though, a mild headache had progressed to a full, persistent throb. Migratory pains appeared in her joints, and an angry, blanching rash—the kind that pales when you press it—was now blooming across her torso.

When Macesic entered her hospital room, the woman, a textile worker, looked more medically stable than he had expected she would. She spoke in measured sentences, with no sign of confusion or delirium. But Macesic was struck by her strange rash—vivid raised red dots coalescing into islands—and the color of her eyes (pink, with streaks of vermillion), which was indicative of conjunctivitis, a symptom of certain viral infections.

Was it dengue? Macesic wondered. Dengue—colloquially known as break-bone fever, because of the intense corkscrews of pain that can occur in the bones, muscles, and joints—is caused by a mosquito-borne virus, and was endemic in the Cook Islands. But the woman's symptoms seemed too mild for dengue: the disease can cause catastrophic drops in white blood cells and platelets, but her blood counts were nearly normal. Could it be chikungunya? Another mosquito-transmitted viral fever, chikungunya can leave its victims with months, or even years, of wracking joint pains. But this woman's joint pains and swellings weren't severe. It was as if she had acquired a milder variant of those diseases—a more temperate cousin. And the conjunctivitis was a tipoff: neither chikungunya nor dengue is usually accompanied by those blood-tinged eyes.

Macesic decided to consult an online reporting system called ProMED, which tracks infectious diseases around the world. Even surfing the site casually takes a fair amount of fortitude: one day this month, there were eleven new reports on the site, including an undiagnosed measles-like disease that killed forty children in rural Myanmar; anthrax outbreaks among deer in Siberia; food poisoning from cyclospora at a Mexican resort; and a form of strep, normally found in horses, that sickened a woman in Washington State and killed her mother.

As Macesic went through previous entries in ProMED's database—malaria in Oman, Lassa fever in Nigeria—he found a cluster of cases in French Polynesia, some six hundred miles east of the Cook Islands, that seemed remarkably similar to the woman's condition: a dengue-like, mosquito-borne viral syndrome, but with a milder course. Those cases had been attributed to a little-known virus called Zika, a member of a family of RNA viruses that includes dengue, West Nile, and yellow fever. (Zika gets its name from the Ugandan forest where the virus was first found, in a monkey, in the nineteen-forties.) Macesic sent the woman's blood to a specialized laboratory for viral analysis.

The next morning, the woman's

ILLUSTRATION BY EIKO OJALA

husband arrived at the hospital, enveloped in the same diffuse, blanching rash. By the end of the week, the woman's blood test had come back positive for the Zika virus. The husband, however, had no detectable virus in his blood: he had seemingly cleared the infection almost completely. In both cases, Macesic noted, the symptoms had also begun to resolve on their own. He figured that the man and the woman had been bitten by Zika-carrying mosquitoes. (The sexual transmission of Zika had been described in one prior case report, but Macesic did not know about it.) Macesic wrote the case up as an abstruse curiosity—a medical "quiz"—for an infectious-diseases journal. "The illness is typically mild and self-limited, with resolution over 1 week," he noted. "In a previous outbreak with 49 confirmed cases of ZIKV, no deaths, hospitalizations, or hemorrhagic complications were reported, but neurological complications . . . have been described."

Medical students are often taught a piece of diagnostic wisdom: "When you hear hoofbeats, think horses, not zebras." But this case, a rare illness that closely resembled common ones, was a classic zebra. Macesic didn't expect to encounter it again—at least, not anytime soon.

It was on March 2, 2015, less than a year after Macesic had seen the two Zika cases from the Cook Islands, that health authorities in Brazil notified the World Health Organization about a viral illness, marked by mild fevers and skin rashes, that was moving swiftly through its northeastern states. By the end of April, nearly seven thousand cases had been reported. Health officials eventually determined that the illness was Zika. One theory, among many, for the virus's appearance in Brazil is that it arrived in 2013, when Tahiti's soccer team, and hordes of fans, descended upon the country for the Confederations Cup. Zika travelled to Brazil, then, as viruses prefer to travel these days—on transcontinental airplanes.

