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Children with CMV infection are at high risk of developing TB disease in childhood

Children that acquire cytomegalovirus (CMV) in the first year of life are at high risk of subsequently developing tuberculosis (TB) disease, a team of University of Cape Town (UCT) and international scientists has found.

The findings suggest that efforts to prevent TB in early childhood in high-burden countries might need to deter or delay acquisition of CMV perinatally or in the first months of life.

Approximately one million children develop TB each year globally, with half occurring in early childhood. The risk of TB disease after recent exposure is greatest before the age of five years, approaching 20% at two years of age post-infection.

This study is part of the Drakenstein Child Health Study and followed a birth cohort in Paarl outside Cape Town. In this birth cohort, 1 225 pregnant women were enrolled, followed through pregnancy and childbirth, and children were followed from birth through childhood. Children were given the Bacillus Calmette–Guérin vaccination at birth as per national policy. Infants were frequently tested for CMV through the first two years of life and children were followed up to nine years of age for TB.

Published in *The Lancet Global Health*, the study found that 42% of children became infected with CMV in the first year of life. The study also found a very high incidence of TB disease through childhood, with some of the highest rates of TB disease globally in children. The average age of TB disease in children was 1.5 years. Infants who were infected with CMV had over a three times higher risk of subsequent TB disease throughout childhood.

"We found this association even when we restricted the outcome to microbiologically confirmed TB. Children with high CMV load were at especially high-risk, implying a biological gradient. This finding was not modified by tuberculin conversion or known TB exposure, suggesting that subsequent immune dysfunction caused by CMV infection may explain these results," said Professor Heather Zar, lead investigator and Chair of the Department of Paediatrics & Child Health at UCT.

Zar said CMV prevalence in communities can reach more than 50% in the first one to two years of life.

"Our findings suggest that breastfeeding is probably a major transmission pathway for acquisition of CMV. Additionally, approximately 2% of participants were diagnosed with congenital CMV.

"Socioeconomic status, household income, and family size were not associated with CMV acquisition, indicating that several factors commonly related to TB disease were not associated with CMV acquisition," she said.

According to Zar, CMV is often asymptomatic and may adversely affect the immune system through CMV-specific memory CD4+ and CD8+ T-cell activation.

Leonardo Martinez, co-lead investigator and assistant professor at the School of Public Health at Boston University, also noted that CMV infection was not associated with tuberculin conversion in infancy.

"Tuberculin conversion and household TB exposure did not act as a mediator between the acquisition of CMV and progression to TB," he said. "The result showing that CMV increases the risk of TB disease, but not recent *Mycobacterium tuberculosis (M. tb)* infection or exposure, suggesting that immunological alterations due to CMV infection might increase the risk of progression from *M. tb* infection to disease in young children."

Martinez shared: "We found consistent evidence suggesting that a dose-response was present between CMV load values and TB risk in early childhood for different timepoints and follow-up time periods. This result further supports a causal relationship between CMV and TB disease. In total, we found that over 40% of TB disease after one year of age was attributable to CMV in the first few months of life."

The findings raise possibilities for new strategies to prevent TB in children that may include prevention or treatment of CMV infection in infants.

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