Microcephaly screening alone won't detect all cases of Zika virus in newborns, study suggests

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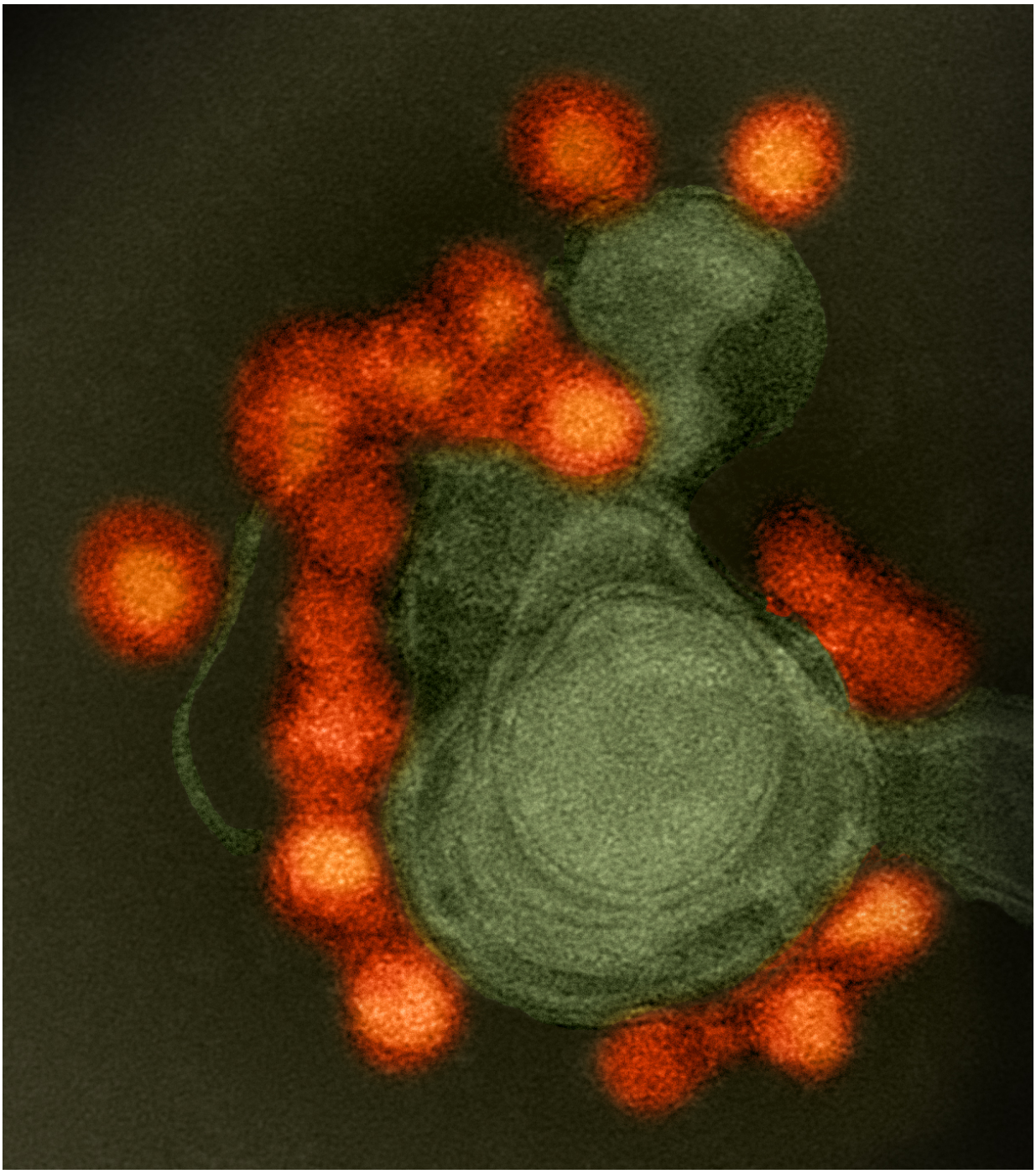

Transmission electron microscope image of negative-stained, Fortaleza-strain Zika virus (red), isolated from a microcephaly case in Brazil. The virus is associated with cellular membranes in the center. Credit: NIAID

Zika virus infection cannot be accurately diagnosed in newborns solely on the basis of microcephaly screening, according to the largest study of its kind to date published in *The Lancet*. The findings suggest that signs and symptoms of brain abnormalities, regardless of head circumference, should also be included in screening criteria to detect all affected newborns.

