The risk of tuberculosis in children after close exposure and recent infection

Leonardo Martinez on behalf of all authors
Stanford University, School of Medicine

Pediatric tuberculosis is a global health issue

Millions of children are exposed to someone with tuberculosis annually

Tuberculosis risk in children is very high, estimated upwards of 50% in children <1 year of age

The individual and population impact of paediatric case finding and preventive interventions is not well elucidated

Dodd et al, 2014; Marais et al, IJTLD, 2004

Majority of our knowledge is based on the historical literature

STATE OF THE ART

The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era

B. J. Marais,* R. P. Gie,* H. S. Schaaf,* A. C. Hesseling,* C. C. Obihara,* J. J. Starke,[†] D. A. Enarson,[‡] P. R. Donald,* N. Beyers*

* Centre for TB Research and Education, Stellenbosch University, Cape Town, Western Cape, South Africa;
[†] Department of Pediatrics, Infectious Diseases Section, Baylor College of Medicine, Houston, Texas, USA;
[‡] International Union Against Tuberculosis and Lung Disease, Paris, France

SUMMARY

The pre-chemotherapy literature documented the natural history of tuberculosis in childhood. These disease vention in this group will reduce the burden of cavitating disease and associated disease transmission in the commu-

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Marais et al, IJTLD, 2004

Risk of Developing Pediatric Tuberculosis After Recent Infection
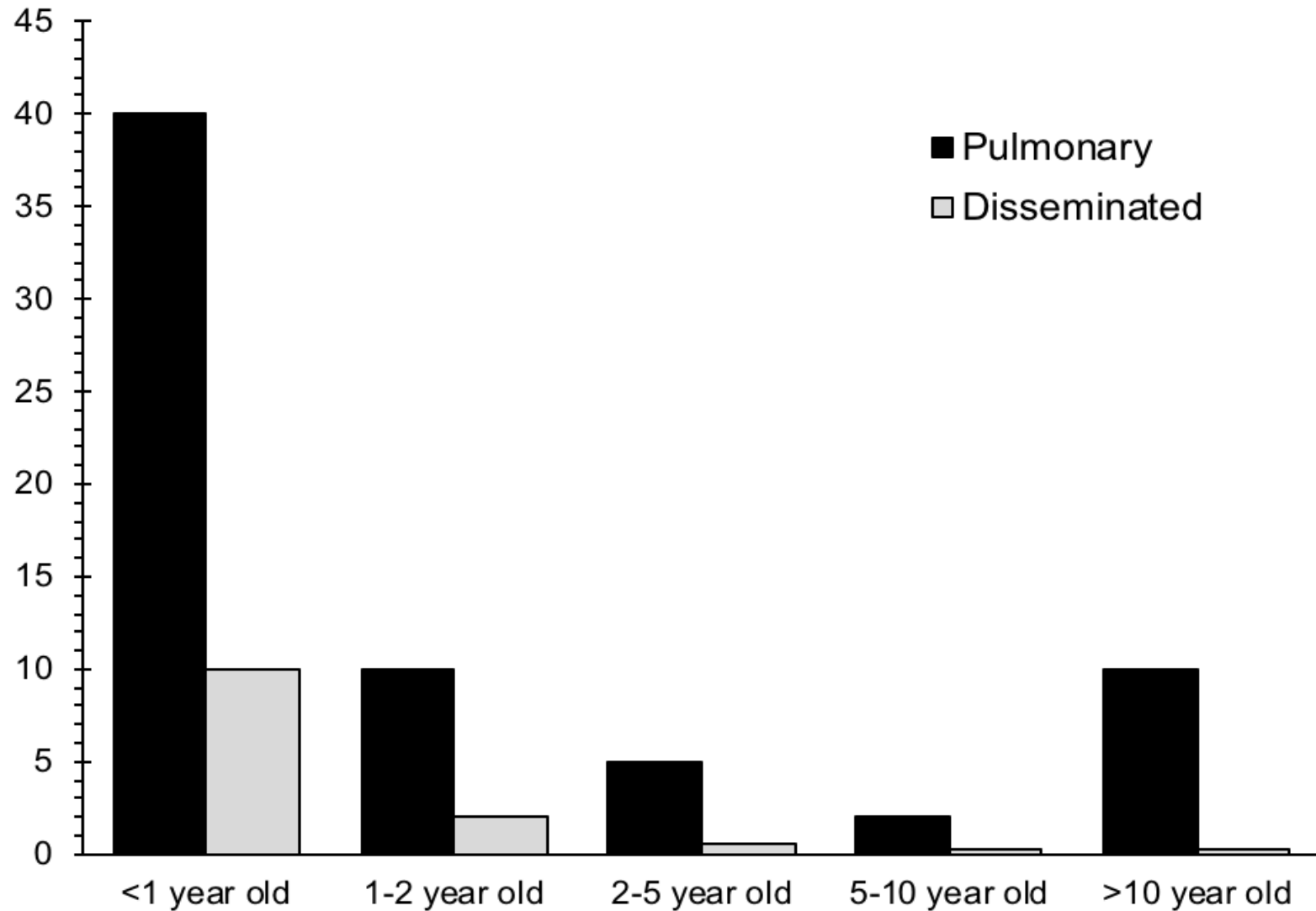
Legend: ■ Pulmonary □ Disseminated

Data adapted from Marais et al, IJTLD, 2004

Major Questions in the Pediatric Tuberculosis Literature:

1) What is the Risk of Developing Tuberculosis Given Recent Tuberculosis Exposure or Infection?

2) What is the individual- and population-level impact of preventive therapy in these children?

