Stopping the virus

Following India's first outbreak of Zika infections in Rajasthan in September 2018, Madhya Pradesh has now reported a second one, with six districts affected. The response from the State administration, however, has been marred by muddled science and poor public health communication, reports **Priyanka Pulla**

Field note: "It is tough to say how big a risk Zika will be to India in the coming days. For now, the two outbreaks, in Rajasthan and Madhya Pradesh, appear to be relatively small." A scene at Kothari, one of the Zika-affected villages in Madhya Pradesh. ▪ A.M. FARUQUI

Maya Madan, 22, lives in a brick hut in Hamid Khedi village. A few feet from her home, which is in Sehore district of Madhya Pradesh, is a narrow street, criss-crossed by ditches full of dirty water. The buzz of mosquitoes breeding in these pools fills the air. It does not come entirely as a surprise that several of the cases of the State's first and India's second Zika outbreak are from Hamid Khedi and its neighbouring hamlets. Zika is spread by the mosquito species, *Aedes aegypti*. It thrives in stagnant water.

Even though the Zika virus only causes mild fever and symptoms such as rashes in most people, Madan has more to worry about as she is three months pregnant. The virus has been linked to birth defects in 5%-15% of children of infected mothers. Such birth defects include an abnormally small head (microcephaly), eye damage, shortened muscles and joints, and hearing damage.

This is why the World Health Organisation (WHO) recommends that in areas with ongoing Zika transmission, pregnant women should be made aware of Zika's dangers. They must use mosquito nets and repellent. Given that Zika can spread through sexual activity, they should avoid unprotected sex, while couples planning to have children should consider delaying pregnancies. Yet, 18 days into the outbreak, Madan hasn't heard anything about it. In fact, public communication about the virus seems to be limited to mosquito-control alone, with no mention of the other ways in which it can spread. Zika has the unique property of causing birth defects, which other mosquito-borne diseases do not. Yet, recently painted signs on the village walls warn about dengue and malaria, but are silent about Zika.

Misinterpreted science

The Madhya Pradesh Public Health & Family Welfare Department's reluctance to counsel citizens quickly is due to an odd misinterpretation of Zika research. On November 3, 2018, a press release from the Ministry of Health and Family Welfare cited the Indian Council of Medical Research's (ICMR) findings to say that the Zika strain – which had earlier caused an outbreak in Rajasthan – did not have "known mutations" for microcephaly. M.P.'s health officials are now waiting for the ICMR to genetically sequence the local Zika strain, as they believe it may also lack those mutations, and so, may not be dangerous to foetuses. Only if the strain turns out to have the dangerous genetic changes, health officials said, would they begin explicitly warning couples about delaying pregnancies during the outbreak. Pallavi Govil Jain, M.P.'s Health Commissioner, says: "Because we still don't know from the Health Ministry whether the strain can cause microcephaly, we have to be cautious about what we tell women. If we tell them that it will impact their children, it will cause panic among the public."

This delay in launching intensive communication campaigns can cost lives, according to Zika researchers, because all Zika strains have been shown to cause birth defects. Contrary to what the Health Ministry's press release suggests, there is no "known mutation" for microcephaly. "People have got to stop saying this,", says Nathan Grubaugh, an epidemiologist at the Yale School of Public Health. "It's going to drive complacency within the general population if they don't believe Zika can cause birth defects," he adds. Grubaugh studied the Brazil and U.S. Zika epidemics, in 2015.

Anant Bhan, a Bhopal-based bioethics researcher, says the State government's concern about causing alarm can be tackled with a good communications strategy. "Contextualise the communication, so that it is done sensitively. But not sharing or withholding information is not acceptable," he says.

One reason why the State Health Department cannot drag its feet about informing people is that Zika epidemics are typically larger than they appear. Nearly 80% of the infected people do not show symptoms. Therefore, surveillance systems detect only a fraction of the cases. This means that even though diagnostic tests have so far uncovered not more than 127 cases with 35 pregnant women in M.P., the actual number could be many times as much. In such a situation, says Grubagh, telling women that Zika is linked to birth defects can motivate them to protect themselves, softening the impact of the virus. "If I were in such a situation, and if there was information that I could use to my benefit, I would want to know it. I don't want people to tell me: Oh, it's not an issue, when it actually is," he adds.

India's first major outbreaks

India's first major Zika outbreak began in September 2018 in Rajasthan. Until then, a surveillance programme run by the ICMR at 35 sites across the country had detected only three isolated cases in Gujarat in 2016-17, and one in Tamil Nadu.

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Then, in September, the surveillance system, which randomly tests a fixed number of fever patients for Zika each month, found an 85-year old woman from Jaipur to be carrying the virus. Over the next few days, more and more cases turned up. Rajasthan then began testing all pregnant women living in a three-km radius around the index case. This effort uncovered a total of 154 cases, with over 60 pregnant women among them. Two of these women have given birth and the babies are healthy, officials say.

