

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

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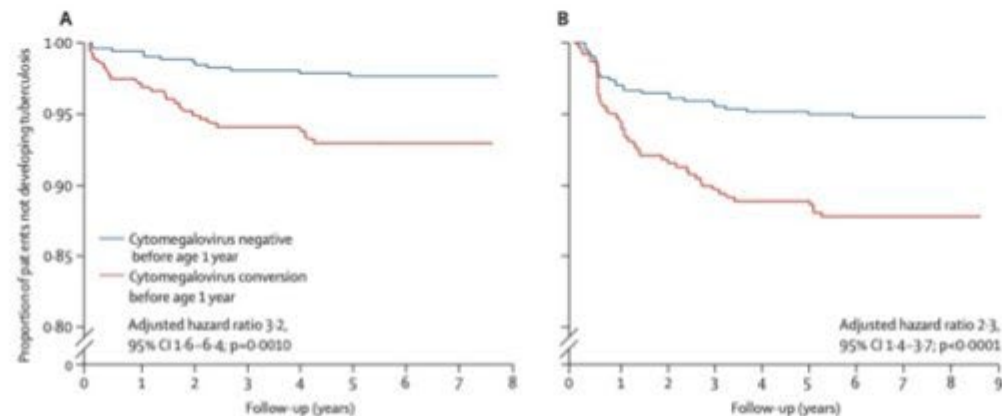
Cytomegalovirus acquisition in infancy and the risk of tuberculosis disease in childhood: a longitudinal birth cohort study in Cape Town, South Africa



Leonardo Martinez, Mark P Nicol, Catherine J Wedderburn, Attie Stadler, Maresa Botha, Lesley Workman, David M le Roux, Heather J Zar



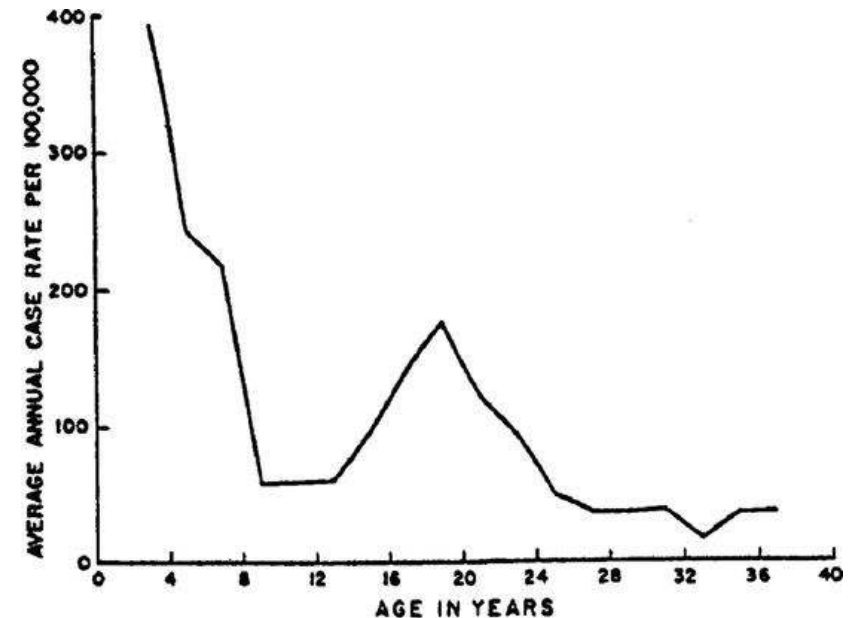
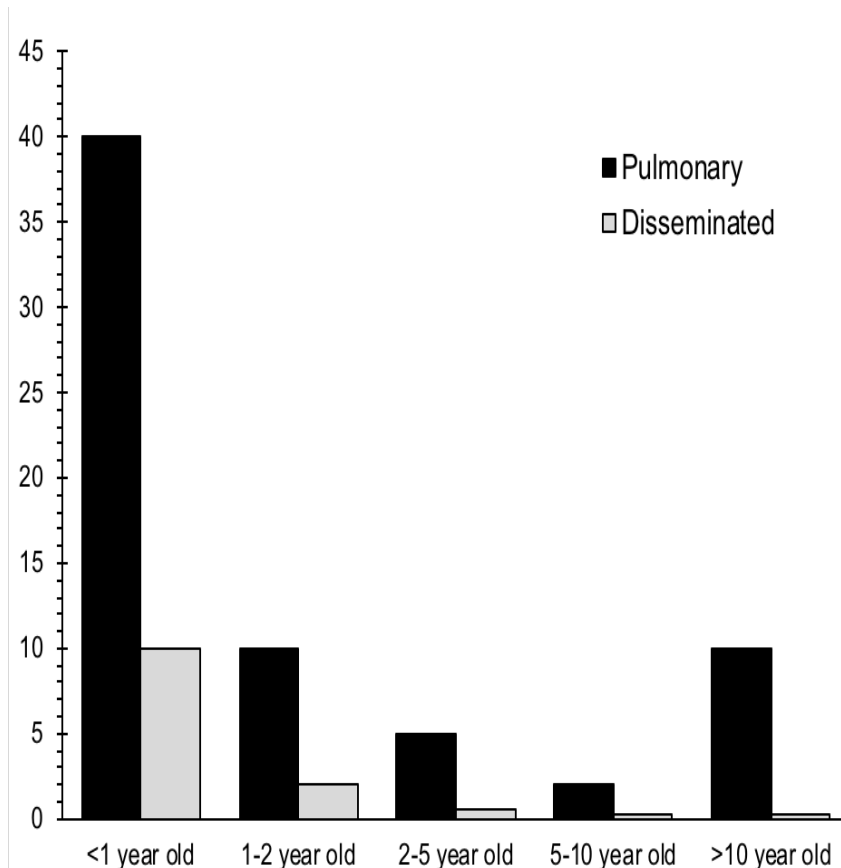
THE LANCET Global Health