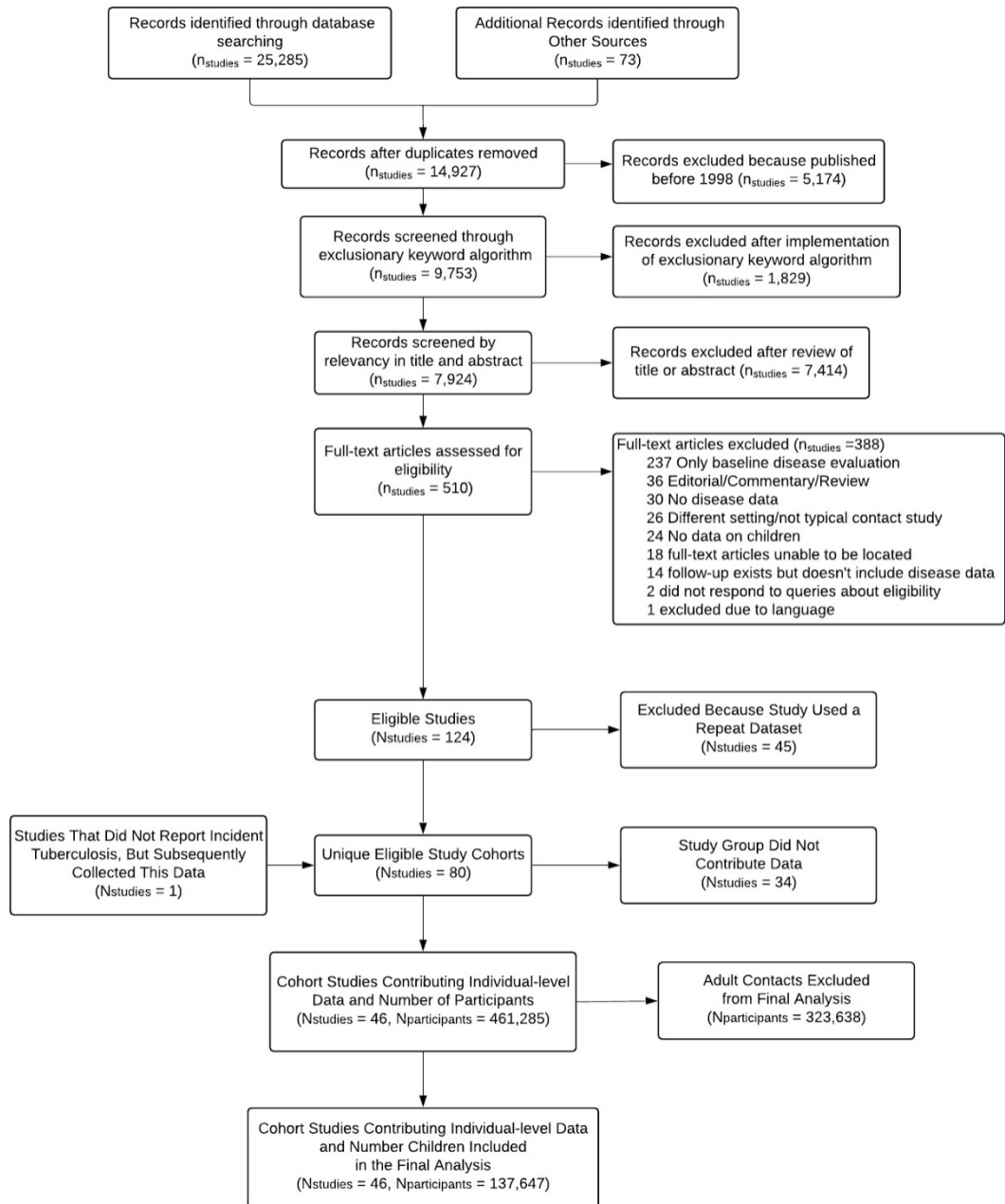Major Questions in the Pediatric Tuberculosis Literature:

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2) What is the individual- and population-level impact of preventive therapy in these children?

Flowchart of Systematic Search Process and Study Selection

Records identified through database searching
($n_{studies}$ = 25,285)

Additional Records identified through Other Sources
($n_{studies}$ = 73)

Records after duplicates removed
($n_{studies}$ = 14,927)

Records excluded because published before 1998 ($n_{studies}$ = 5,174)

Records screened through exclusionary keyword algorithm
($n_{studies}$ = 9,753)

Records excluded after implementation of exclusionary keyword algorithm
($n_{studies}$ = 1,829)

Records screened by relevancy in title and abstract
($n_{studies}$ = 7,924)

Records excluded after review of title or abstract ($n_{studies}$ = 7,414)

Full-text articles assessed for eligibility
($n_{studies}$ = 510)

Full-text articles excluded ($n_{studies}$ = 388)
237 Only baseline disease evaluation
36 Editorial/Commentary/Review
30 No disease data
26 Different setting/not typical contact study
24 No data on children
18 full-text articles unable to be located
14 follow-up exists but doesn't include disease data
2 did not respond to queries about eligibility
1 excluded due to language

Eligible Studies
($N_{studies}$ = 124)

Excluded Because Study Used a Repeat Dataset
($N_{studies}$ = 45)

Studies That Did Not Report Incident Tuberculosis, But Subsequently Collected This Data
($N_{studies}$ = 1)

Unique Eligible Study Cohorts
($N_{studies}$ = 80)

Study Group Did Not Contribute Data
($N_{studies}$ = 34)

Cohort Studies Contributing Individual-level Data and Number of Participants
($N_{studies}$ = 46, $N_{participants}$ = 461,285)

Adult Contacts Excluded from Final Analysis
($N_{participants}$ = 323,638)

Cohort Studies Contributing Individual-level Data and Number Children Included in the Final Analysis
($N_{studies}$ = 46, $N_{participants}$ = 137,647)

Martinez et al, *The Lancet* 2020

Flowchart of Systematic Search
Process and Study Selection

14,927 articles reviewed

80 study cohorts were eligible

46 study cohorts participated including 461,000 contacts

We restricted our analysis to children (N=137,647)

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Table 1. Demographic Descriptions of Included Cohort Studies.

Characteristic	Number of Studies (N=46)	Percentage
Prospective Study Design	29	63
World Health Organization High-burden†	18	38
Tuberculosis Incidence Burden, per 100 thousand persons‡		
<50	16	36
50–100	9	19
>100–200	9	19
>200	12	23
World Health Organization Region		
African	10	22
Americas	15	33
Eastern Mediterranean	1	2
European	7	15
Southeast Asia	4	9
Western Pacific	9	20
Income Group§		
High	14	3
Upper-middle	18	39
Lower-middle	8	17
Low	6	13
HIV reported	22	47

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Table. Demographic Description of Included Cohort Studies.

|		
Study Quality Assessment		
High	32	71
Moderate	11	24
Low	2	4
Mean Study Follow-up		
<2 years	24	56
2–4 years	13	30
5–7 years	3	11
>7 years	3	7
Participant size		
<1000	20	43
1000-5000	14	30
>5000	12	26
Exposed to Drug Resistant Index Cases		
Only Drug-Resistant Index Cases	3	6
Both Drug-Resistant and Susceptible Index Cases	12	26
Only Drug-Susceptible Index Cases	2	4
Preventive Therapy included	32	70
QuantiFERON or Tuberculin Skin Testing	37	80
Total		
Total Persons-years of Follow-up	427,677	…
Total Individuals Evaluated for Prevalence	137,647	…
Total Individuals Evaluated for Incidence	126,473	…