In mid-July, 2015, there was more disturbing news. Forty-nine cases of Guillain-Barré syndrome—a neurological condition, marked by flaccid paralysis, that can be associated with an aberrant immune response to a virus—were reported in Brazil, echoing a sharp increase in the syndrome which was noticed in Polynesia during the Zika outbreak there. Zika had also begun to move through Cape Verde and Colombia. Macesic recalled tracking it on ProMED—"following Zika around the globe had become my small addiction," he told me. "But the most devastating complication, the one that virtually no one had really anticipated, was still to come."

In the late summer, doctors in Brazil noted an unusually large number of babies born with microcephaly. Such babies have smaller heads and shortened foreheads, a result of the inadequate growth of parts of the fetal brain; they can suffer cognitive dysfunction, seizures, developmental delays, and problems with hearing and eyesight. In early November, Brazilian health officials reported a hundred and forty-one suspected cases of microcephaly. By late January, the number of reported cases skyrocketed to nearly four thousand. Alarmed by this sudden rise—in previous years, the nationwide annual incidence had been estimated at fewer than two hundred cases—epidemiologists began to investigate. Scouring through case reports and histories, they converged on a prime candidate: Zika infection during early pregnancy. In some cases, scientists suspect, the virus crosses the placenta, infects the developing brain, and kills nerve progenitors. For Zika-infected pregnant women, estimates of the risk of birth defects range widely, from one per cent to thirty per cent.

"We still don't understand the factors that contributed to the striking number of congenital birth defects seen during this pandemic," Eva Harris, a professor at U.C. Berkeley's School of Public Health who studies dengue, Zika, and other emerging infections, told me. "Possible explanations include the vast number of people infected—a numbers game. There could be other factors, such as the viral strain, the genetics of the host, environmental exposures, or immune-related factors, such as prior dengue infection."

Stevens Rehen, a neurobiologist at the D'Or Institute for Research and Education and the Federal University of Rio de Janeiro, who led one of the first efforts to understand Zika's propensity to attack human nerve-cell progenitors, wondered whether microcephaly might represent the tip of an iceberg of deficits. "A group of radiologists in Brazil have noted changes in the brain's cortex and calcium deposits in the brains of Zika-exposed fetuses," Rehen says. "It's hard to know the extent of the consequences—it might take a few more years to determine the long-term effects in Zika-infected infants *without* microcephaly."

Even the most cautious estimates of harm rise with the incidence of infection. Teams of scientists, including Rehen's, are hunting for medicines that might work against Zika. And public-health experts have been dispatched to eradicate reservoirs of breeding mosquitoes. Those efforts might help—but there's little that can stop an epidemic in its tracks as effectively as a vaccine.

"The first time I thought seriously about Zika was January, 2016," Dan Barouch told me. Barouch directs the Center for Virology and Vaccine Research, at Beth Israel Deaconess Medical Center, in Boston. It was a muggy July morning; the sky threatened a downpour, but would not deliver. The corridors of the lab were lined with newspaper pictures of the black-and-white striped mosquito *Aedes aegypti*, the predominant carrier of Zika. Signs outside one of the laboratory doors read "Zika Work Ongoing" and "No Food or Chewing Gum." On a whiteboard, someone had scribbled a cartoon version of a virus: a blob with spikes sticking out, like a hundred antennae.

"If you had come to the lab back then, there would have been no mosquito pictures, and no mention of Zika," Barouch said. "No one was working on Zika, and barely anyone had even heard of it. I'm board-certified in infectious diseases and I've worked in virology for more than a dozen years, but I had never seen Zika mentioned outside a textbook." It was, he said, "like watching a stampede of zebras."

When Barouch heard about the cases being reported in Brazil, he began to search through GenBank, a public database of genetic sequences, and found the sequences of four Zika strains. "The first thing that struck me was the genetic similarity between the strains," he recalled.

For Barouch, who has spent nearly a decade trying to develop an H.I.V.

vaccine, the contrast between Zika and H.I.V. was particularly illuminating. "If you look at H.I.V. sequences, there's enormous variability between one strain and the next," he said. "In one infected person, some subpopulation of the virus might be changing every day." H.I.V. is also designed to thwart an immune response; the virus integrates itself into the genome and kills the very immune cells that threaten it. The Zika virus seemed a much more tractable target. For one thing, it didn't seem to mutate that much. "That was the first good sign," Barouch said. And when he read the medical-journal articles about Zika—"I must have found Macesic's Cook Islands case reports that afternoon"—he learned that the patients cleared the virus and recovered fully on their own, which was another positive sign. The fact that patients developed *natural* immunity to the virus suggested that if a person's immunity could be boosted prior to exposure it should be able to resist infection in the first place.