Around mid-November, State officials declared that their extensive larvicidal and fogging activities had "controlled" the outbreak. According to Govind Pareek, Deputy Director, Public Relations for the Government of Rajasthan, no new cases were found in the two weeks leading up to the announcement.

However, by this time, the ICMR's surveillance system in Bhopal had picked up a second outbreak. As this story goes to print, M.P.'s officials say that there are 127 infections in six districts of the State. But according to B.N. Chouhan, the State's Director of Health Services, the outbreak seems to be slowing down due to intensive mosquito-control activities.

Silent epidemics

Yet, there are several questions about whether the outbreaks in Rajasthan and M.P. have truly been extinguished. Zika cases typically rise and drop with the seasonal prevalence of the *Aedes* mosquito, which means the drop in November may have as much to do with the weather as with antilarval activity. Says Grubagh, "Control of an outbreak is quite hard to define. First, not detecting Zika cases doesn't necessarily mean that transmission stopped, because the vast majority of cases are asymptomatic."

Second, the ICMR's surveillance system relies on a technique called Reverse Transcription-Polymerase Chain Reaction (RT-PCR), which looks for Zika's genetic signature in patient blood samples. But RT-PCR tends to throw up false-negatives when there is too little virus in the patient's blood, something that happens frequently with Zika, says Grubaugh. Such barriers mean that the best of surveillance systems catch only a fraction of the incidence. After an outbreak in Salvador, Brazil during 2015, researchers found that the number of people who had Zika antibodies – indicating that they had been infected in the past – was roughly 40 times the number of detected cases. If the same multiple is applied to MP, then, given its 127 detected cases, the potential number of infections could be as high as 5,080.

Sometimes outbreaks may escape notice altogether. Grubaugh describes one such suspected outbreak in Cuba in 2017. When his team analysed the number of Zika cases among travellers entering Florida, U.S., and several European countries, they found a spike in both regions during the summer of 2017. All cases were those of recent travel to the Caribbean nation. The researchers estimated that Cuba likely saw an outbreak in 2016-2017, with around 2,000-20,000 cases. Yet, local reporting systems in the Caribbean country detected only 187 cases in 2016 and none the next year. The virus, which had seemingly stopped in its tracks in the dry season of 2016, had re-emerged the next year.

If epidemics can persist quietly long after surveillance systems suggest they have ended, they can also begin before surveillance picks them up. During Brazil's first Zika outbreak in 2015, for example, genetic sequencing of the circulating strains suggested that the virus had entered the country more than a year before the first case was detected.

This could well be the case in M.P. and Rajasthan too. If so, the number of pregnant women infected would be even larger, and communicating Zika's danger to them would become even more crucial.

Study of a mutation

The M.P. government's lackadaisical approach to counselling people in the affected areas seems to be driven by the Ministry of Health press release, highlighting the importance of clear communication by premier research agencies such as ICMR (whose work was cited). But why did the press release suggest that the Rajasthan strain had no known mutations for microcephaly? Responding to a questionnaire from *The Hindu*, Nivedita Gupta, a virologist at the ICMR, referred to a *Science* study in 2017 to support the claim. Here, Chinese researchers found that when they infected new-born mice with a Zika strain that contained a mutation called S139N, the mice had more damaged brain cells when compared to animals infected with other strains. This suggested that the mutation had a role to play in making the Zika virus more virulent to foetal brain cells.

When the ICMR sequenced the virus that triggered the Rajasthan outbreak, they did not find the S139N mutation. This led to the Health Ministry announcing that the Rajasthan virus did not have "known mutations" for microcephaly.

The problem, according to Grubaugh and other researchers, is that the hypothesis of the *Science* study has not stood the test of time. Later studies have found microcephaly cases associated with strains that lacked the S139N mutation. Meanwhile, researchers who repeated the mouse experiments did not get the same results.

This is why the ICMR's claim about "known mutations" is misleading, according to him. Other scientists agree. "It is still too early to conclude that any particular strain cannot cause microcephaly," says Scott C. Weaver, a microbiologist at the University of Texas, who worked on the Brazilian outbreak. When asked if the ICMR would issue a clarification, Gupta responded that there were no errors in the press release.

Tackling the mosquito menace

The good news is that even though M.P. is dawdling in its public-communication campaign, it is implementing mosquito-control measures. "Our initial plan of action is vector control," says Pallavi Govil Jain. But the challenge is a steep one. Due to persistent neglect by local municipal bodies, says Praveen Kumar Tiwari, most Zika-affected villages were in a bad state at the beginning of the outbreak. When Tiwari, an entomologist from the Regional Office of Health and Family Welfare was deputed to Sehore's Kothari village earlier this month, dozens of houses were found to have mosquito larvae-infested water.