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Statistical Analysis

- Disease prevalence – mixed-effects logistic regression

- Disease incidence – parametric survival-time models

- Impact of preventative therapy – propensity score analysis

Tuberculosis Risk is Very High in the Youngest Children with Tuberculosis Infection
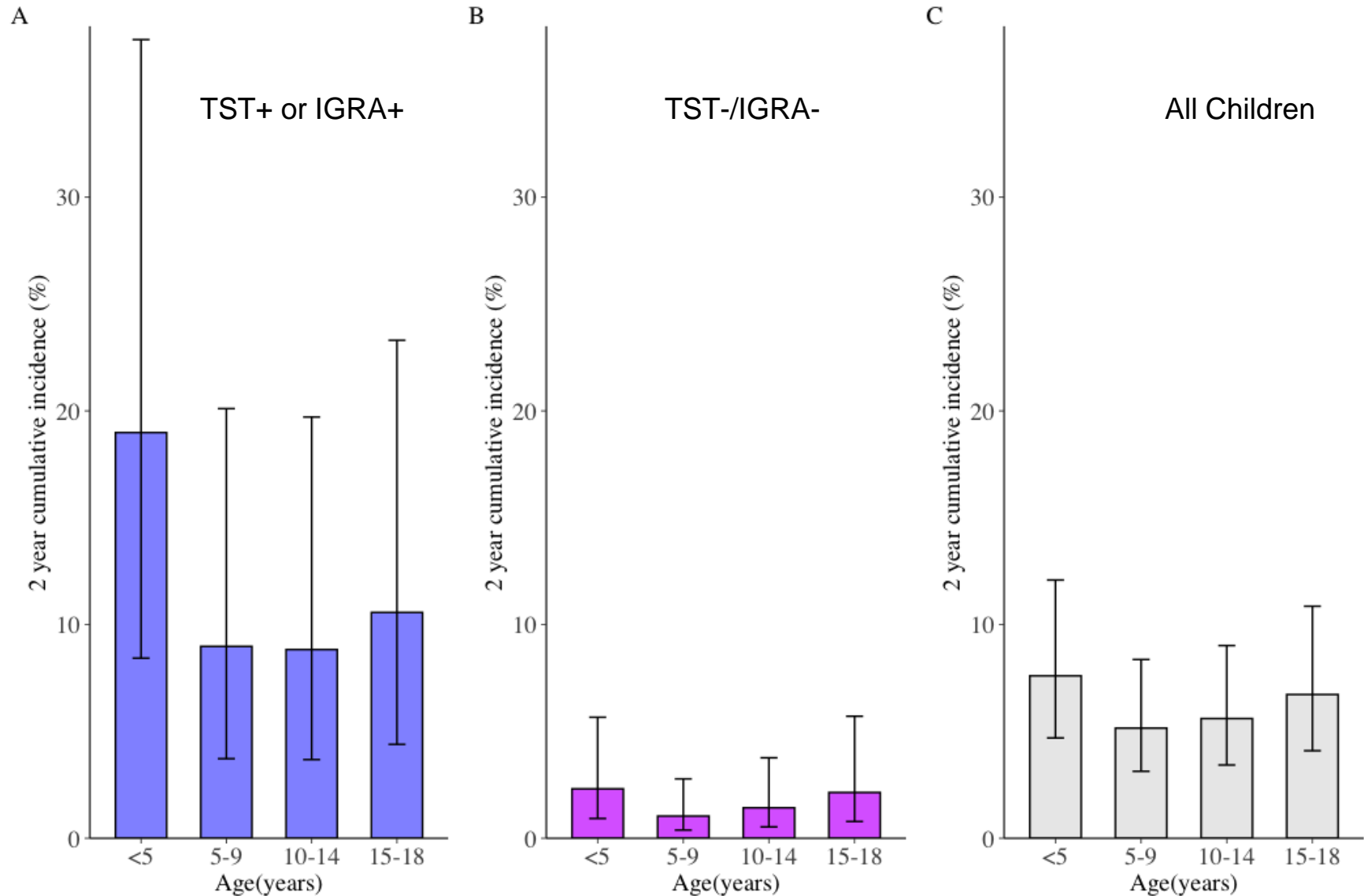
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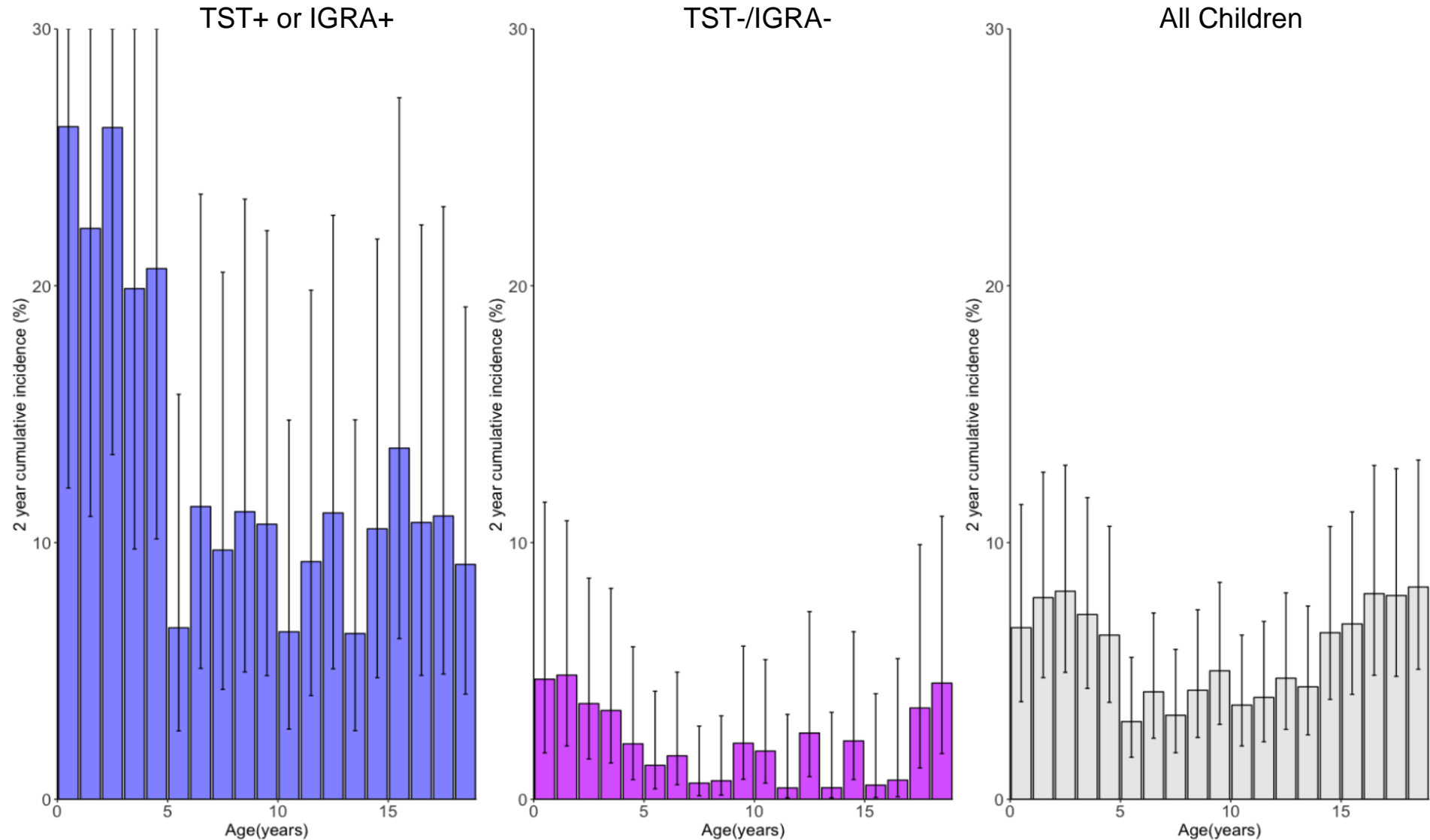
Contemporary Estimates Differ
From Historical Estimates
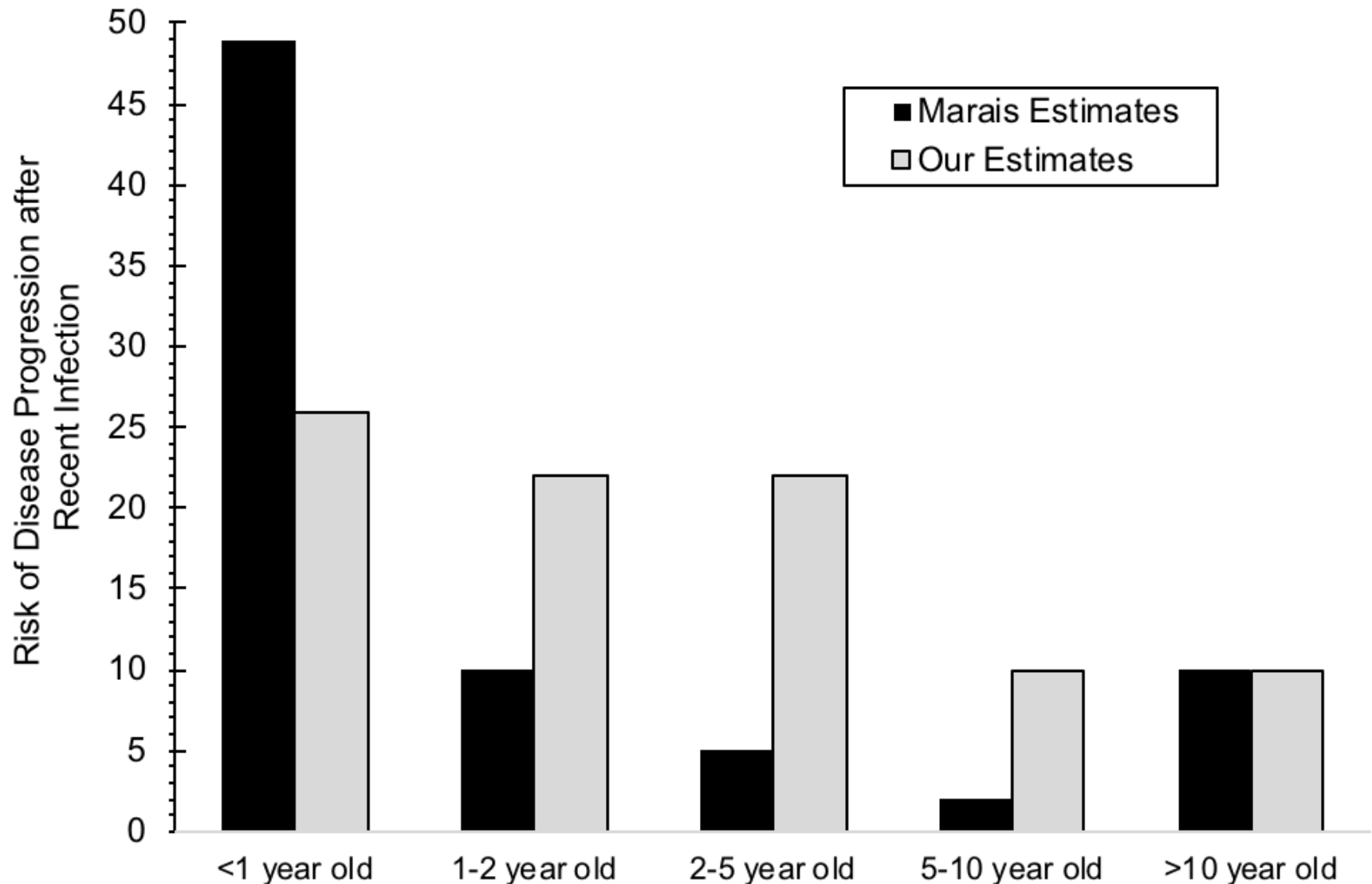
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Protective Factors for Tuberculosis Progression Amongst Children

