Responding to Brazil's microcephaly crisis

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Credit: Yale University

Josely taps on the wooden door and is welcomed into the simple concrete house perched on the rim of a ravine of one of the sprawling favelas in Salvador, Brazil.

She is a nurse and has come to see the baby.

Wearing a diaper and sucking a blue pacifier, the two- month-old boy with a shock of black hair is carried in by his avó, or grandmother, and laid upon the white sheet of his parents' bed. His crib, covered in a fine mesh to repel mosquitoes and adorned with a colorful mobile, stands at

the foot of the bed. A small lizard, no larger than a paper clip, noiselessly traverses the ceiling directly overhead.

Josely bends over the baby and coos soothing words in Portuguese as she caresses his little bare feet and legs and begins her examination. He looks like any other baby— except for the size of his head. Like thousands of other newborns in Brazil over the past few years, this baby was born with microcephaly, a condition marked by a smaller-than-average head circumference.

Josely places the infant on her portable digital scale and then measures his height. She makes some loud noises to gauge his responses. The baby screeches with each encroachment until his pacifier is reinserted. His subdued family studies each step. Next, Josely tenderly measures the circumference of his head. Twenty-nine centimeters. She enters the number into her report. The average circumference is about 34 centimeters for a baby this age. A smaller head frequently means a smaller, less-developed brain and, potentially, severe brain damage.

Like so many others recently born with microcephaly in Brazil and beyond, this baby's prospects for the future are described as "uncertain."

Zika

News of the microcephaly is everywhere here— chimed over airport public address systems—a confident voice intoning Brazilians will not be beat. The message is picked up on domestic air flights and then, again, by a talkative cab driver whose route is studded with billboards warning of the health crisis.

During the height of the epidemic in 2015 and into 2016—and to this day—microcephaly commands the attention of some 200 million Brazilians. And their obvious question—What's happening?—drives a

researcher from the Yale School of Public Health and his Brazilian colleagues at Salvador's Oswaldo Cruz Foundation (also known as Fiocruz, a branch of the federal health ministry), who share a commitment to address an emerging public health crisis before the human devastation worsens.

Albert I. Ko, M.D., professor and chair of YSPH's Department of Epidemiology of Microbial Diseases, is a slender and seemingly tireless man who has devoted his professional life to tropical infectious diseases and the burden these diseases place on the urban poor; to educating the next generations of scientists; and to the future well- being of Brazil.

Ko's suspicions soon after the outbreak, shared by others, fell on an exotic and largely unheard-of virus became a household word: Zika. The disease was reported in this vast South American nation for the first time shortly after the country hosted the 2014 World Cup. While notable, it did not cause much alarm. That would happen in about nine months.

As viruses go, Zika had been regarded as a minor its existence was first documented in Uganda in the late 1940s, Zika never caused widespread illness, and when it did strike, the human symptoms were generally minor— rashes, low-grade fever, fatigue—and these were usually short-lived. It rarely made headlines. In a world contending with a swarm of other ruthless pathogens—Ebola, HIV/ AIDS and malaria, among them—Zika seemed almost benign.

That changed sharply upon its arrival in Brazil and throughout most of South America. In the preceding years, the virus is believed to have spread from its African origins, traveling eastward across Asia and then the South Pacific, island hopping until, finally, it reached the landmass of South America. Once it went viral. In short order Zika spread throughout Brazil and made quick inroads into much of South and Central America, the Caribbean islands and southern regions of the

United States.

It was here the virus, perhaps mutated and more virulent than its ancestors, found a huge population with no viral immunity; an almost complete lack of awareness of the emerging danger; and multitudes of an established and aggressive vector—the Aedes aegypti mosquito. It was a recipe for mayhem.

Ko and his colleagues, however, wanted scientific proof that a virus virtually unknown even a few years before suddenly to upend public health in much of the Western Hemisphere. If this virus caused microcephaly as suspected, they wanted to know how and why and to understand its transmission dynamics and risk factors.

Also, could it cause other illnesses or deformities? Could it kill?

These scientific inquiries at Fiocruz and in Ko's New Haven laboratory at the Yale School of Public Health were simultaneously being accompanied by an aggressive public health outreach in the poor neighborhoods ring Salvador's affluent enclaves. It was a concerted effort to help the parents of children born with microcephaly, as well as the babies themselves. Ko's involvement spanned both efforts.

"This epidemic has devastated Brazil's poor communities," Ko said. "Salvador and northeastern Brazil were the epicenter of the outbreak. The impact was disproportionately felt by the disadvantaged communities we have worked in for the past 20 years."

Responding to an Epidemic

Ko and colleagues quickly pivoted from their focus when they observed an unusual number of cases of microcephaly in the Pau da Lima neighborhood where their research on another infectious disease,

leptospirosis, has been ongoing for years. The number of babies born with the condition continued to increase, and the public's fear and anxiety mounted. People wanted answers and protection, but scientists in 2015 and early 2016 remained divided on the precise causes and risks.

"We still don't have good diagnostics, we still don't have a good way to treat pregnant women affected by the virus and we don't have an effective way to prevent [Zika]," Ko said in early 2016 in one of dozens of media interviews on the topic as the Zika virus came to dominate international news.

To determine a link between the virus and the birth defects, Ko and colleagues began recruiting female volunteers seeking prenatal care (and their babies when they were born) to determine conclusively if Zika was the culprit rather than exposure to something else, such as rubella or syphilis. They were also testing samples of the virus collected in different countries to determine if it had mutated and was more lethal in some places than others and also more easily transmitted.

