

# Yellow fever virus is detected in urine and semen almost a month after infection

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The presence of yellow fever virus in urine and semen samples from an infected patient who survived was detected almost a month after infection, according to a study conducted by researchers at the University of São Paulo's Biomedical Science Institute (ICB-USP) in Brazil in collaboration with colleagues at Butantan Institute, Emílio Ribas Infectology Institute, and Pontifical Catholic University of São Paulo (PUC-SP). The discovery is described in an article published in *Emerging Infectious Diseases*.

The researchers followed a 65-year-old patient in São Paulo who did not enter the toxic phase of the disease. They detected a significant amount of viral RNA (genetic material) in the patient's [urine](#) and semen 15 and 25 days after the initial symptoms of yellow [fever](#) appeared.

"In a previous study conducted in collaboration with Edison Durigon [a professor at ICB-USP] and his group, we identified the presence of [dengue virus](#) and Zika [virus](#) in the urine of infected patients, as well as in their semen in the case of Zika. For this reason, we decided to see whether the same was the case for yellow fever virus," said Paolo Zanutto, a professor at ICB-USP and one of the authors of the study.

"This detection is a matter for serious concern, above all because it suggests that the transmissibility period for yellow fever virus may be longer than expected in the case of an acute infection [typically not more than 10 days]," the researcher noted.

According to the current model, yellow fever virus transmissibility begins between 24 and 48 hours before the appearance of the first symptoms and lasts until between three and seven days thereafter. In most cases, the symptoms disappear after three or four days. A small percentage of those infected enter a second, more toxic stage within 24 hours of recovery from the initial symptoms, and half of these die within a period of seven to 10 days.

"This latest discovery suggests yellow fever virus is another arbovirus that can be excreted by the urinary system." Arbovirus, short for arthropod-borne virus, refers to a type of virus transmitted by insects that feed on the blood of vertebrate hosts such as humans and monkeys. The researchers do not yet know what the implications of the presence of yellow fever virus in urine and semen may be, with what frequency this occurs, or how long it persists in these biological materials since they analyzed only one patient.

In the case of Zika, previous studies conducted in collaboration by Durigon's and Zanotto's groups showed that the virus remained in patients' semen for months, with viral loads declining slowly. They also confirmed that Zika virus can be sexually transmitted. "We don't yet have enough samples to determine how long yellow fever virus can be detected in urine and semen, but our monitoring of the patient for 21 days after observing the first symptoms of the disease suggests the virus can be detected in these biological materials for almost a month after infection, if not longer," Zanotto said.

The researchers sequenced the genome of the virus isolated from the patient's urine. The analysis showed that the virus belonged to a group of genotypes isolated in South America, including two isolated in 2017 in Espírito Santo State. The researchers believe tests designed to detect the presence of yellow fever virus, especially in the urine of patients with suspected infection, can facilitate and improve diagnosis of the disease.

Clinical confirmation of incipient infection by yellow fever is currently based on detection of viral RNA in the blood by serologic testing, real-time polymerase chain reaction (RT-PCR) assays or enzyme-linked immunosorbent assays (ELISAs), which measure blood levels of certain antibodies, such as immunoglobulin M (IgM), made by the immune system to combat invading microorganisms (antigens).

These tests are usually performed when patients with a suspected infection arrive at the hospital. More than 50% of people infected by yellow fever virus, however, do not display symptoms of the disease, such as high temperature, chills, fatigue, headache, muscle pain, nausea, and vomiting. "The people who are admitted to hospital are those who have symptoms. These are the relatively severe cases, representing the tip of the iceberg as far as the problem of infection by yellow fever in Brazil is concerned since a large proportion of those infected is asymptomatic," Zanotto said.

Detection of the virus in urine could facilitate and speed up diagnosis of these asymptomatic patients, especially in places where deaths from yellow fever have been reported, the researchers noted. Testing urine and semen samples to diagnose yellow fever could also reduce false-negative results and strengthen the reliability of epidemiologic data during outbreaks of the disease, such as the ongoing outbreak in São Paulo and Minas Gerais states, they added.

"Detection of the virus in urine has been used to confirm infection by other flaviviruses, such as West Nile, Zika and dengue. In the case of dengue, this method won't become standard yet because we aren't sure how many infected people do in fact have the virus in their urine. This must now be investigated," Zanotto said.

Because detection of yellow fever virus in urine is non-invasive (in contrast to serology), it has proved useful and has become routine for

several groups of researchers who are studying the current outbreak of the disease in São Paulo State, he added.

The researchers are verifying the presence of yellow fever virus in autopsy materials, including various cellular tissues, from patients diagnosed with yellow fever who entered the toxic phase of the disease. Preliminary analysis of these materials points to significant amounts of the virus in various organs, including the brain.

"We're finding the virus in practically all samples collected by Professor Duarte Neto from the organs of these infected patients who failed to survive the disease," Zanotto said. "Various tests designed to detect the virus in organs are being replicated at Adolfo Lutz Institute, FM-USP's Gastroenterology Department and ICB-USP in order to bolster the reliability of the results."

The researchers at ICB-USP are sequencing and trying to isolate the virus in order to perform in vitro studies of viral viability in different tissues. They also want to find out what any differences may mean in terms of behavior and infection capacity in human cells and vectors. "In collaboration with Professor João Renato Rebello Pinho and his group in FM-USP's Gastroenterology Department, we're comparing viral diversity among patients who died and those who recovered," Zanotto said.

"Moreover, in light of observations made by researchers in FM-USP's Pathology Department, we need to find out whether the virus that's circulating in São Paulo is the same as or a variant of the one we found in the urine and semen of the surviving patient we studied: this virus caused an outbreak in Minas Gerais, came to São Paulo, and is now infesting the city's environs."

The researchers are planning field research, alongside teams from other units of USP and groups led by Renato de Souza, a researcher at Adolfo Lutz Institute's Arbovirology Unit, and Margareth Capurro, a researcher

in ICB-USP's Parasitology Department, with the aim of finding out whether urban transmission of yellow fever virus has occurred via the mosquito *Aedes aegypti* in São Paulo.

"Despite the situation we're in, with a large number of cases of infection in the city of São Paulo, we don't yet have unequivocal, concrete evidence that urban transmission has occurred," Zanotto said. "This information is crucial to enable us to evaluate possible strategies to respond to the virus, including vaccination strategies. We'll try to obtain these answers in the weeks ahead."

**More information:** Carla M. Barbosa et al, Yellow Fever Virus DNA in Urine and Semen of Convalescent Patient, Brazil, *Emerging Infectious Diseases* (2017). [DOI: 10.3201/eid2401.171310](https://doi.org/10.3201/eid2401.171310)

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