All Studies (N=137,647)

Incident Tuberculosis Adjusted Hazard Ratio (95% CI)

Preventive Therapy
All Children, Propensity-Score Matched	0.36 (0.29, 0.46)
TST+ or IGRA+, Propensity-Score Matched	0.09 (0.05, 0.15)
TST-/IGRA-, Propensity-Score Matched	0.66 (0.40, 1.10)

Protection did not differ in high- and low-burden settings

Most Pediatric Cases Occur Within 90 Days
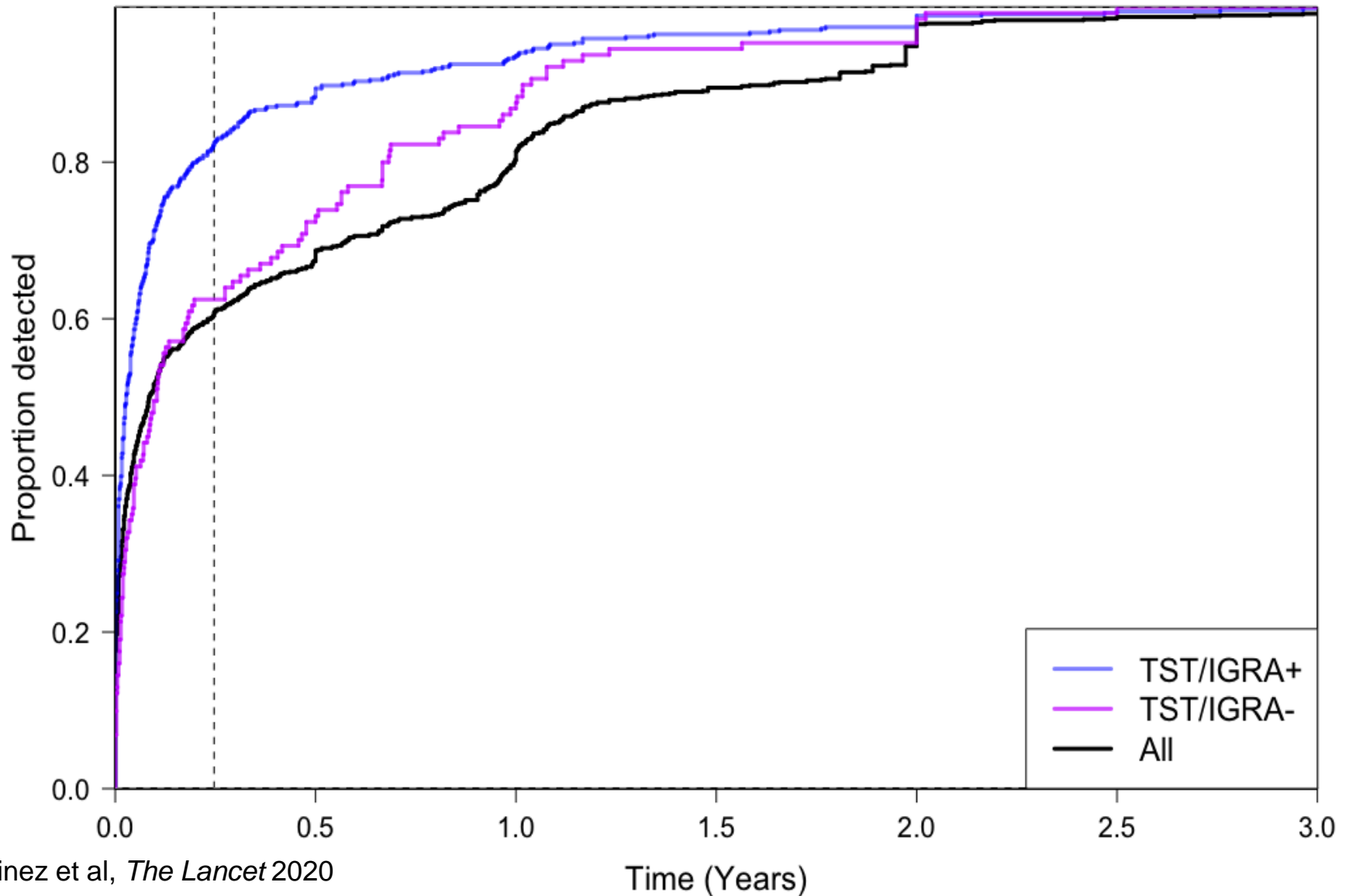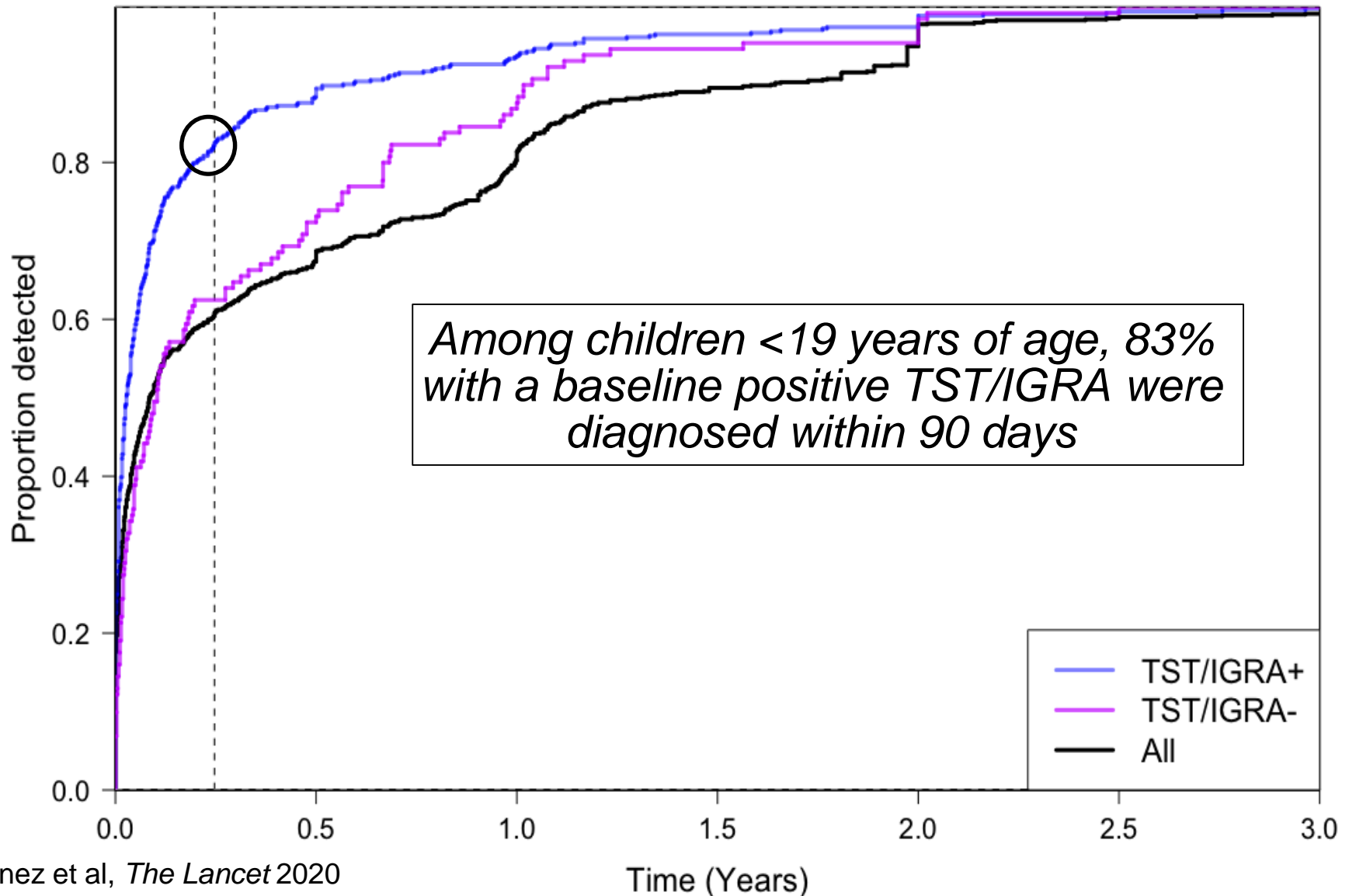
Martinez et al, *The Lancet* 2020

Most Pediatric Cases Occur Within 90 Days

Among children <19 years of age, 83% with a baseline positive TST/IGRA were diagnosed within 90 days

Legend:
- TST/IGRA+
- TST/IGRA-
- All

Martinez et al, *The Lancet* 2020

Most Pediatric Cases Occur Within 90 Days

Martinez et al, *The Lancet* 2020

Most Pediatric Cases Occur Within 90 Days

Among children <5 years of age:
- 83% were diagnosed within 90 days
- 96% with a baseline positive TST/IGRA were diagnosed within 90 days

Legend:
- TST/IGRA+
- TST/IGRA-
- All

Proportion detected (y-axis: 0.0 to 1.0)
Time (Years) (x-axis: 0.0 to 3.0)