In Bethesda, Maryland, Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases (NIAID), was also struck by these two features of the virus, and by the rapidity of its spread. By December, 2015, Fauci had already assembled a group of researchers at his institute's Vaccine Research Center to discuss a Zika strategy. The team included John Mascola, the V.R.C.'s director, a handful of virologists, and other scientists in the institute who had spent years working on a dengue vaccine. "We've made incredibly successful vaccines for yellow fever, and for some strains of dengue," Fauci told me. "Conceptually, there was no reason that a vaccine for Zika would not work."

As news of a looming Zika epidemic swept through the media this winter, Barouch approached Peter Abbink and Rafael Larocca, two researchers in his lab. Abbink, who came from Leiden, in the Netherlands, is the lab's virology expert. Larocca, stocky and affable, with close-cropped hair, is Brazilian; his country's flag, in yellow, green, and blue, is tacked above his lab bench. He had come to Barouch's lab to study H.I.V., but was looking for a new project. Barouch had one for both of them.

That same day, Larocca e-mailed two colleagues at the University of São Paulo, who had isolated Zika virus from the blood of infected patients, used mosquito cells to grow the virus in their lab, and then injected the virus into mice to re-create the infection. As with humans, the infection in pregnant mice had caused microcephaly and growth retardation in their fetuses. The pups had small brains with dying neurons chock-full of the virus; their developing retinas had involuted and shrunk into small gray nubs.

"The Brazilian scientists were immediately interested in collaborating with us on vaccine development," Barouch said. In early February, a vial of frozen Zika virus was shipped from São Paulo to Boston. Abbink thawed the virus and figured out how to coax it to grow in monkey-kidney cells. Then Larocca injected the virus into mice. One mouse strain, the researchers found, was particularly susceptible to infection. Using molecular tools, Larocca and Abbink could track the precise dynamics of the infection in the mice—the proliferation of the virus, the rise of immune factors targeting it, and the eventual clearing of the infection. It was a simple but pivotal breakthrough: they had created an animal model of Zika infection with which to test a pilot vaccine.

A vaccine is an immunological bait-and-switch: you rouse the immune system with something that elicits immunity but does not cause disease. A weakened virus, an inactivated virus, a viral protein, or even something that simply shares a distinctive marker with the virus can be used. The immune system is provoked by the agent and retains a memory of it; when the real pathogen tries to establish an infection, it is swamped by the pre-roused immune system. But which method would work best against Zika?

It was a strategic decision as much as a scientific one. One option was to use a weakened, or attenuated, form of the virus to make a vaccine. By growing the pathogen repeatedly in chicken eggs, say, technicians can make it less virulent in humans. But the process can take months, even years—far from ideal while in the throes of an epidemic.

Inactivating the virus can be a faster process. The virus loses its capacity to infect but still elicits a specific immune response. That response is sometimes less robust than the one provoked by the attenuated virus—hence the agonizing modern ritual of dragging children to get booster shots for some vaccines—but the method has been used to make vaccines for decades.

Barouch and Fauci were also drawn to a newer approach. For more than a decade, vaccine researchers have known that injecting a viral gene into an animal can elicit an immune response. Whole viruses, or their embalmed remnants, aren't needed; here, the inoculum consists of a piece of DNA that encodes a gene or genes from the virus, and pieces of genetic machinery that turn on those viral genes in animal cells. The cells in the vicinity of the injection

"I'll need you to sign this binding agreement acknowledging that you said no, you didn't want any dessert, and that you give up all claim to mine."

take up the DNA, and begin to synthesize proteins associated with the virus. The immune system mounts a response to these antigens.