"Our study, which included all suspected cases of microcephaly in newborns in Brazil up to February, discarded three out of five cases after a full investigation as most suspected cases ended up being normal newborn babies with small heads. However, one in five definite or probable Zika cases had head circumference values in the normal range. Therefore, the current focus on microcephaly screening alone is too narrow", explains lead author Professor Cesar G Victora from the Universidade Federal de Pelotas in Brazil.

Zika virus is known to cause microcephaly, a birth defect marked by smaller head and brain size. Following the 2015 Zika outbreak in northeast Brazil, the Brazilian Ministry of Health (MOH) set up a surveillance system for microcephaly, and suspected cases were selected on the basis of small head circumferences. By February 27, 2016, nearly 5909 suspected cases were reported, including 5554 (94%) live births.

In the largest case series on suspected Zika virus infection to date, Victora and colleagues used data from the Brazilian MOH surveillance system to describe the clinical (eg, sex, gestational age, imaging findings, maternal history of rash, mortality) and anthropometric (eg, head circumference and birthweight) characteristics of live born babies. In total, they reviewed all 1501 live born cases (27%) that had been fully investigated. Suspected cases were divided into five categories according to diagnostic certainty of Zika infection: definite, highly probable, moderately probable, somewhat probable, and discarded (not deemed to be Zika).

The findings showed that compared with 899 cases who were discarded, the 602 definite or probable cases had small head circumference at birth and their mothers were more likely to experience a rash during pregnancy (21% vs 61%). They were also four times more likely to die in the first week of life.

Rashes in late pregnancy were linked with brain abnormalities despite normal head sizes. Development of the cranium largely occurs by week 30, so children can be born with normal sized heads but still have important brain damage. This finding raises the possibility that Zika virus infection in newborn babies might lead to brain damage, say the authors.

Importantly, over 100 of the definite or probable cases had head circumferences within normal range and would not have been included in an analysis for Zika if smaller cutoffs had been used (table 2). "Although we believe that the underreporting of microcephaly cases is rare during the epidemic, newborns infected with the virus late in pregnancy may go unreported due to their head size being within normal range", says Victora. "Moreover, for a third of these definite or probable cases there was no history of rash during pregnancy."

According to Victora, "Our findings suggest that among pregnancies affected by Zika virus, some foetuses will have brain abnormalities and microcephaly, other will have abnormalities with normal head sizes, and others will not be affected. A surveillance system aimed at detecting all affected newborns should not just focus on microcephaly and rash during pregnancy and should be revised, and examination of all newborns during epidemic waves should be considered."

However, the authors note that these findings should be taken with caution, particularly because of the missing data that is inevitable when using routine surveillance systems. They also cannot yet determine the

ideal cut-off point for head circumference with certainty, as knowledge about Zika virus congenital syndrome is quickly evolving.

The authors also show that the peak of the microcephaly epidemic occurred at the end of 2015, about 6 to 9 months later than the peak of the Zika virus epidemic in northeast Brazil. Since then, the numbers of newly reported cases of microcephaly have been falling steadily. Victora predicts that, "Because a new wave of Zika virus infection took place in Southeastern Brazil in early 2016, there could be a second wave of microcephaly at the end of the year."

Writing in a linked Comment, Dr Jörg Heukelbach from the Department of Community Health, School of Medicine, Federal University of Ceará, Brazil, and Dr Guilherme Loureiro Werneck from the Department of Epidemiology, Social Medicine Institute, State University of Rio de Janeiro, Brazil, say: "For incorporating new information besides microcephaly and rash during pregnancy to detect all affected cases, neurological signs and symptoms could be eligible, but might be difficult to obtain in most settings because of insufficient specialised personnel. The development of an accurate serological test that could be incorporated into routine prenatal care will be essential, and its validation a research priority...While the current outbreak is a paradigmatic example of how quickly evolving systematic scientific evidence can (and should) change the view on a disease within months, it can be expected that public health authorities, and also the scientific community, will struggle for many years with Zika epidemics and its consequences in Brazil and elsewhere."

More information: *The Lancet*, www.thelancet.com/journals/lan … (16)30902-3/abstract

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