Martinez et al, *The Lancet* 2020
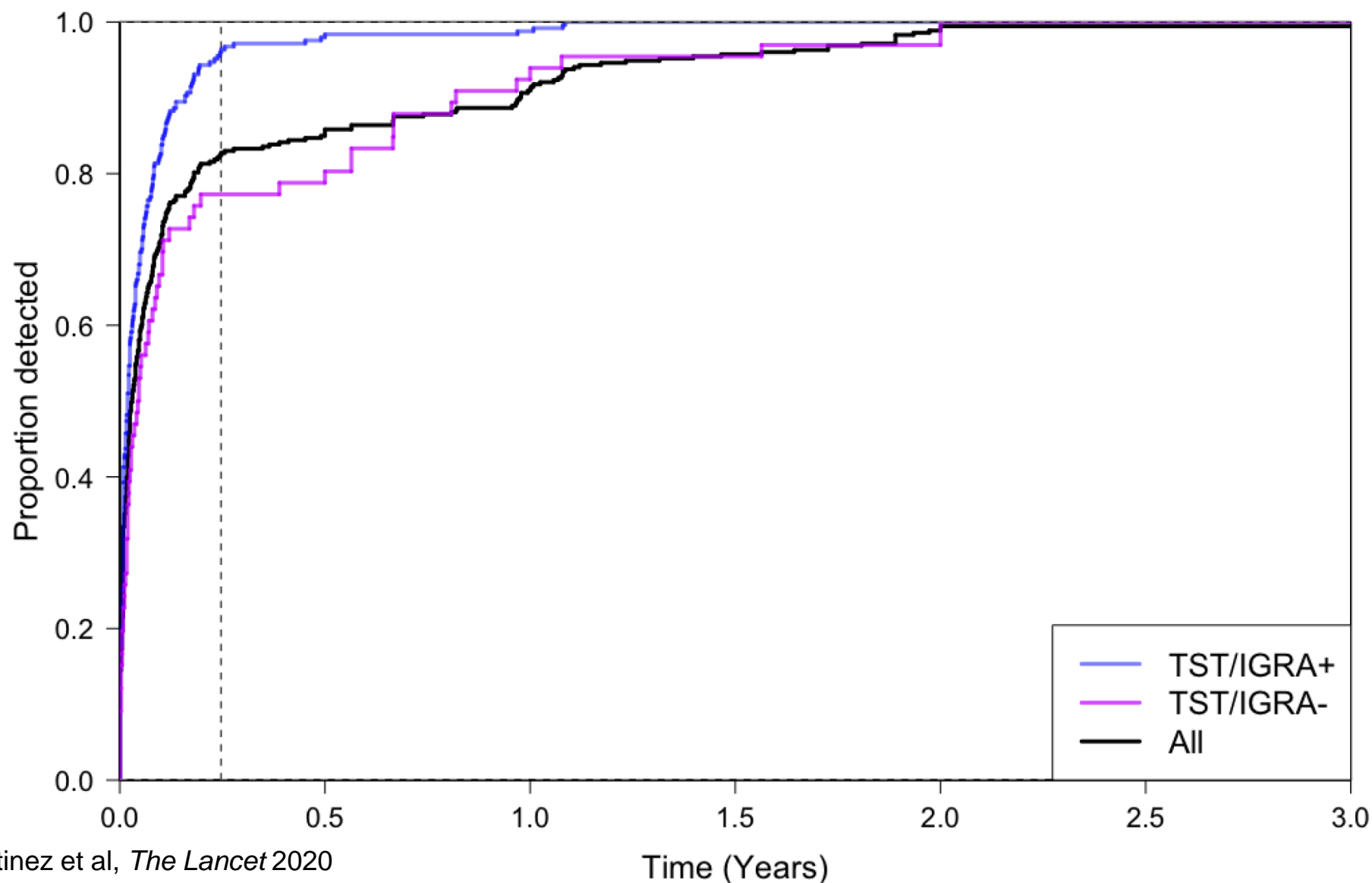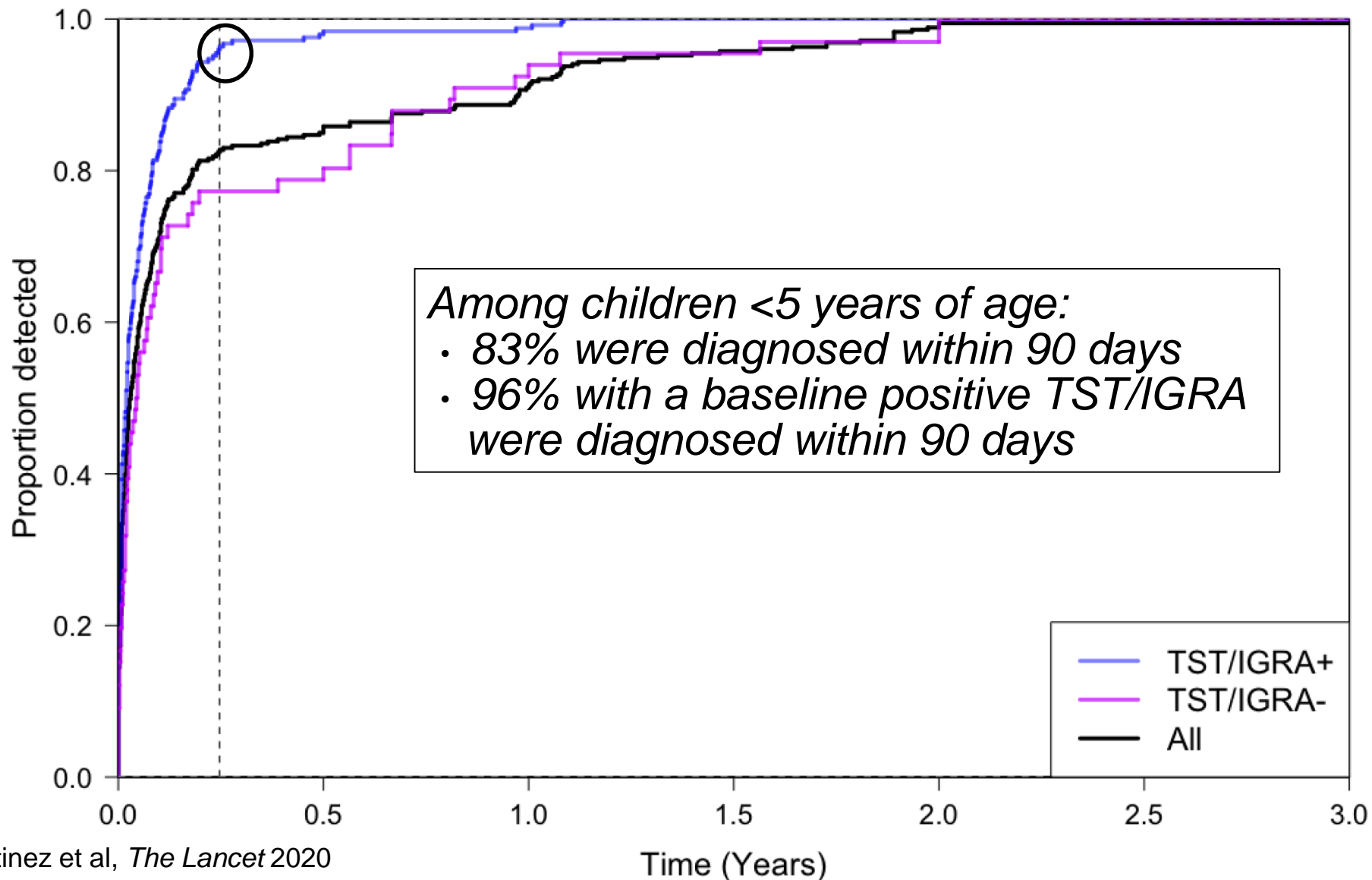
Conclusions

