http://nyti.ms/1KxyKmM

Health

How a Medical Mystery in Brazil Led Doctors to Zika

A sudden, sharp increase in babies with “no foreheads and very strange heads” was baffling doctors in Brazil. That set off a search for answers that led to a little-known pathogen, the Zika virus.

By **DONALD G. McNEIL Jr.**, **SIMON ROMERO** and **SABRINA TAVERNISE** FEB. 6, 2016

Something strange was happening last August in the maternity wards of Recife, a seaside city perched on Brazil’s easternmost tip, where the country juts into the Atlantic.

“Doctors, pediatricians, neurologists, they started finding this thing we never had seen,” said Dr. Celina M. Turchi, an infectious diseases researcher at the Oswaldo Cruz Foundation, a prominent scientific institute in Brazil.

“Children with normal faces up to the eyebrows, and then you have no foreheads and very strange heads,” she recalled, referring to the condition known as microcephaly. “The doctors were saying, ‘Well, I saw four today,’ and, ‘Oh that’s strange, because I saw two.’”

Aside from their alarming appearance, many of the babies seemed healthy.

“They cried,” Dr. Turchi said. “They breast-fed well. They just didn’t seem to be ill.”

Doctors were stumped.

They did not know it then, but they were seeing the first swell of a horrifying wave. A little-known pathogen — the Zika virus, carried by mosquitoes — had been circulating in Brazil for at least a year. It would later become the chief suspect in the hunt to work out what had happened to those newborns.

Since then, those tiny babies have led the World Health Organization to declare a public health emergency. They have prompted warnings to pregnant women to avoid countries where the virus is circulating, even to refrain from unprotected sex with men who have visited those countries, following a report of sexual transmission of the virus in Dallas last week.

They have led health ministers of five countries to say something so unthinkable that none had ever uttered it before: Women, please delay having children.

The virus now threatens the economies of fragile nations and the 2016 Summer Olympics in Rio de Janeiro. It has opened a new front in the debate in heavily Roman Catholic countries about a woman's right to birth control and abortion.

And the children stricken with microcephaly, or abnormally small heads, have doctors everywhere asking: What is this virus? How could it have been around for almost 70 years without us realizing its power? What do we tell our patients about a bug that can hide in a mosquito's proboscis and a man's semen, even in human saliva or urine? What do we tell young women who ask if their unborn babies are safe?

"This epidemic is an unfolding story," said Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases. "As with Ebola, this virus is something that could exist for years under the radar, and we don't know until we get thousands of cases what it really does."

"With Zika, we're seeing new twists and turns every week."

To doctors in Recife, whatever was striking the babies seemed to have fallen like a bolt from the blue.

In reality, it had been building for months. It had even been frequently discussed among clinicians — but no one had realized what was on the horizon.

Seeing the Same Symptoms

A year earlier, doctors say, the first patients had started trickling into public hospitals in Natal, capital of the state of Rio Grande do Norte, about 200 miles up the coast from Recife.

It was a few weeks after the 2014 World Cup, and Natal had been one of the host cities of the soccer championship, which draws fans from all over the world.

Many patients lived on the city's margins, others in settlements dotted across the sertão, northeast Brazil's arid hinterland.

Almost all had the same symptoms: a flat pinkish rash, bloodshot eyes, fever, joint pain and headaches. None were desperately ill, but the similarities were striking.

"That scared some patients and doctors, and my team," said Aline Bezerra, a nurse and the municipal epidemiologist. "We knew nothing other than that it might be some kind of light dengue."

Tests ruled that out, along with other common viruses, but the patients kept coming. One day in January 2015, 100 showed up at the state's hospitals.

"We alerted the federal authorities that we were dealing with something urgent and new," said Dr. Kleber Luz, an infectious diseases specialist at the

Federal University of Rio Grande do Norte. “But their reaction was sluggish.”

By last March, the spread of a “doença misteriosa” — the mystery disease — had become impossible to ignore. It appeared in two more states nearby. Then it reached Salvador, a city of 2.5 million.

Doctors speculated that it was an allergy; that it was roseola, a childhood illness; that it was a new variant of Fifth Disease, a facial rash that gives children a “slapped-cheek” look.

“People were claiming it was polluted water,” said Dr. Gúbio Soares, a virologist at the Federal University of Bahia in Salvador. “I began thinking it was something transmitted by mosquitoes.”

Working in his modest lab with a colleague, Dr. Silvia Sardi, Dr. Soares kept testing blood samples.

Other doctors were doing the same. Over 6,800 samples were tested, according to news reports, from victims ranging from 4 months to 98 years old. Parvovirus, dengue, chikungunya and other suspects were all ruled out.

Finally, in April, Dr. Soares and Dr. Sardi were sure: It was Zika.

