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Change in vaccination strategy averted outbreak of urban yellow fever in São Paulo State

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The virus spread at a speed of 1 km per day in the latest sylvatic outbreaks in São Paulo State, between 2016 and 2019, reaching cities never affected before. Credit: Tomaz Silva - Agência Brasil

Yellow fever is a non-contagious viral disease with two transmission cycles, sylvatic (in wild animals) and urban. Sylvatic yellow fever circulates among monkeys, and in Brazil is transmitted by mosquitoes of the genera Haemagogus and Sabethes, which bite an infected monkey and then infect others. Urban yellow fever circulates among humans and is transmitted by the mosquito Aedes aegypti (human-mosquito-human). Brazil has had no urban yellow fever cases since 1942, but the sylvatic version can accidentally infect people who live near or visit forest areas.

This is what happened in the latest outbreaks of sylvatic yellow fever in São Paulo between 2016 and 2019. According to an article published in *Scientific Reports*, in which Brazilian researchers analyze the process of diffusion in the state, the disease was caught by people in places very close to the state capital and cities such as Campinas without vaccine recommendations because they had never been affected. The researchers show that if vaccination strategy had not been adapted to the circumstances, the impact could have been far worse, resulting in more deaths.

"We ran a very high risk of seeing urban yellow fever reintroduced in cities near the state capital. An urban epidemic would have had very serious effects and would have been a major setback," said Francisco Chiaravalloti Neto, a professor in the Department of Epidemiology of the University of São Paulo's School of Public Health (FSP-USP), and last author of the article. The study was supported by FAPESP.

Two outbreak waves were identified between 2016 and 2019, one from west to east (2016-17) and the other from Campinas to cities near the borders with Rio de Janeiro, Minas Gerais and Paraná states, and coastal cities in São Paulo (2017-19). The first wave left São José do Rio Preto in April 2016 and reached Campinas in August 2017, advancing 1 km per day. "The number of cases in humans rose at that point, because of low vaccination coverage, and the disease spread toward the state capital,

the coast, the Paraíba Valley region [in the east of the state] and Sorocaba at the same rapid pace. It also spread more slowly to the Ribeira Valley region [in the south of the state]," Chiaravalloti Neto said.

The vaccination strategy followed by the Ministry of Health and São Paulo's Health Department in these cases is to immunize the city at risk as well as its neighbors. "But when the disease reached Campinas, the state immunization division relinquished this strategy, which would have required vaccination of the city's entire population as well as those of nearby cities such as Indaiatuba and Paulínia, deciding instead to vaccinate cities such as Jundiaí, Jarinu and Itatiba, because they realized this was where the virus was heading. Campinas and its neighbors then had more than 1 million inhabitants, but fewer than 1 million doses were available," said Adriano Pinter, a scientific researcher in the Center for Endemic Disease Control (SUCEN) at the São Paulo State Department of Health, and penultimate author of the article.

Vaccination coverage was close to 80% in Mairiporã, a city with 181 cases in humans, when the disease arrived there—unfortunately not long before Christmas, when the number of visitors increases. "If Mairiporã had more than 100 deaths with over 80% vaccination coverage, imagine what would have happened without vaccination," Pinter added, noting that coverage is typically about 5% in most cities without vaccination recommendations. "People usually want the vaccine only when they're about to travel."

An outbreak of the kind seen in 2016-9 could happen again, the scientists warned. "We have to be very watchful. We know how quickly the disease can spread," Pinter said. "Studies have shown that waves of yellow fever start in the Amazon, spread via forest corridors to Tocantins state, Goiás state and the Minas Triangle [Southeast Brazil], and reach São Paulo, moving southwards along the coast. The wave has now gone as far south as Rio Grande do Sul state [bordering Uruguay].

These waves are believed to occur every five years. Campinas had never been affected by the sylvatic cycle. This was the first time. We describe the process in detail in the article."

Until 1999, sylvatic yellow fever was confined to the North and parts of Central Brazil, with sporadic cases in the Southeast. Since 2000, however, São Paulo has been one of the epicenters of its expansion and circulation. Between 2016 and 2019, 648 human cases were confirmed in the state, with 230 deaths, as well as 850 cases in monkeys or groups of monkeys. Symptoms are mild in most cases, but the death rate in severe cases is 40%.

