Cytomegalovirus Acquisition in Infancy and the Risk of Tuberculosis in Childhood: A Prospective South African Birth Cohort

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Cytomegalovirus acquisition in infancy and the risk of tuberculosis disease in childhood: a longitudinal birth cohort study in Cape Town, South Africa

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THE LANCET

Global Health
Tuberculosis risk is highest among young children

Marais et al, 2005 IJTLD

Comstock et al, 1974 Am J Epi
Tuberculosis risk is highest among young children

Gupta et al, 2020
Nature Medicine

Martinez et al, 2020
The Lancet
Acquisition of viral infections

• Acquisition of viral infections, such as cytomegalovirus, in early life may alter the immune system

• However how this impacts later development of tuberculosis is not well understood
Drakenstein Child Health Study, 2012 – 2021

Pregnant Women
20 – 28 weeks gestation

Infant-birth
Baseline Evaluations

Follow-up for disease

Tuberculosis-related Tests:
1) Tuberculin skin testing at 6 and 12 months and then annually until 3 years old
2) Tuberculosis continuously evaluated at regular and sick visits
Research Question

• Is there a relationship between cytomegalovirus infection in infancy and the subsequent development of tuberculosis disease in childhood?

• Is there a dose-response relationship between cytomegalovirus load and tuberculosis disease risk?

• What proportion of tuberculosis in childhood is attributable to cytomegalovirus infection in infancy?
Cytomegalovirus testing

- Cytomegalovirus was assessed in children through cytomegalovirus-specific DNA using nasopharyngeal swabs
- We performed quantitative, multiplex, real-time PCR
- Children had nasopharyngeal swabs taken at birth and then multiple time points throughout the first 2 years of life
Tuberculosis evaluation

- Children were followed up for tuberculosis disease from birth until April 2021.

- Sputum smear specimens and induced sputum in duplicate for tuberculosis culture and Xpert MTB/RIF from all children with a TST induration >10 mm, and from children with suspected tuberculosis disease.

- Chest radiographs were taken in all children with suspected tuberculosis.
963 children with 1 or more CMV test

Median 6 (IQR, 2-11) CMV tests per child

89% of CMV tests were performed prior to 1 year of age
Cumulative prevalence of CMV reaches ~40% at one year old

Large jump from 6 to 24 weeks
Cytomegalovirus strongly related to breastfeeding

- CMV <12 weeks: 3.2 (95% CI, 1.4-7.6)
- CMV <24 weeks: 4.7 (95% CI, 2.5-9.0)
- CMV <52 weeks: 4.6 (95% CI, 2.4-8.9)
- CMV <104 weeks: 3.7 (95% CI, 2.1-6.5)
Cytomegalovirus acquisition is a major risk factor for childhood tuberculosis

Cytomegalovirus <1 year old

Tuberculosis incidence >1 year old

Highly significant no matter when CMV occurred
Consistent results regardless of timing of CMV

<table>
<thead>
<tr>
<th>Timing of Cytomegalovirus Positivity</th>
<th>Follow-up for tuberculosis</th>
<th>AHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months and before</td>
<td>&gt;6 months of age</td>
<td>3.1 (1.8-5.5)</td>
</tr>
<tr>
<td>12 months and before</td>
<td>&gt;12 months of age</td>
<td>3.2 (1.6–6.4)</td>
</tr>
<tr>
<td>24 months and before</td>
<td>&gt;24 months of age</td>
<td>3.0 (1.2-7.2)</td>
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</table>
Consistent results with additional adjustment

<table>
<thead>
<tr>
<th>Regression adjustment</th>
<th>Adjusted Hazard Ratio</th>
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<tbody>
<tr>
<td>Base model adjusted for demographic and maternal factors</td>
<td>3.2 (95% CI, 1.6–6.4)</td>
</tr>
<tr>
<td>Additionally adjusted for tuberculin skin test conversion</td>
<td>3.7 (95% CI, 1.7–8.4)</td>
</tr>
<tr>
<td>Additionally adjusted for household TB exposure</td>
<td>3.2 (95% CI, 1.6–6.5)</td>
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</tbody>
</table>
Dose-response with viral load

Dose-response relationship seen between lower and high CMV viral loads

Children with higher CMV viral loads were at greatest risk
What proportion of tuberculosis in childhood is attributable to cytomegalovirus acquisition in infancy?

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<th>PAF (95% CI)</th>
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<tr>
<td>6 months and before</td>
<td>&gt;6 months of age</td>
<td>42.2 (21.8–61.0)</td>
</tr>
<tr>
<td>12 months and before</td>
<td>&gt;12 months of age</td>
<td>47.9 (20.5–69.3)</td>
</tr>
<tr>
<td>24 months and before</td>
<td>&gt;24 months of age</td>
<td>48.3 (8.9–74.4)</td>
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</table>
Could we prevent tuberculosis through prevention of CMV?

- Not enough empirical evidence
- We need further immunological and epidemiological data
- Multiple phase 3 trials on prevention of CMV ongoing
Conclusions

• Cytomegalovirus may be an important driver of high tuberculosis risk in young children

• Deterring or delaying acquisition of cytomegalovirus perinatally or in the first months of life may be necessary to control pediatric tuberculosis
Funding Support:
– Bill and Melinda Gates Foundation # OPP 1017641
– Medical Research Council South Africa
Thank you for listening

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