High-risk in children <5 years old with tuberculosis infection
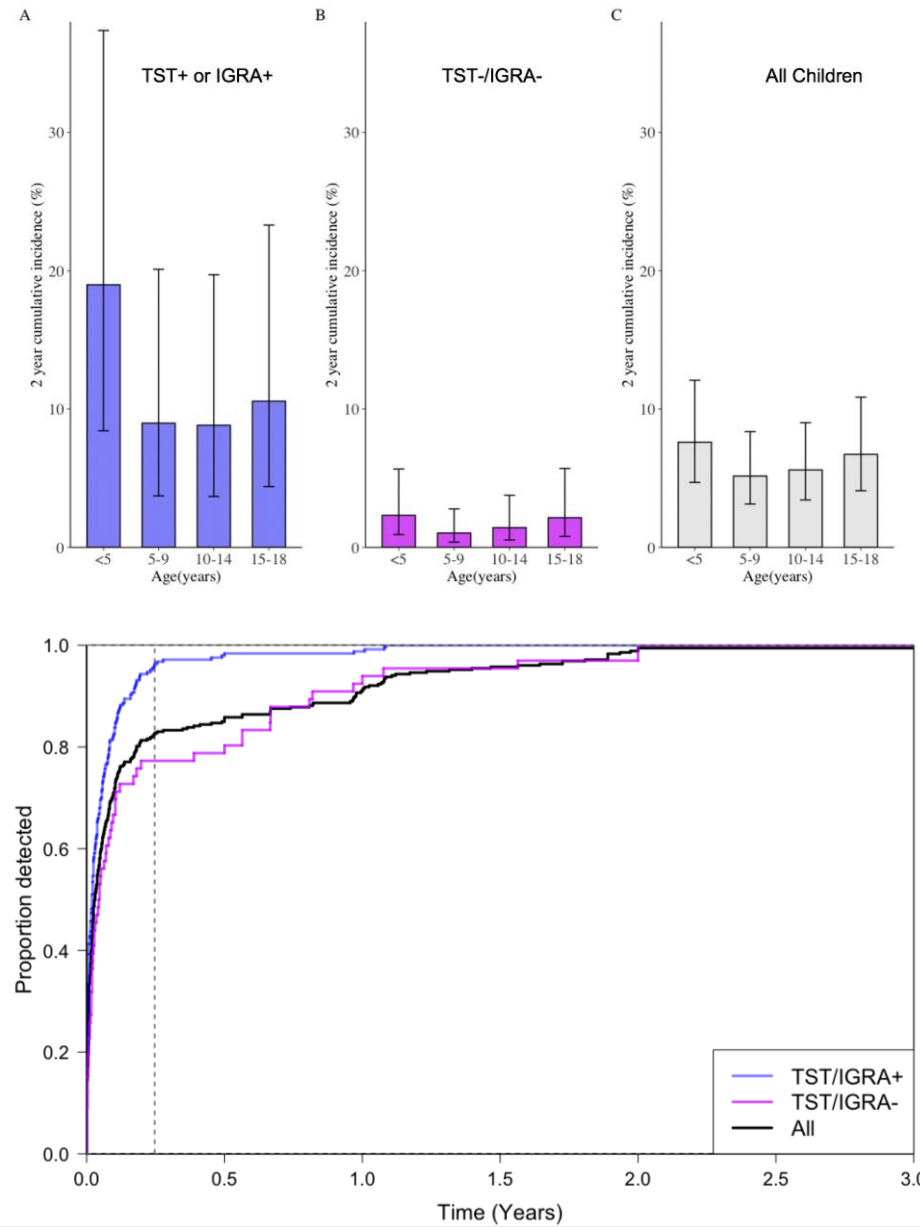
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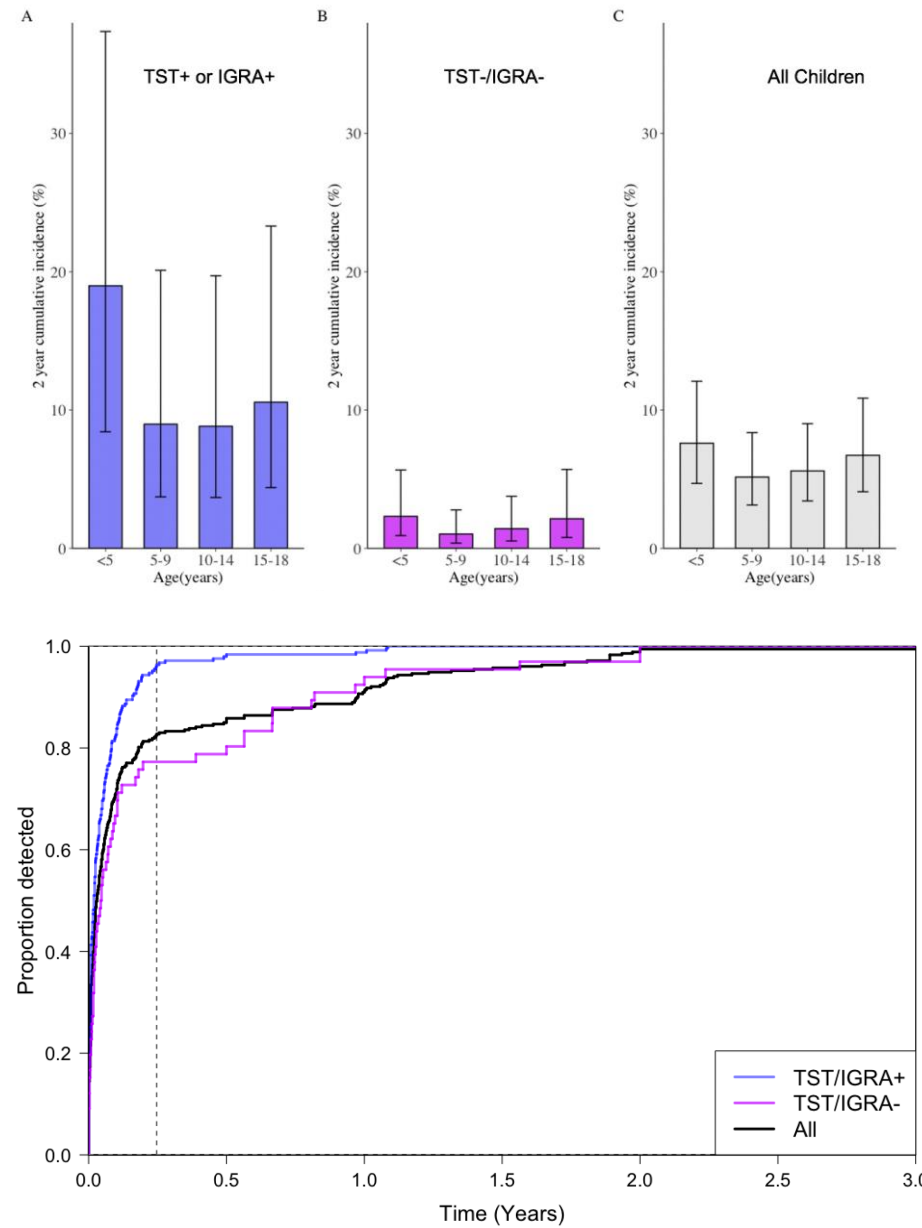
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Preventive therapy is a highly effective individual-level tool
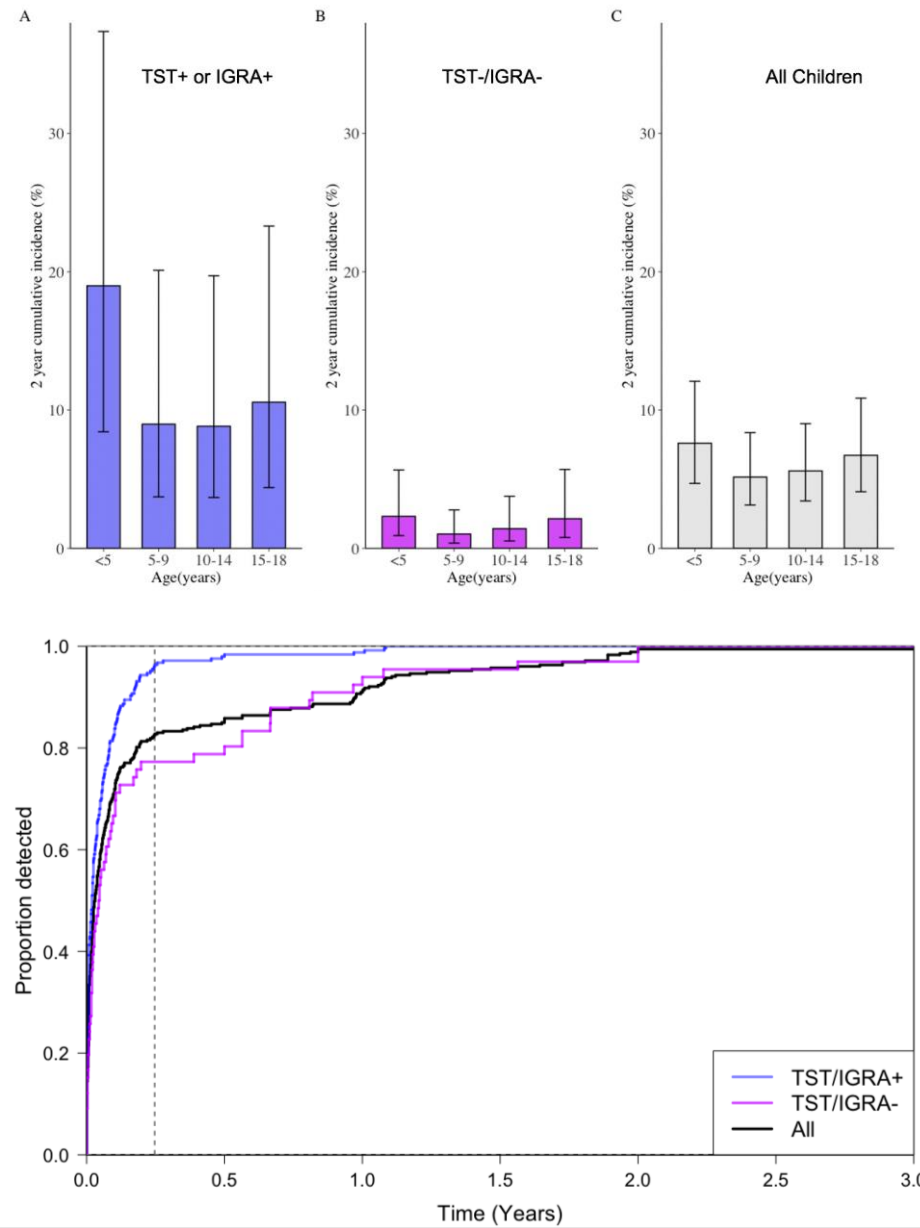
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High-risk in children <5 years old with tuberculosis infection