Tuberculosis risk is highest among young children

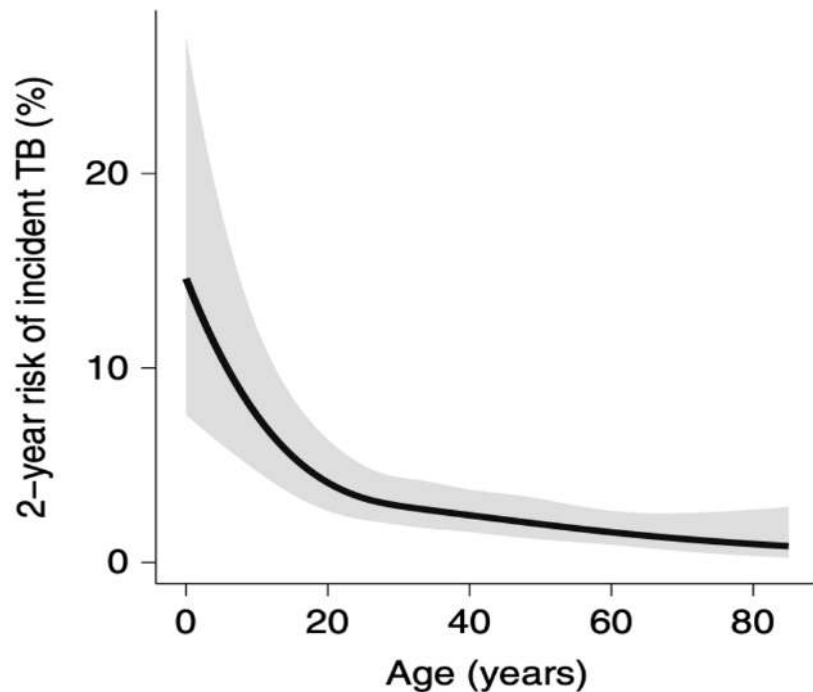
Comstock et al, 1974 Am J Epi

Marais et al, 2005 IJTLD

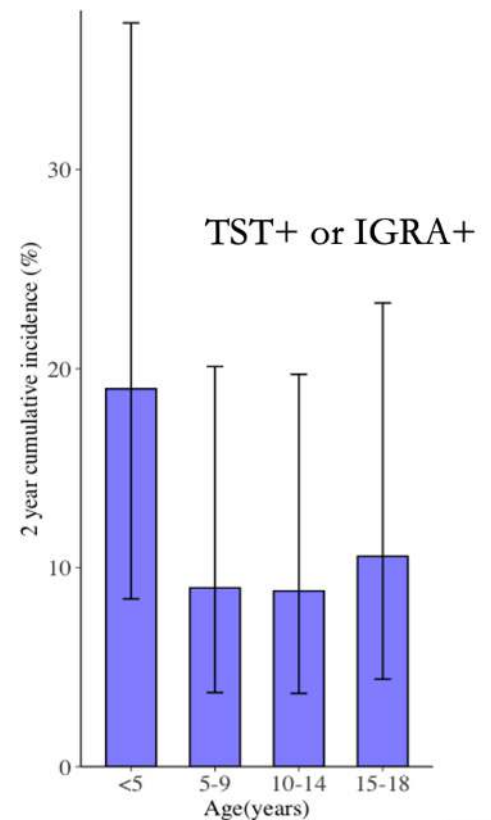


Tuberculosis risk is highest among young children

Gupta et al, 2020
Nature Medicine



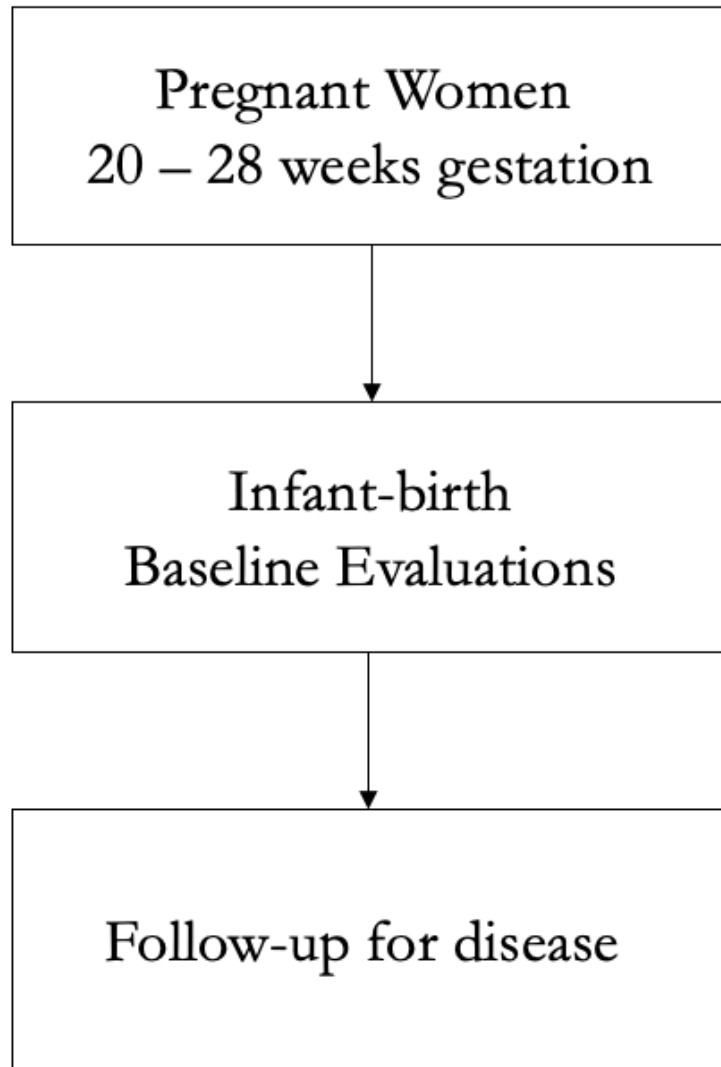
Martinez et al, 2020
The Lancet



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



Tuberculosis-related Tests:

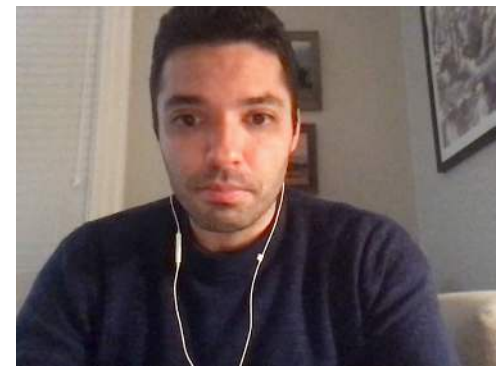
- 1) Tuberculin skin testing at 6 and 12 months and then annually until 3 years old
- 2) Tuberculosis continuously evaluated at regular and sick visits