"Naked DNA" vaccination, as this method is called, has pros and cons. On the one hand, naked DNA is easy to produce in the lab: various genetic parts of a virus can be cloned and tested in animal models to identify the components that provoke the strongest response. But would it be strong enough? "There's a suspicion that it might be less immunogenic than whole inactivated virus," Barouch concedes. A more significant problem has to do with scale. Viruses are, as it were, designed to go viral. One virus replicates to create a hundred viruses—the infection propagates more infection—and an exponential expansion ensues. This growth can be crucial in producing adequate amounts of vaccine for an epidemic in which one human carrier might infect a hundred others. The naked-DNA inoculum, by contrast, is usually produced in bacterial cultures; it's technically challenging to create the material in the necessary quantities.

Despite these difficulties, Barouch saw the promise of the naked-DNA technique. If it could be perfected, dozens of vaccine candidates for dozens of pathogens could be tested without having to grow buckets of those pathogens in labs. The scale-up issues would still need solving, but the painstaking, often artisanal process of growing viruses in tissue culture or in eggs—the tedium of isolation and decontamination, gowns, masks, face shields, doubled-up gloves—would be vastly diminished. If the naked-DNA vaccine works against Zika—"the big if," as Barouch puts it—it will have a transformative impact not just on this epidemic but on vaccine technologies in general.

"It would be a game-changer for vaccinology," Colonel Stephen Thomas, an infectious-diseases physician and a vaccinologist at the Walter Reed Army Institute of Research (WRAIR), in Silver Spring, Maryland, said. "Perhaps the effort to create a Zika vaccine is where the DNA vaccine will demonstrate its potential." At least one trial involving a DNA-based vaccine for H.I.V.—a far more difficult target—failed to show a benefit. And although a DNA vaccine for West Nile virus has been used successfully in horses, no DNA vaccine has so far been licensed for human use. "DNA vaccines may be the vaccines of the future," Barouch said, "but they haven't had much of a track record in clinical medicine so far." Given the uncertainties, he wanted to compare both old-school and new-school vaccines, head-to-head, using the mouse model for Zika infection.

In the third week of March, as the epidemic barrelled ahead in South America, and the C.D.C. was warning pregnant women against travelling to the Rio Olympics, Barouch called Nelson Michael, a physician-scientist and, like Thomas, a colonel in the U.S. Army. A military scientist with steel-gray hair who swaps his lab coat for a blue uniform at official functions, Michael works at WRAIR, and is one of the world's foremost authorities on vaccination. He had collaborated with Barouch in the past—they share a long-standing interest in the development of H.I.V. vaccines—but this was the first time they had spoken about the Brazilian epidemic.

"Have you guys been working on Zika?" Barouch asked.

Michael was on his cell phone in his car, and he pulled into a parking lot. "Every day," he replied. By early January, working with Thomas, Michael's group had acquired a Zika strain from Puerto Rico and started growing the virus in the lab. He planned to use the tried-and-true method of inactivation to make a vaccine.

Tried-and-true doesn't mean straightforward. The inactivation of a virus is as much a culinary exercise as a chemical one. If you "overcook the virus," Michael says, "you can damage it to the point that there's no resemblance to the original, and the immune response becomes useless to combat the native virus." The "cooking" process consists of growing the virus in cells using enormous roller bottles. The liquid containing the virus—more than five gallons of it—is then purified on long glass columns packed with filtering resin. Formaldehyde—the mortuary chemical—is added to preserve the virus's structural components but destroy its capacity to infect cells and reproduce. (Heat or radiation can also be used.) The formaldehyde is then removed, and the inactivated virus is packaged in rubber-topped glass vials, ready for inoculation. Every batch must be tested and retested to confirm complete inactivation: even the barest trace of an active virus in a vaccine might unleash an infection in a vaccine recipient.

Barouch asked Michael whether he would consider collaborating. "We have an animal model to test the vaccine, and we can start testing it anytime," Barouch told him. By the time Michael got out of his car, the deal was essentially done. "It took just one phone call," Michael recalled, still sounding amazed. "That was the sense of urgency in the field." Before long, the first batch of inactivated virus was shipped from the Walter Reed Institute to Barouch's lab.