Diffusion pattern

Although yellow fever is not a contagious disease, the diffusion pattern described by the researchers is known as "spread by contagion", a term that in this context refers to transmission through contiguous and nearby areas, as if forest fragments were contagious to each other.

According to the first author of the article, Alec Brian Lacerda, the disease can spread by expansion, relocation, or a combination of the two. "There are two kinds of spread by expansion, involving contagion, which is based on territorial proximity, and spatial hierarchy, usually via big cities but jumping instead of being continuous, which may be a sign of an outbreak of urban yellow fever," he said.

Relocation involves migration, as the disease leaves the point of origin, where it stops spreading, and migrates to a more favorable location, creating a fresh point of origin. "This happens, for example, when unvaccinated people leave areas without the vaccine recommendation and enter areas with the recommendation. Hybrid diffusion also involves relocation, but with the old point of origin still active. We characterized the processes on this basis and assembled maps showing cities and cases

in humans, monkeys or both," said Lacerda, who began the study with the support of a scientific initiation scholarship from FAPESP.

According to Pinter, when vaccination was proposed the rationale was that the virus was believed to be spreading only sylvatically and diffusion would be only via territorial contiguity because the insects concerned do not fly far. "However, whether humans participated in transmission was still unclear," he said. "In the article, we confirm that they didn't, showing that transmission indeed occurred only among mosquitoes and non-human primates. Humans were sometimes infected but didn't transmit the disease, and transmission didn't occur in cities. If humans had participated in transmission, it would have been hierarchical: people would have been infected in big cities and transmission would have jumped from one location to another. On the contrary, we found that the virus spread in small cities by territorial contiguity."

Direction and speed

Lacerda explained that the group used epidemiological data for cases involving monkeys and humans, by city, from the São Paulo State Department of Health's Professor Alexandre Vranjac Center for Epidemiological Surveillance (CVE), and vaccination coverage data for 2015-18 from the National Immunization Program (PNI).

"We used vaccination coverage data for the under-fives as a proxy for the total population. The data available for this age group provides a more accurate record of how the health system reaches the population, and the Ministry of Health itself recommends its use in studies such as ours," he said.

The researchers used a statistical technique called kriging to analyze the data in pursuit of diffusion patterns. Named for South African mining engineer Danie Krige, kriging is a type of spatial interpolation that uses

mathematical formulas to estimate values at unknown points based on the values at known points. "For each municipality, we began with the date of the first case, whether in humans or monkeys, created a numerical sequence corresponding to the months, and connected the municipalities to the months in which diffusion began. We used kriging to create maps of the diffusion process in space and time, with curves showing its direction and speed. We then compared these with maps of vaccination coverage, finding out that the epidemic reached Campinas, for example, when vaccination coverage was very low, or that there was no vaccination recommendation," Chiaravalloti Neto explained.

Warmer winters

The fact that the disease spread to places where it had never been reported before suggests several hypotheses that need to be tested. "The explanation that makes most sense to me has to do with warmer winters," Pinter said. "There shouldn't be winged mosquitoes in winter. There should only be eggs. The larvae don't survive cold weather. However, we saw transmission even during the winter in 2017. In other words, the mosquitoes were flying in winter."

Cold winters may have blocked transmission of the virus in the past, protecting cities such as Campinas and Mairiporã. "We now have warmer winters. The difference isn't huge, but it does reach 2 °C or 3 °C," he said. "There are studies on dengue showing that temperatures in the range of 20 °C are good for the mosquito, whereas it can't survive at 16 °C. More or less the same thing applies to yellow fever. What makes sense to me amid so many hypotheses is that we've had less cold winters, and the warmer the weather, the faster the virus spreads."

The main symptoms of yellow fever are nausea, headache, sudden onset of fever, aches, chills, fatigue, vomiting and diarrhea, but it can also affect the kidneys and liver. Fortunately, there is a yellow fever vaccine,

which Brazil has produced since 1937. It is offered by the national health service (SUS), and provides lifelong protection. "Our advice to the public is to take the vaccine," all three authors agree.

More information: Alec Brian Lacerda et al, Diffusion of sylvatic yellow fever in the state of São Paulo, Brazil, *Scientific Reports* (2021). DOI: 10.1038/s41598-021-95539-w

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