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



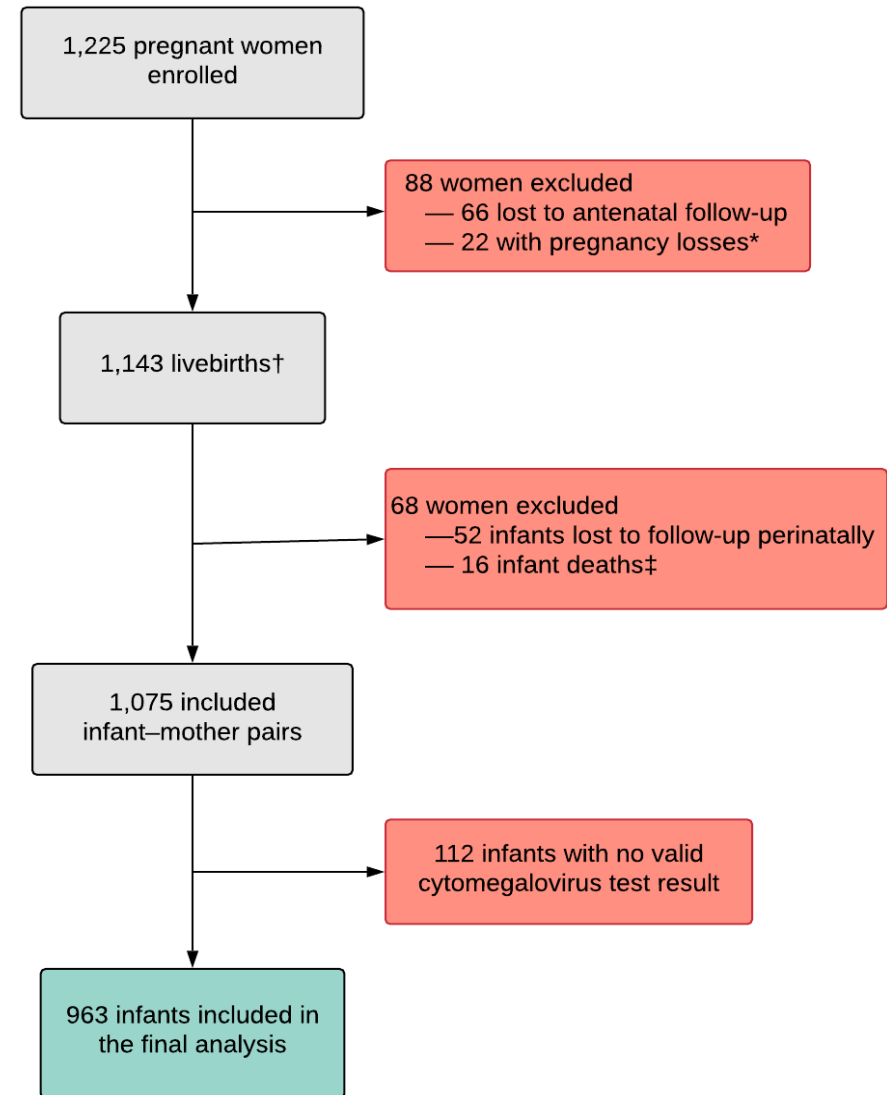
Tuberculosis evaluation

- 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

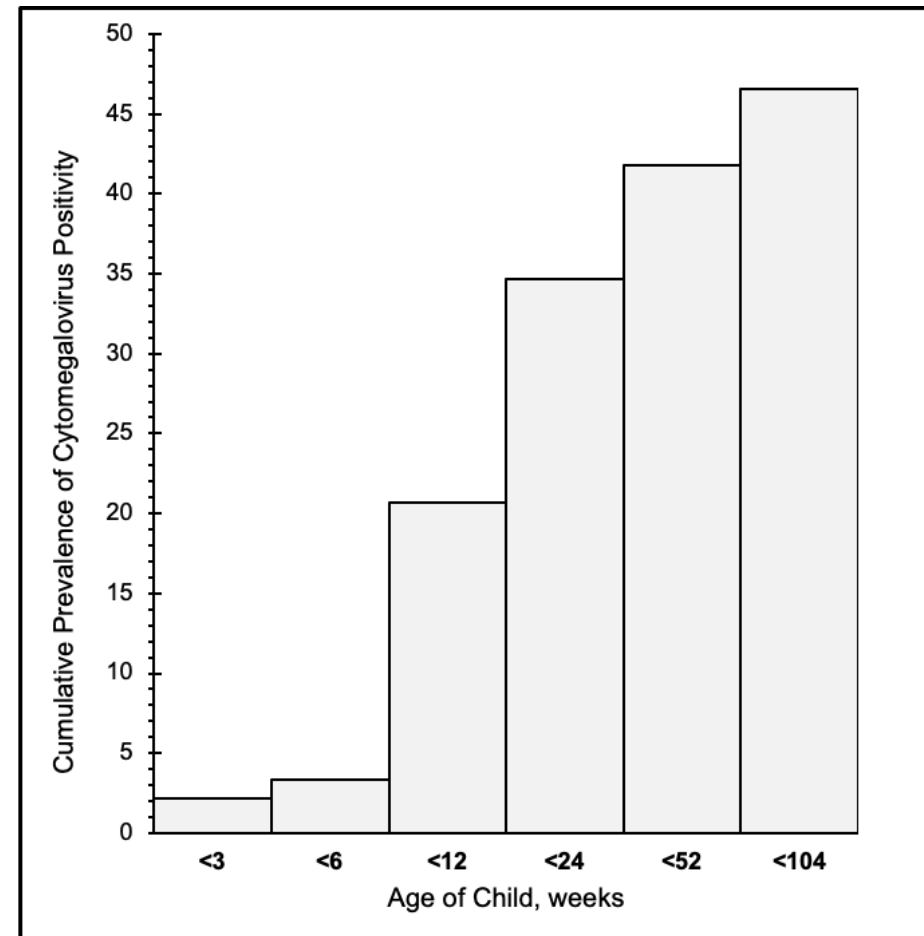
Median 6 (IQR, 2-11) CMV tests
per child