“I actually felt a sense of relief,” Dr. Soares said. “The literature said it was much less aggressive than viruses we already deal with in Brazil.”

In the capital, Brasília, the health minister at the time, Dr. Arthur Chioro, felt the same way.

“Zika virus doesn’t worry us,” he told reporters in May, after the Oswaldo Cruz Foundation had confirmed Dr. Soares’s findings. “It’s a benign disease.” Dengue hemorrhagic fever, on the other hand, killed hundreds of Brazilians each year.

But on ProMed Mail, an online service run by the International Society for

Infectious Diseases, the reaction was not so sanguine.

"The arrival of Zika virus in Brazil is not good news," wrote Thomas M. Yuill, an emeritus professor of veterinary science and wildlife ecology at the University of Wisconsin-Madison.

Not only did Brazil have "abundant mosquitoes and a large population of susceptible people," he wrote, but so did much of the Americas.

Two weeks earlier, an American mosquito disease expert working in Rio de Janeiro had scoffed on Pro-Med about an unconfirmed report that it was Zika. The virus fit the symptoms, he wrote, but it was circulating only in Africa and Asia, and in the South Pacific, half a world away, in a different ocean.

He was right about where the virus had been, but not about where it was now.

An Island-Hopping Virus

For years, virus hunters on ProMed and other outbreak alert networks had been watching, fascinated, as Zika made long, slow and erratic progress eastward across the Pacific, island-hopping as American forces had done during World War II, albeit in reverse.

In 2007, it hit Yap Island, in Micronesia, just west of the Philippines and north of Australia. It could have come to Yap from anywhere in Asia.

In October 2013, the Zika virus raced through the many islands of French Polynesia, including Tahiti and Bora Bora. In early 2014, it bounced to the Cook Islands, just to the west, and New Caledonia, close to Australia.

It also leapt to Easter Island, home of the giant stone heads, its official arrival in the Western Hemisphere.

It is still island-hopping. American Samoa and Tonga are having

outbreaks now.

Scott C. Weaver, a virologist at the University of Texas Medical Branch in Galveston, wrote an article in 2009 warning that Zika was approaching the Americas. The virus was so obscure that, trying to be helpful in an interview, he explained: “Its closest relative is Spondweni” — a virus named for a place in South Africa that is no longer even on maps.

The Zika Forest in Uganda still is; the virus was discovered there in a monkey in 1947. Since then, the Zika virus had been considered mild compared to its killer cousins: yellow fever, dengue, West Nile and Japanese encephalitis. Until 2013, there was no evidence Zika had ever hospitalized anyone.

Tracking Its Path to Brazil

Back in Brazil, on May 14, it was definite. The mysterious outbreaks — by then in cities all over Brazil, including Rio de Janeiro — had all been caused by Zika.

Who had brought the virus to Brazil? There are two theories.

The first, offered by Brazilian scientists who analyzed airline flight patterns, was that it arrived in the crowds of soccer fans who had flocked to the 12 host cities in the 2014 World Cup. If the Natal outbreak was truly the first, that theory has credence.

A second, proposed by French scientists connected to the Pasteur Institute in Paris who had investigated the outbreak in Polynesia, was that it arrived a few weeks later, during the Va’a World Sprint, a canoe race in Rio that attracted teams from several Polynesian islands.

Since the virus is believed to persist in the blood for up to 10 days, it presumably came from an island then having an outbreak. But in a world as

interconnected as ours has become, it may be spread not by a foreigner from faraway lands, but by any international traveler.

The first case of Zika infection detected in New York City was found in December 2013 — six months before the virus is thought to have reached Brazil — in a 48-year-old traveler who lives near Central Park but has asked to remain unidentified.

When he walked into Traveler's Medical Service on Madison Avenue, he had just returned from a long trek through Ecuador, Peru, Bolivia, Chile, Easter Island and Hawaii, with a stopover in French Polynesia.

Dyan J. Summers, the nurse who first saw him, said he pulled his shirt out of his bluejeans and peeled it off, exposing a pinkish rash he said he had had for 11 days.

"I took one look and said, 'Dengue fever,'" she recalled in an interview last week. "He said, 'I'm not so sure. I think it's Zika.'"

Ms. Summers was startled: "I'd heard of Zika, but nobody was thinking about Zika."

"But this is a very, very bright guy," she continued. "He travels a lot, he knows about safe water and safe altitudes for malaria. He was right on the money, that guy. In Polynesia, he had read articles in the local paper about Zika."

She took blood immediately and again 20 days later, and sent both samples to the Centers for Disease Control and Prevention in Atlanta. Their tests showed that he had antibodies to dengue, West Nile and Zika, but the count of Zika antibodies had shot up.