Different labs have mastery of different techniques. The Walter Reed group had perfected the art of viral inactivation. In Boston, meanwhile, Barouch's team had deftly used gene-engineering methods to stitch together the naked-DNA vaccine. "By April, all the critical pieces to start the real vaccination experiments had been assembled," Barouch recalled. "We had the virus, the mouse model, and two vaccines to test."

Barouch's and Michael's teams were now racing forward with their Zika project. "It became a major focus for all of us," Barouch said. A frenetic energy took over the lab: postdoctoral researchers and graduate students stayed late into the evening, wolfing down takeout dinners and shuttling samples between the centrifuges and incubators.

The vaccination experiments were launched in early April. Larocca immunized the mice with a "sham" shot, the naked-DNA vaccine, or the inactivated-virus vaccine. They waited for four weeks for the inoculum to generate an immune response. Then Abbink—gloved and gowned, draped in a sterile blue smock in the isolation room—prepared the so-called challenge virus, which had been kept in tissue-culture flasks brimming with red broth, and they injected the mice with the virus.

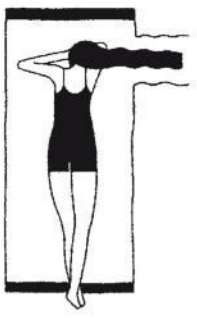
In all the sham-treated mice, the viral load spiked—by tenfold, a hundredfold, and, finally, more than a millionfold in some animals. In the mice that were given either the naked-DNA or the inactivated-virus vaccine, there was no sign of infection. "The viral load was a flat line," Barouch said. Larocca told me,

"We had expected a vaccine response, but not *this* kind of vaccine response."

On May 30th, after confirming that antibodies were responsible for the protective effects, the team sent a manuscript describing the findings to the journal *Nature*. It was speedily reviewed by experts and accepted less than a month later.

The mouse experiments were a run-up to monkey experiments. In late April, a group of macaque monkeys was inoculated with three vaccine candidates: naked DNA, the inactivated virus from Nelson Michael's lab, and a third, "viral vector" vaccine, derived from a cold-causing virus that had been engineered in Barouch's lab to express a Zika gene. Other monkeys were merely given a sham shot. As with the mice, the inoculated monkeys developed immunity: all three vaccines protected completely against infection. Barouch's team tested the body fluids of monkeys that received the inactivated virus. While the sham-treated monkeys exuded virus into their blood, urine, brain fluids, saliva, and vaginal secretions, these inoculated animals had no measurable levels of the virus anywhere. Barouch submitted a paper on the results to *Science*, which reviewed and accepted it in just seven days, the fastest publishing turnaround in Barouch's career.

It's hard to convey the magnitude of what Barouch's and Michael's teams had managed to do—take a little-known virus and develop an investigational vaccine in a hundred and eighty days. The early-phase development of most vaccines, Michael estimates, can take between four and six years. When Barouch and Michael talk about speed, they bring up their years of H.I.V. research. Mouse models, monkey models, vaccine strategies, the molecular tools to track viral loads: every technical element in the work toward a Zika vaccine had been tweaked and tested on the long road to developing an H.I.V. vaccine. As Michael put it, "The playbook was there. The players were there. Teams were formed. We just turned to a new enemy."



Both Barouch and Michael are enthusiastic but cautious about human trials. "The most powerful thing about our studies is not that we developed a vaccine," Barouch says, "but that we've demonstrated that vaccination is feasible." Vaccines that look promising in lab experiments can certainly fail in the field. The inoculum may not stimulate enough immunity to resist the viral challenge. The virus may mutate and become resistant. Or the vaccine can turn out to have unexpected side effects. For Zika, that's a particularly ominous consideration. In the case of dengue, Zika's distant cousin, there's some evidence—debated among virologists—that immunization against one strain might *increase* the severity of disease with another strain. Other studies have suggested that antibodies to some strains of dengue might cross-react with Zika proteins, promoting Zika immunity in dengue-exposed patients. How a Zika vaccine might perform in areas with endemic dengue, or chikungunya, remains an open question. "The most conclusive way to find out," Michael said, "is to challenge animal models with these viruses, but to also test a pilot vaccine in a real trial in the field."