89% of CMV tests were
performed prior to 1 year of age

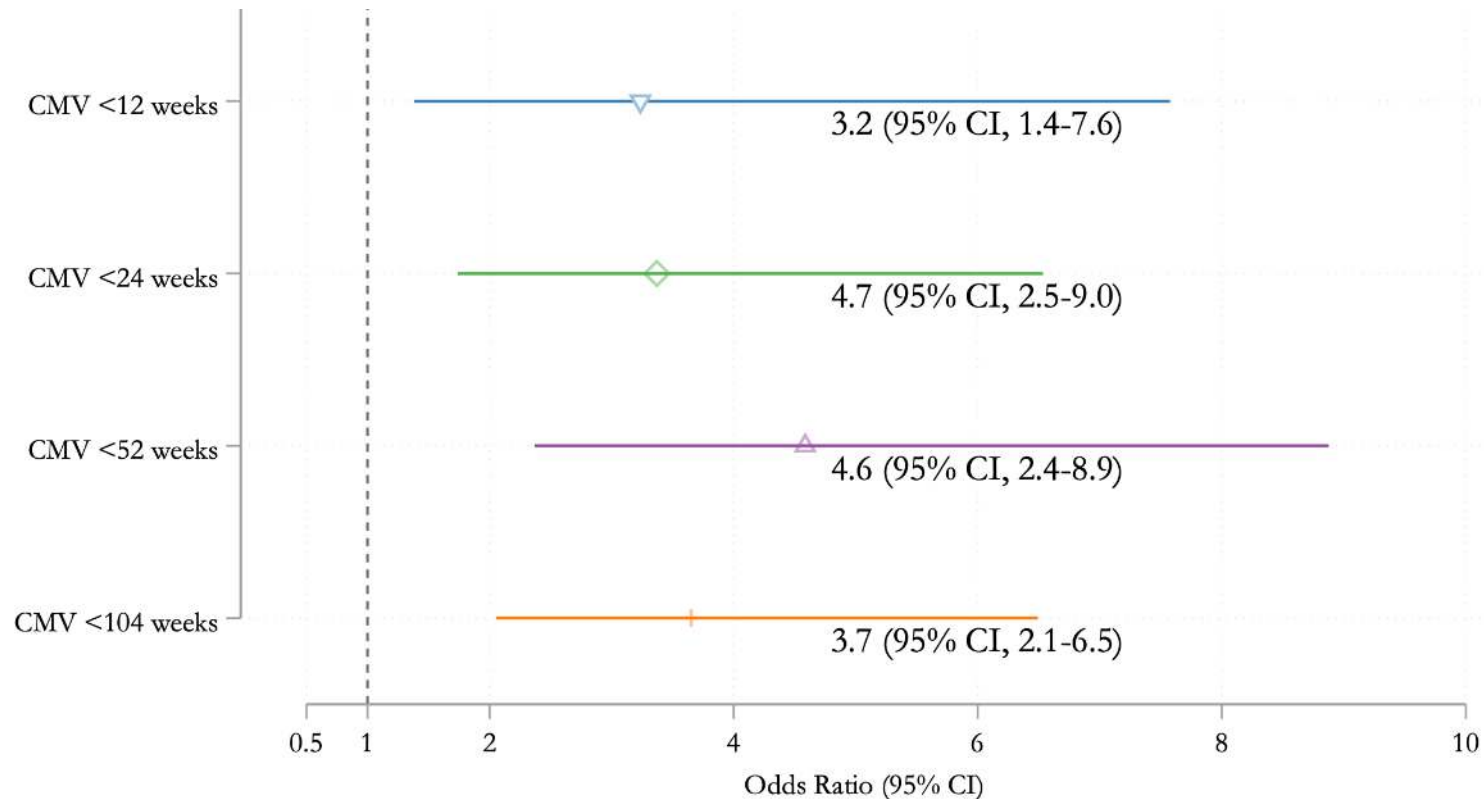


