

# Zika virus and birth defects: correlation or causation?

Earlier this year, World Health Organization experts said that “a causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, though not yet scientifically proven”.

How might scientists prove such a link?

**R**ossi A. Hassad, an epidemiologist and professor of statistics at Mercy College, New York, writes: It is no longer just an association. The US Centers for Disease Control and Prevention has concluded that the mosquito-borne Zika virus is a cause of fetal microcephaly (smaller-than-normal head) and other severe abnormalities ([1.usa.gov/1SaYTYV](http://1.usa.gov/1SaYTYV)). This was based on an evaluation of data encompassing the current outbreaks in Brazil and Colombia, as well as in French Polynesia in 2013–2014, using established scientific criteria ([bit.ly/24lUsU4](http://bit.ly/24lUsU4); [bit.ly/1qoczMH](http://bit.ly/1qoczMH)). Such scrutiny was particularly necessary given the reliance on evidence from observational or non-experimental studies, and hence, concerns about confounding. Data from experimental studies using animal models are not yet available.

A strong and consistent association between maternal Zika virus infection and babies born with microcephaly was observed; fetal abnormalities were detected by ultrasonography in 12 of 42 Zika-positive women (29%) and in none of 16 Zika-negative women ([bit.ly/22mY7MU](http://bit.ly/22mY7MU); [bit.ly/1QxQVJW](http://bit.ly/1QxQVJW)). This suggested that women with Zika virus infection are at greater risk of adverse pregnancy outcomes; however, the researchers had to rule out confounding or plausible alternative explanations, such as other infections, medications, and chemical exposure.

The key evaluation criterion was the temporality or time sequence

of the association: for there to be a causal relationship, the maternal Zika virus infection must precede the fetal microcephaly and occur at a critical stage of the pregnancy. The evidence revealed multiple cases (based on reported symptoms or laboratory confirmation) where the mother was infected in the first or early second trimester of pregnancy, a timing consistent with the development of such fetal disorders. Also, the Zika virus outbreak preceded the substantial increase in microcephaly cases for the current and past epidemics. Furthermore, the pattern of fetal abnormalities (including severe microcephaly) has been characterised as distinctive and is being referred to as “congenital Zika syndrome”, and such specificity of outcome supports causal inference.

## Based on the totality of the evidence, it is reasonable to infer that maternal Zika virus infection is a cause of fetal microcephaly

An overarching criterion was the biological plausibility of this association. In other words, does it make medical sense that maternal Zika virus infection can cause microcephaly? Indeed, microcephaly is known to be caused by other infectious pathogens, and the Zika virus was recently isolated from the

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brain tissue of fetuses and infants with microcephaly – directly implicating the virus in this disease process.

Finally, a causal criterion, particularly relevant to this context, is the concept of an association between “a rare exposure and a rare defect”. The logic of this approach is that an association between a rare pregnancy exposure (Zika virus) and a unique pattern of fetal brain malformations implies causation because of the “unlikelihood of the two events occurring together”. Zika virus infection is widespread in Brazil. However, it is rare in terms of the number of pregnant women who became infected after travelling to countries where the Zika virus epidemic is active, and who subsequently had babies with a severe form of microcephaly, a rare defect which is estimated to occur in 6 infants per 10 000 liveborn infants in the United States

Based on the totality of the evidence, including the absence of plausible alternative explanations for this association, it is reasonable to infer that maternal Zika virus infection is a cause of fetal microcephaly and other severe abnormalities. This means that women with Zika virus infection possess an increased risk of having a baby with such abnormalities. It does not mean, that all women who have Zika virus infection during pregnancy will have babies with these abnormalities. Researchers are seeking to identify factors that either increase or decrease the risk of these adverse pregnancy outcomes, and to quantify the risk more precisely. ■