In researching Zika, Ms. Summers said, her very bright patient had found an article about a scientist in Colorado who had infected his wife with the virus after returning from Africa.

"Because of that paper, I advised him not to have unprotected sex with his common-law wife," she said.

"What's weirder," she added. "He knew there were cases of Guillain-Barré connected to it."

Their exchange was strangely prescient.

At the time, Polynesian and French doctors were just beginning to diagnose Guillain-Barré syndrome, a form of temporary paralysis that starts in the hands and feet. Along with infant microcephaly, the syndrome has turned out to be one of the Zika epidemic's chief fears.

It is an autoimmune attack on nerve cells that can be triggered by several viruses or bacteria. It is usually temporary, though it can last for weeks; but if the paralysis reaches the muscles powering the lungs, and the patient is not quickly put on a respirator, it can kill.

Ms. Summers's caution was right: last week, the Centers for Disease Control and Prevention gave similar advice about unprotected sex to all Americans.

Hints a Virus Isn't Benign

In May, after it was confirmed that Zika was circulating in Brazil, it took only a few weeks for doctors to suspect that Dr. Chioro, the health minister, had been mistaken. There were hints that the virus was anything but benign.

In Maceió, Recife and other cities, cases of Guillain-Barré began to spike. Dr. María Lúcia Brito, a neurologist in Recife, saw 50 patients with it in 2015, up from 14 the year before.

"It was obvious — a shift occurred when Zika cases started to rise," she said.

Then, in July, a pair of twins were born in Recife. One was healthy; the other was microcephalic. Their parents took them in early August to be examined by Dr. Vanessa van der Linden, a prominent neurologist.

She diagnosed the cause as an infection that had reached one baby in the womb, and tested mother and baby for rubella, syphilis and toxoplasmosis, three known causes of microcephaly.

The results were negative, so she started testing for genetic mutations like Down syndrome.

In September, the Hospital Barão de Lucena, the public hospital in Recife where she works, saw a surge in cases: five microcephalic babies were suddenly in her care.

The same thing was happening elsewhere. The hospital where her mother was a pediatric neurologist suddenly had seven cases.

“That’s when I thought, ‘Something is terribly wrong,’ ” Dr. van der Linden said.

She soon learned that several of the mothers remembered having the “mystery disease” — the Zika rash — early in their pregnancies.

But tests of the infants for the Zika infection were all negative. Their mothers had been ill months earlier, and in adults the virus usually disappears in 10 days or less. It is still unclear how long it persists in a fetus.

In early October, the national health ministry asked Dr. Turchi, the Oswaldo Cruz Foundation epidemiologist, to investigate. She went to hospitals, including those in Recife. Doctors were running tests for various viruses, but they were all coming up blank.

“The pediatricians were saying, ‘We’ve never seen anything like this,’ ” she said. “These kids are different. This is something new.”

Young Mothers in Shock

Dr. Kátia Petribu, a hospital psychiatrist in Recife, remembers the mothers. They were ghosts — mute, expressionless figures in corridors holding babies whose foreheads seemed to have vanished.

Many of the mothers were young, one just 14. “They were in a state of shock,” she said. “They were unable to talk.”

Dr. Petribu had trouble sleeping. She could not get them out of her mind.

Normally, she worked with patients with obsessive-compulsive disorder. But she decided to refocus on these women, who so clearly needed help.

“They come with nothing,” she said. “No food. They travel by bus for hours, arrive at 7 a.m., and wait for hours to be seen.”

Many were young rural women with no understanding of why their children looked so different. A 16-year-old showed up with her own mother, who was worried about missing a perfect day to sell cold drinks on the beach.

Dr. Mauricio L. Nogueira, a doctor from southern Brazil who had seen no cases in his region, which is as far from the tropical north as Quebec is from Miami, remembers visiting a hospital in the northern city of Salvador. He is still haunted by what he saw: 25 microcephalic children, all born in the previous 10 days.

That was “really shocking for me,” he said. “Until then, I was just reading reports.”

One mother, he said, looked up at him and asked, “Hey, doctor, his head is going to grow, right?”

“It was really painful,” he said.

Frustration was growing, too, for Dr. Turchi, the epidemiologist. “If we

had known what was going on, that would have been one thing," she said. "But there was no book to follow. We had no map."

She shelved her work on the dengue virus and skipped Christmas with her mother.

"I couldn't sleep for several weeks," she said. "It was the most important thing I have seen in my entire career. It was a tragedy, but it was like we were seeing history in front of us, day by day. It was a living history, and we were part of it."

Zika's connection to microcephaly was suspected but very difficult to confirm. Dr. Turchi set up a quick "case control" study, the epidemiologist's classic tool, comparing babies born with the condition and those without it.