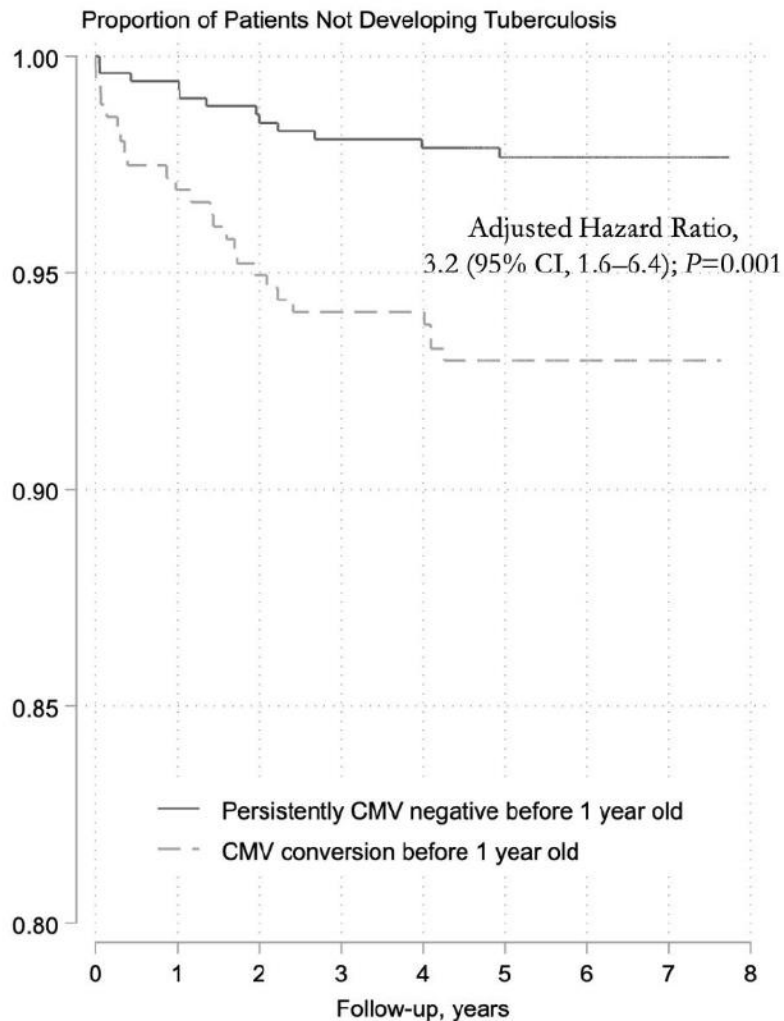
Cumulative prevalence of CMV reaches ~40% at one year old