As Barouch and Michael continued their experiments on animal models, NIAID's Vaccine Research Center was experimenting with its own candidate for a naked-DNA vaccine. "These were powerful studies, carried out with intense precision and intense speed," Fauci said, "and they give us a strong hint that there's a real possibility that we might develop a Zika vaccine." But the next steps were the most critical: testing the vaccine in humans.

The V.R.C.'s human trials began on August 2nd. At the N.I.H. Clinical Center, in Bethesda, Mascola and Fauci watched a volunteer—a twenty-nine-year-old woman—receive the first dose of the DNA inoculum. During the Phase I study, eighty volunteers will be given the DNA vaccine so that its safety can be assessed and their immune responses can be monitored over time. Fauci estimates that the V.R.C.'s Phase I study will cost around four million dollars, and will be completed by December. There are several other vaccine candidates in contention. A Pennsylvania-based biotech company, Inovio Pharmaceuticals, has also developed a DNA-based vaccine candidate. Inovio hopes to "enhance the uptake of the DNA vaccine by cells," as Joseph Kim, its C.E.O., put it, thereby triggering a more potent immune response. By October of this year, meanwhile, the Walter Reed Institute will launch a parallel effort to test the inactivated virus in human patients, in collaboration with NIAID, the Biomedical Advanced Research and Development Authority, and Beth Israel Deaconess Medical Center.

"In early 2017," Fauci says, "we will transition straight into the Phase II studies"—controlled trials to compare vaccinated and unvaccinated populations, which will enroll between twenty-four hundred and five thousand subjects. These studies, which may involve DNA vaccines, inactivated viruses, or other candidates, will cost about a hundred and fifty million dollars, and will answer the critical question of whether these vaccines actually work. If those trials go as predicted—if every step goes exactly as planned—the first Zika vaccines may be ready in early 2018 or soon afterward.

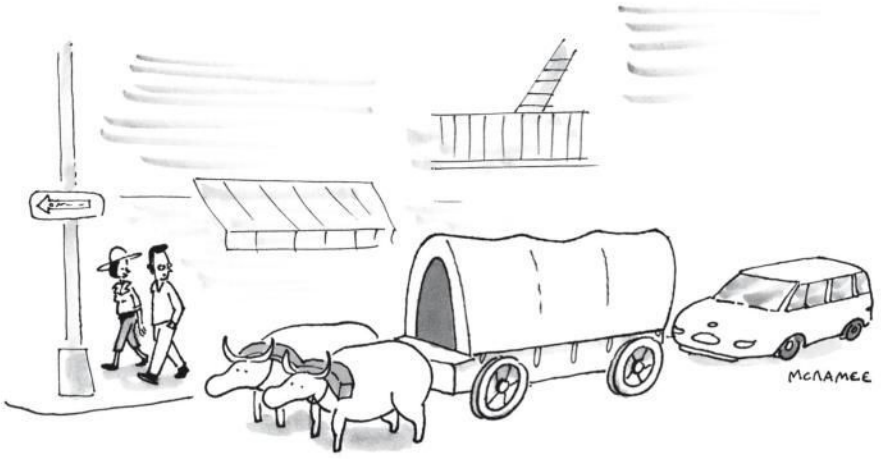
Fauci is frustrated that Congress still hasn't authorized emergency funds for the Zika effort. (President Obama requested $1.9 billion in February.) "We have had to borrow money from other accounts to get our work started," Fauci said. "If we don't receive the requested appropriations very soon, this will slow down the important preparations for the Phase II trial."

Yet, even if a vaccine is shown to be safe and effective, there's the pressing question of how to scale up production. Swerving the course of an epidemic might take as many as tens of millions of vaccinations, even hundreds of millions. Nelson Michael and his team have signed an agreement with Sanofi Pasteur to produce enough inactivated virus for human vaccine trials. "We need an experienced company that can produce inactivated virus in quantity to the F.D.A.'s specifications," Michael said. "It isn't easy to produce."

The DNA-based formulations face particular hurdles here. "We're growing bacteria in five-hundred-litre vats at our facility in Houston, Texas," Joseph Kim, of Inovio, says. One litre of such a culture, he estimates, would yield enough

DNA for about twenty-five to fifty vaccines. (Under standard lab conditions, the yield is about a tenth as much.) Ten million inoculations, then, would require at least a swimming pool's worth of bacteria—achievable, but a formidable challenge.