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Patients at the civil hospital in Sehore district. ▪ A.M. FARUQUI

One reason for all the stagnant water in Kothari is the lack of a sewerage system. Open drains line the narrow streets, which are dotted with potholes. Moreover, the village suffers from chronic water shortages. "We don't have tap water at home. We have to bring it [water] from the public tap. So, we fill buckets and store water for days," says Shweta Singh, who is in her second trimester of her pregnancy and also diagnosed as Zika positive. Some homes have built septic tanks for their toilets, but are using them to store water instead.

As a result, the Breteau index (BI) – a measure of the number of containers such as tyres and buckets containing larva per every 100 households – was between 10 and 15 in Kothari. Any index above 5 increases the chances that larvae will turn into adults, Tiwari explains.

With intensive insecticide use, he says, the BI in the village has come down to below five. The problem is that as long as the Kothari Nagar Panchayat does not prohibit water storage in open tanks and fill potholes, the mosquitoes will return. Tiwari is frustrated because, according to him, the upcoming State elections have drawn field staff away. Standing astride one of the many water-filled potholes on the village street, he exclaims, "I can put larvicide in the water, but what can do I about these potholes? When the larvicidal activity stops, the mosquitoes will come back."

How wide will Zika spread?

It is tough to say how big a risk Zika will be to Indians in the coming days. For now, the two outbreaks, in Rajasthan and Madhya Pradesh, appear to be relatively small, with 154 and 127 detected cases, respectively. But given the number of asymptomatic cases, it is difficult to rule out the possibility of Zika cases elsewhere in India. "I would not be surprised if the Zika virus were already present in other parts of the region, but has remained undetected due to the lack of active surveillance in the absence of an overt outbreak," says Weaver.

On the other hand, one speed-breaker for the epidemic could be herd immunity. If Zika has already been in India for some time, and Indians have antibodies to it, the virus would not move as quickly. But as on today, there is no data on herd immunity in the Indian population. In a 1954 survey of people, from across the country, researchers had found 33 of 196 people to have antibodies that neutralised the Zika virus, suggesting that the virus was circulating here.

What researchers did not know then was that flaviviruses – a genus to which the Zika, dengue and Japanese encephalitis viruses belong – are notorious for a phenomenon called cross-reactivity. This means that human antibodies to one flavivirus, such as dengue, can neutralise another one, such as Zika. So, the 1954 study was not conclusive evidence of Zika's presence in India, because it could just as well have been evidence of dengue.

In other words, if Zika hasn't been widespread in India before, the lack of herd-immunity would mean it would blaze its way quickly to other States. Says Weaver, "Without good information on herd immunity, I think we should assume that there is risk wherever *A. aegypti* is present and temperatures are permissive." One good way to visualise how Zika will spread is to think of the mid 2000s chikungunya epidemic in India. After not being recorded in the country for nearly 32 years, the virus, which is also spread by *A. aegypti*, showed up in 2005. Within the next 12 months, it had infected 1.4 million people in 15 States. Says Grubaugh: "Think of what chikungunya did, and the number of cases it caused. Now replace the name with Zika, and there you have the epidemic."

Tracking through health systems

If Zika spreads, India's antenatal healthcare systems will be critical in screening pregnant women for foetal abnormalities, and helping them decide if they want to terminate the pregnancy. The good news is that birth defects such as microcephaly, contractures and clubfoot can be picked up during sonography at around 17 to 18 weeks of pregnancy, according to Vijay Sadasivam, a radiologist at SKS Hospital, in Salem, Tamil Nadu. Ideally, around five sonographies should be done to find any anomalies, he adds.

M.P. State officials have begun tracking pregnant women diagnosed with Zika, and say they are drawing up guidelines for monitoring them. But if the outbreak returns or grows larger next year, the State's antenatal health-care system will have to gear up substantially, because it does not reach enough women today.

According to National Family Health Survey-4 data, 80% of pregnant women deliver in hospitals in M.P.'s urban areas, while only 76% do so in the rural areas. Out of the women who do deliver in hospitals, estimates Archana Mishra, Deputy Director, Maternal Health at National Health Mission in M.P., only around half receive at least one sonography during pregnancy.

At this rate, it is likely that pregnant women who ought to get screened will not be. This is another reason to inform all women of reproductive age of Zika's dangers so that they may seek care on their own. "Why should health officials be shielding the populace from a truly scary scenario by withholding information? This is our paternalistic healthcare approach at its worst," says Sadasivam.

Back in Hamid Khedi, Maya Madan says she has been using a mosquito net and repellent because the local healthcare worker has advised her to do this to avoid illnesses such as dengue. If she knew that using condoms during sexual activity or getting an extra sonography would help her child, she would likely do it quite gladly.

Names of Zika-infected patients have been changed to protect their identities.