Large jump from 6 to 24 weeks



Cytomegalovirus strongly related to breastfeeding





Cytomegalovirus acquisition is a major risk factor for childhood tuberculosis

Cytomegalovirus <1 year old

Tuberculosis incidence >1 year old

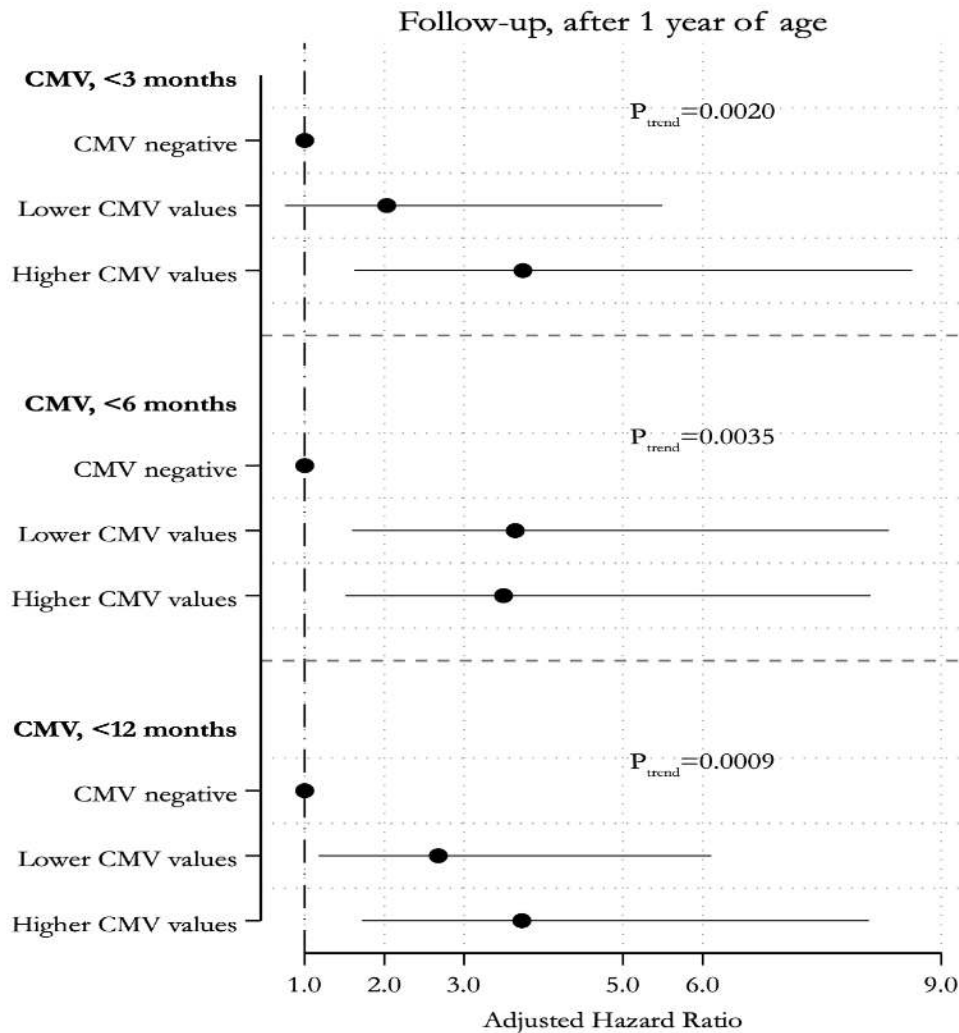
Highly significant no matter when
CMV occurred

Consistent results regardless of timing of CMV

Timing of Cytomegalovirus Positivity	Follow-up for tuberculosis	AHR (95% CI)
6 months and before	>6 months of age	3.1 (1.8-5.5)
12 months and before	>12 months of age	3.2 (1.6–6.4)
24 months and before	>24 months of age	3.0 (1.2-7.2)

Consistent results with additional adjustment

Regression adjustment	Adjusted Hazard Ratio
Base model adjusted for demographic and maternal factors	3.2 (95% CI, 1.6–6.4)
Additionally adjusted for tuberculin skin test conversion	3.7 (95% CI, 1.7–8.4)
Additionally adjusted for household TB exposure	3.2 (95% CI, 1.6–6.5)



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?

Timing of Cytomegalovirus Positivity	Follow-up for tuberculosis	PAF (95% CI)
6 months and before	>6 months of age	42.2 (21.8–61.0)
12 months and before	>12 months of age	47.9 (20.5–69.3)
24 months and before	>24 months of age	48.3 (8.9–74.4)

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



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Thank you for
listening

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