

Children with cytomegalovirus infection by age one more likely to develop tuberculosis in childhood

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Tuberculosis (TB) is among the top 10 causes of global child mortality, and children are at highest risk of developing the disease within the first

few years of life. One hypothesis for this increased risk of TB early in life is altered immunity induced by viral infections. While a few studies have cited a possible association between TB and the viral infection cytomegalovirus (CMV), large, community-based studies with long-term follow-up have not been performed, until now.

A new study by researchers at Boston University School of Public Health (BUSPH) and the University of Cape Town, South Africa has found that infants who contract CMV are at a significantly higher risk of developing TB later in their childhood.

Published in the journal *The Lancet Global Health*, the study found that babies infected with CMV in the first year of life were more than three times more likely to develop TB after age 1 than [children](#) who had not become infected with CMV.

Although it is one of the most common [viral infections](#) among people of all ages, many people are not familiar with—or aware that they have contracted—CMV, because it is usually harmless and often remains dormant once a person is infected. Most people who have it show no signs or symptoms. However, pregnant women who acquire CMV during pregnancy can pass the virus to their babies, who occasionally experience severe complications such as hearing loss, neurologic deficits, or death.

The study findings suggest that CMV may weaken babies' immune systems, leading to a higher risk of developing TB beyond age 1.

"CMV is an understudied pathogen and there is much we do not know about how it transmits, as well as its immunological and public [health](#) impact," says study lead author Dr. Leonardo Martinez, assistant professor of epidemiology at BUSPH. "Young children who acquire CMV in the first few months of life may be impacted immunologically by exposure to the virus, even if they are not impacted clinically, putting

them at higher risk for other diseases such as tuberculosis. This was the hypothesis we wanted to test in this study."

This research is part of the multidisciplinary Drakenstein Child Health Study, and is the first birth cohort study to examine potential links between CMV infection and subsequent development of TB disease. In the community-based study outside of Cape Town, South Africa, Martinez, and colleagues followed approximately 1,000 pregnant women and their children from 2012 onwards. The researchers tested the newborn babies for CMV at birth, age 3 and 6 weeks, and age 3, 6, 12, and 24 months. The children were then evaluated for TB disease for a median of 6.9 years, and up to age 9.

In their first year of life, 42 percent of infants tested positive for CMV, and the babies who were breastfed were more likely to test positive for CMV. The researchers estimated that 48 percent of TB among children older than 12 months was attributable to a CMV infection before age 1.

Notably, children who had a high viral load of CMV were at an even higher risk of TB, indicating a "dose-response effect," says Dr. Martinez.

Dr. Heather Zar, principal investigator of the Drakenstein Child Health Study and study senior author and chair of the Department of Paediatrics and Child Health at the University of Cape Town, says that among the study population, the team found "some of the highest rates of TB disease in children in the world—despite no child HIV infection, good nutrition and excellent coverage for childhood immunizations, including 100 percent coverage for BCG. We also found that TB occurred commonly with acute pneumonia, highlighting that TB is common as a cause of pneumonia but under-recognized in areas with high TB prevalence."

New strategies to prevent this high burden of TB disease in children are

crucial, the researchers say.

While more research is needed, they say that these findings open several potential mitigation efforts to reduce the risk of babies acquiring TB through the prevention of CMV, such as CMV vaccines and anti-viral agents, which are currently being tested in clinical trials.

"Unfortunately, development of TB vaccines has been very slow—we haven't had a new TB vaccine in over 100 years," Dr. Martinez says. "If further studies confirm that this relationship between CMV and tuberculosis is causal, a CMV vaccine could potentially have indirect effects on tuberculosis and would be a major game-changer." Other recent trials have suggested that certain antibiotics may prevent vertical transmission of CMV from mother to child.

Overall, "our study suggests that prevention of CMV infection perinatally or early in life may be a novel potential strategy to prevent the large burden of TB disease in children," Dr. Zar says. "This is an exciting possibility for which further clinical studies are needed."

More information: Leonardo Martinez et al, Cytomegalovirus acquisition in infancy and the risk of tuberculosis disease in childhood: a longitudinal birth cohort study in Cape Town, South Africa, *The Lancet Global Health* (2021). [DOI: 10.1016/S2214-109X\(21\)00407-1](https://doi.org/10.1016/S2214-109X(21)00407-1)

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