"There are yet other ways of making vaccines that haven't even entered the picture here," Ian Lipkin, a Columbia University infectious-disease expert, told me. "You can make a vaccine by making a viral protein in yeast or insect cells." Indeed, a host of biological techniques might be tried—but all of these have significant ramp-up times. "It's hard to test all of these in parallel in the midst of an epidemic," Lipkin said.



"You don't give up a spot like that."

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Is it possible that Zika will burn itself out, like a short, hot fuse, before a vaccine can be developed? Natural immunity can actually thwart vaccine development. How do you prove the benefit of a vaccine in a population where most people have become naturally immune through viral infection? (Such a scenario would come at a terrible human cost: thousands of babies born with neurological damage, among other complications.)

The successful *containment* of an epidemic—a public-health triumph—would likewise impede vaccine development. Again, without a cohort of men and women who might acquire an infection, it's impossible to assess whether the vaccine works. "Not everyone appreciates how complex it is to identify and develop potential vaccine testing sites," Stephen Thomas said. "In an animal trial, you can create conditions of experimental infection. But a human trial depends on the occurrence of natural infection." Fauci notes, "That's what happened with Ebola. Containment halted the spread of the infection—a great thing—but it made it difficult to test the vaccine."

There's a strange quandary, then, for the development of certain vaccines. Too fast an epidemic, and a vaccine may become untestable (prospective trial subjects are already exposed and therefore immune, obviating the need for a vaccine). Too slow an epidemic, and the vaccine becomes untestable again (prospective trial subjects aren't exposed to the viral infection at a significant rate, so a vaccine's benefits can't be demonstrated).

Dan Barouch doesn't foresee any such issues with Zika, though. Containment would be difficult: patients often develop only transient, mild symptoms, if they have symptoms at all, and many may not even know that they are carrying the virus, making it impossible to identify and isolate carriers. Nor has it been easy to combat mosquitoes in endemic zones, although a genetically modified strain, designed to produce sterile offspring, has just been released in Florida and may prove helpful. The rapid burnout of the epidemic is also unlikely: Zika is just beginning to reach parts of the world, including the United States, where there is no natural immunity.

In the fall of 2015, Nenad Macesic moved to Columbia University, as a fellow in infectious diseases. Zika migrated as well. This May, Macesic had his third encounter with the virus: a woman in her fifties with the same blanching rash that he recalled so vividly from the Cook Islands cases. She had just returned to New York from a visit to the Dominican Republic. Her sister, the woman explained, had also had a fever and a rash, then had become weak and progressively paralyzed; she was still in an intensive-care unit, likely suffering from Zika-associated Guillain-Barré syndrome. Macesic had the woman's blood tested for Zika. The test was positive. "When I wrote my medical quiz in 2014, I had not imagined seeing another case of Zika for quite a while, but here it was again," he told me.

But the stakes had changed. Macesic is the rare doctor who has witnessed Zika morph from an illness smoldering in a far-flung Pacific island to an international medical crisis. On a recent afternoon, when I met him at his office at Columbia, he recalled the last paragraph of his 2014 article. "It's funny, but that paragraph has turned out to be prescient," he said. Zika virus, he had written, "is an emerging pathogen, and may have the potential to cause endemic transmission. . . . Further study is needed to understand the more rare complications of ZIKV and its propensity to cause future outbreaks."

That morning, there were news reports of ten Zika cases in Florida that may have been transmitted by local mosquitoes. (Prior cases in the United States had been reported in travellers, or in people who had bodily contact with Zika-infected patients.) "The transmission of Zika through mosquitoes is worrisome," Macesic said, "because it suggests the potential of an outbreak in parts of America." On a computer screen, a video recapitulated the movement of Zika throughout the world. It was like watching an already swift-moving epidemic on fast-forward. As the clock at the bottom of the screen ticked from 2015 to 2016 in the course of a few minutes, a series of crimson dots appeared on a map. Macesic pursed his lips as he looked at the advancing front of the infection. Polynesia, the Cook Islands, Brazil, Cape Verde, Colombia, Puerto Rico, and the southern edges of the United States—the screen was soon pockmarked by a rash of dots. ♦