Ko and his colleagues also had other research under way, and the findings further heightened concern. The team published the first report demonstrating that the Zika virus can cause glaucoma in infants who were exposed during gestation. This finding was followed by a separate study of a pregnant Brazilian woman who was infected with the Zika virus and who had a stillborn baby with signs of severe tissue swelling as well as central nervous system defects that caused near-complete loss of brain tissue. It was the first report indicating a possible association of congenital Zika virus and damage to tissues outside the central nervous system. Ko said the case provided evidence in addition to microcephaly, congenital Zika infection might also be linked to hydrops fetalis (abnormal accumulation of fluid in fetal compartments), hydranencephaly (almost complete loss of brain tissue) and fetal demise (stillbirth).

While this research was ongoing, the need to directly respond to the crisis in and around Salvador was growing. In partnership with the Geral Roberto Santos Hospital, where many babies with microcephaly were born and waiting rooms were crowded with young parents and their newborns, a series of support programs was created to help those affected. Many families did not have the means to come back to the hospital repeatedly, so the hospital started sending nurses like Josely to the homes in Pau da Lima and beyond to meet with the parents and monitor the babies' growth and development.

These nurses help families learn how to care for a baby with special needs and provide them, oftentimes, with much-needed emotional support. This was bolstered with a support group for new parents, with activities bonding and address specific issues, such as convulsions. Other personnel, including social workers, physical and speech pathologists, were also made available.

"Many of these families are really struggling," said Ridalva Felzemburgh Martins Dias, a director of the outreach effort along with Federico Costa, Ph.D., a researcher at Fiocruz and an adjunct associate professor at YSPH. "We do care and we do want to help."

A Tragedy

Due to a variety of factors, many of the babies afflicted with microcephaly are born to poorer families, who can least afford the services and will certainly be necessary as their sons and daughters mature. The condition further strains families who are living in Brazil's marginal enclaves, where day-to-day living conditions, by anyone's standards, are challenging. For many residents of places such as Pau da Lima, is no running water, trash removal or sewers. Homes here are simple concrete blocks with ample openings for disease-carrying mosquitoes—and the pervasive rats—to gain easy access. Meanwhile,

those living in Salvador's high-rise apartments—in some cases only a 15-minute cab ride away—face nowhere near the same risk of infection for Zika and a number of other diseases.

So the poorest of Brazil's poor bear a double burden— subsistence in barely livable conditions and a greatly increased risk of infection from a variety of infectious diseases—maladies such as leptospirosis, dengue fever and schistosomiasis, among others—and now Zika as well.

"This is really a tragedy," said Mitermayer Galvão dos Reis, M.D., Ph.D., senior researcher at Fiocruz. "It's really very challenging for us. [Mothers- to-be] are really scared. They want to know if their babies are okay."

Reis grew up in Pau da Lima, the very favela where Ko has done much of his research and an area hit hard by Zika. "I love that place," he said. When he was a student in Boston in the 1980s he met Ko, and the two have been close colleagues since. Reis introduced Ko to Brazil.

The worsening Zika outbreak rapidly became a priority for Fiocruz and was no choice but to shift its resources toward a health threat that was steadily worsening, said Manoel Barral Netto, M.D., Ph.D., who was director of the Salvador center at the height of the crisis in early 2016.

He credited Ko and the Yale School of Public Health with providing assistance and leadership during the crisis. Ko, in particular, knows Salvador and the Brazilian health system well, and he has worked closely with the city's public health professionals to help coordinate the city's response.

"Albert has been very important [in our response]," he said. "He has been involved from the start."

While science has the potential to eventually protect people from Zika by successfully developing a vaccine, other viruses, currently unknown like Zika was a few years ago, will likely emerge, and it will be the poor who again will suffer the most, Reis said. The underlying issues of poverty and health inequity are even tougher to resolve.

"I don't think anyone has the magic bullet to solve these social and political problems," he said.

Brazil

Now fluent in Portuguese, Ko first traveled to Brazil in the early 1990s and was quickly captivated by the people and culture, as well as by Brazil's vibrancy and potential.

As a young doctor, he could also see the serious health challenges facing the country.

Ko has since become a leading expert on leptospirosis, a neglected tropical disease that particularly afflicts the urban poor in Brazil and other parts of the developing world.

From the Salvador headquarters of Fiocruz, he works with and helps train the next generation of Brazilian scientists who will continue the fight against this rat-borne infection. YSPH students, meanwhile, routinely travel to Salvador to work with Ko and conduct field research.

Ko knows this expansive city intimately and is able to navigate his small car through a confusing and often congested network of roads with apparent ease. Brazilians seem to know him wherever he goes, and he enjoys a spectrum of local culture from raucous soccer games played in the city's gleaming new stadium to intensely competitive dominoes with people who take the game seriously.

The experience with Zika has left scientists like Ko wondering if the epidemic was an anomaly. He thinks probably not. Chikungunya appeared suddenly in the Americas just a few years before, and Ebola nearly burst out of its traditional borders during the 2014 outbreak. Where will the next disease come from? No one knows for sure, but factors such as changing weather patterns and mass human migration are shifting the equations. Diseases no longer stay put. Traditional borders are melting, and the next pandemic can originate anywhere and reappear thousands of miles away virtually overnight.

And while the number of new Zika cases slowed and the epidemic started to fade from the headlines in 2016, it continues to take a heavy toll on Brazil. There is a generation of Zika babies who will need enormous resources going forth, and science, despite some concrete gains, still has much to learn about just this one virus.

"Zika is one of many infectious diseases we have to face, particularly in poorer countries," Ko said. "This makes it even more essential we invest in young people in Brazil and elsewhere and train them to be the next generation of scientists."

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