Dr. David L. Heymann, chairman of the World Health Organization committee that recommended the declaration of the public health emergency, said in an interview last week that very tool — a case control study following two sets of pregnant women, some who had Zika and some who did not — was what his committee needed to prove whether Zika causes microcephaly, and whether it does so alone or requires a cofactor like a prior infection with dengue.

"Sorting out a rare event will take a lot of women," he said, and they must be followed for months.

At Last, 'a Road to Follow'

But Dr. Turchi did not have months.

She called every scientist she knew, and they came from all over Brazil. One flew in from London. Dr. Turchi gave the group a name: MERG, the Microcephaly Epidemic Research Group.

"It was like a house on fire — everyone grabs a bucket and does what they can," she said. Some scientists stayed in her apartment, talking late into the night. "It's like when you like something and you have people who like the same thing, you can talk for hours without feeling tired," she said. "It's like discussing football. You never stop talking. It's an obsession."

A turning point came in early November: Dr. Adriana Melo in Paraíba State, just north of Recife, had drawn amniotic fluid from a pregnant woman and found Zika virus in it. Then brain tissue from two stillbirths was tested. Again, Zika.

"At last we had a road to follow," Dr. Turchi said. "A map."

One of those who flew in to help in the detective work was Dr. Laura C. Rodrigues, an epidemiologist at the London School of Hygiene and Tropical Medicine on contract to the Pan American Health Organization.

"It was the kind of call where you dropped everything," she said. "There had never been a congenital malformation by mosquito before, not ever. It was totally outside our experience."

With the discovery of Zika in malformed fetuses, Dr. Turchi's team has been able to turn to the kind of task Dr. Heymann described. They have recruited about 1,000 pregnant women with Zika symptoms, and are following healthy and microcephalic newborns in the same areas. They work nights and weekends, eating sandwiches from the institute's shop or meals of rice, beans and chicken provided by a research assistant's mother.

There are now so many reported cases of microcephaly that a new problem has arisen: too many false alarms.

Anxious obstetricians across Brazil have reported babies who merely have small heads, or babies whose mothers had other problems, like severe alcoholism or family histories of malformations, conditions that should have

excluded them from the research.

Brazil has already changed its definition of a small head, to 32 centimeters around from 33 centimeters, and may revise it again soon.

Dr. Turchi defends those decisions, saying a broad net had to be cast at first because so little was known.

“We didn’t want to get just the severe cases; we wanted to look at the broadest possible spectrum of the disease,” she said. “Then we can narrow it later.”

‘Perfect Epidemic Curve’

Loosed on a continent where no one is immune, Zika has the potential to infect tens of millions of people. It is now being transmitted in 33 countries with about 600 million inhabitants, the W.H.O. says. Health officials in Brazil are investigating thousands of reported cases of microcephaly that may be linked to the virus.

Now a bright spot has appeared.

In Recife, and Pernambuco State around it, microcephaly cases have been declining for about three weeks. It is unclear exactly why, but researchers are starting to wonder if the epidemic has peaked.

“It looks like a perfect epidemic curve,” Dr. Turchi said. “You see where it started, then went up, and now it’s going down.”

But that decline, and the general sigh of relief it portends, is occurring only in the one spot in the hemisphere where transmission of the virus hit earliest and was most intense.

Zika was just getting started there a year before the microcephaly cases began. And now the virus is virtually everywhere south of Florida and Texas.

And Guillain-Barré, the harbinger of microcephaly, is being spotted farther from the epidemic's epicenter in Brazil.

Colombia, Venezuela, Suriname and El Salvador, where mosquitoes thrive year-round, all have reported Guillain-Barré cases. Colombia has "an explosion" of them, its health minister said, with three deaths.

There have also been dozens of confirmed Zika rashes and fevers in the United States, all so far in returning travelers, except for the person infected through sex in Texas by a traveler returning from Venezuela.

Air travel maps show the United States' potential to be a kind of viral pincushion; Zika may arrive from anywhere. Since four out of five victims never have any symptoms, there is no way to spot it at the border.

The C.D.C. thinks it is all but inevitable that there will be at least small outbreaks here. But how far they spread will depend on how aggressively mosquitoes are killed.

Now that the world is alert to the danger and is fighting back, and women are even contemplating delaying pregnancies, scientists say it is unlikely that Brazil's national nightmare will be repeated elsewhere on such a scale.

In Recife, Dr. Turchi was hopeful.

"I'm more comfortable now," she said. "I see so many people working as a team and so much international concern. Now it has become clear to the whole world."

Donald G. McNeil Jr. reported from New York; Simon Romero from Recife, Brazil; and Sabrina Tavernise from Washington.

A version of this article appears in print on February 7, 2016, on page A1 of the New York edition with the headline: Medical Mystery With a Global Reach.