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Preventive therapy is a highly effective individual-level tool

Can we make it more effective as a population-based tool?
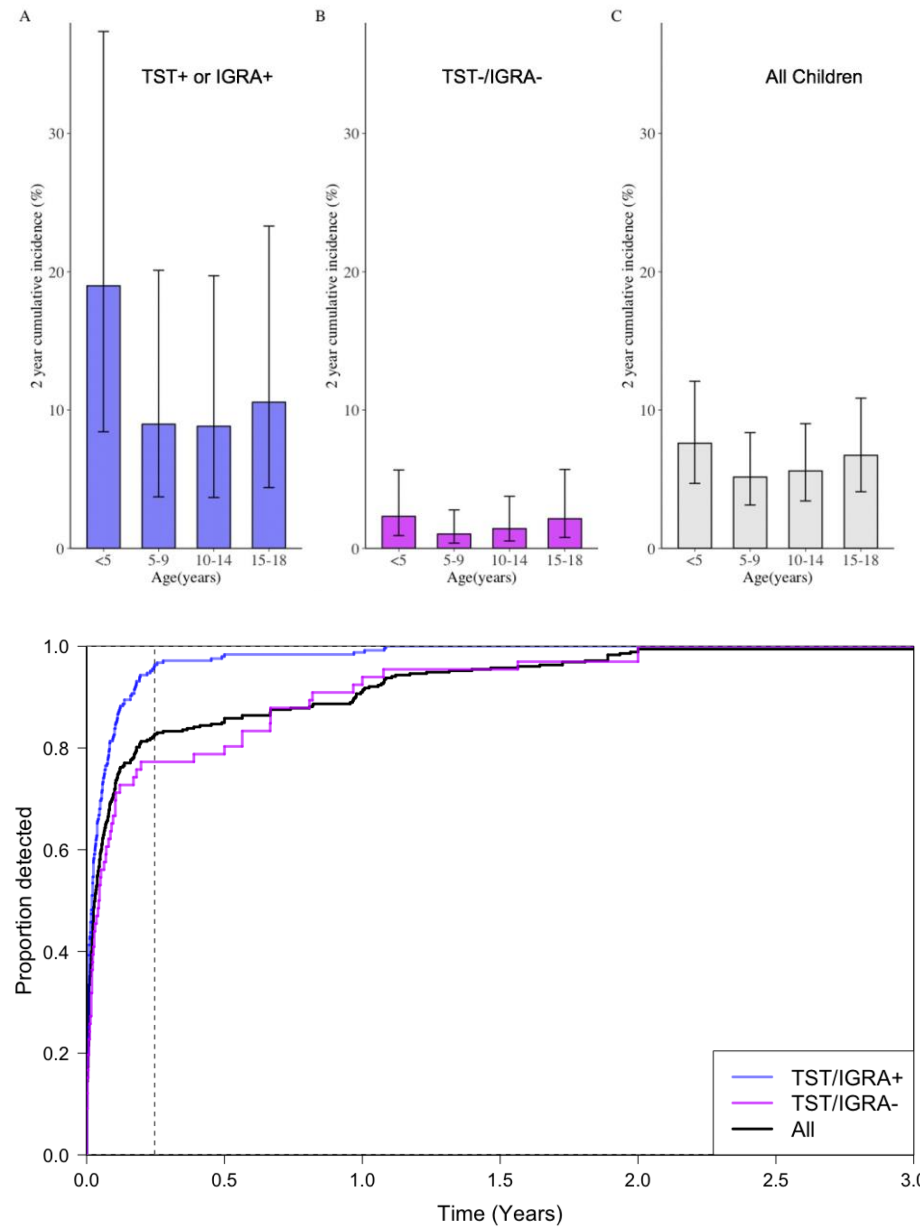
<u>Study Group Members Contributing Individual Data and advisement on the results:</u>

Carlos Acuna-Villaorduna, Shama Ahuja, Neus Altet, Davit Baliashvili, Mercedes Becerra, Maryline Bonnet, W. Henry Boom, Martien Borgdorff, Fadila Boulboul, Anna Cristina C. Carvalho, Joan Cayla, Tsira Chakhaia, Anita Pei-Chun Chan, Li-Min Huang, Helena del Corral, Julio Croda, Sumona Datta, Justin T. Denholm, Claudia C. Dobler, Simon Donkor, Jerrold J. Ellner, Marcos Espinal, Carlton Evans, Chi-Tai Fang, Katherine Fielding, Greg J. Fox, Alberto L. García-Basteiro, Steffen Geis, Stephen M. Graham, Louis Grandjean, Djohar Hannoun, Anja Hauri, Anneke C. Hesseling, Philip C. Hill, H. Simon Schaaf, Helena Huerga, Beate Kampmann, H. Lester Kirchner, Afrânio Kritski, Luis F. García, Christoph Lange, Meng-Rui Lee, Li-Na Lee, Chih-Hsin Lee, Antonio Carlos Lemos, Du-Lin Ling, Qiao Liu, Rufaida Mazahir, Maarten F Schim van der Loeff, Elisa Lopez, Peng Lu, Matthew Magee, Richard Long, LaShaunda Malone, Anna M. Mandalakas, Seiya Kato, Giovanni Sotgiu, Neil A. Martinson, Megan B. Murray, Eduardo Martins Netto, Larissa Otero, Julie Parsonnet, LaShaunda Malone, Christian Lienhardt, Arthur Reingold, Cari van Schalkwyk, James A. Seddon, Surendra Sharma, Jitendra Singh, Sarman Singh, Rosa Sloot, Giovanni Sotgiu, Catherine Stein, Patrick Van der Stuyft, Jayne Sutherland, Najeeha Iqbal Talat, Rina Triasih, Lisa Trieu, Richa Vashishtha, Leonardo Martinez, Julian Villalba, Jann-Yuan Wang, Guy Marks, Jean-Pierre Zellweger, Christopher C. Whalen, Limei Zhu

Thank you for listening.
Questions?

Heterogeneity
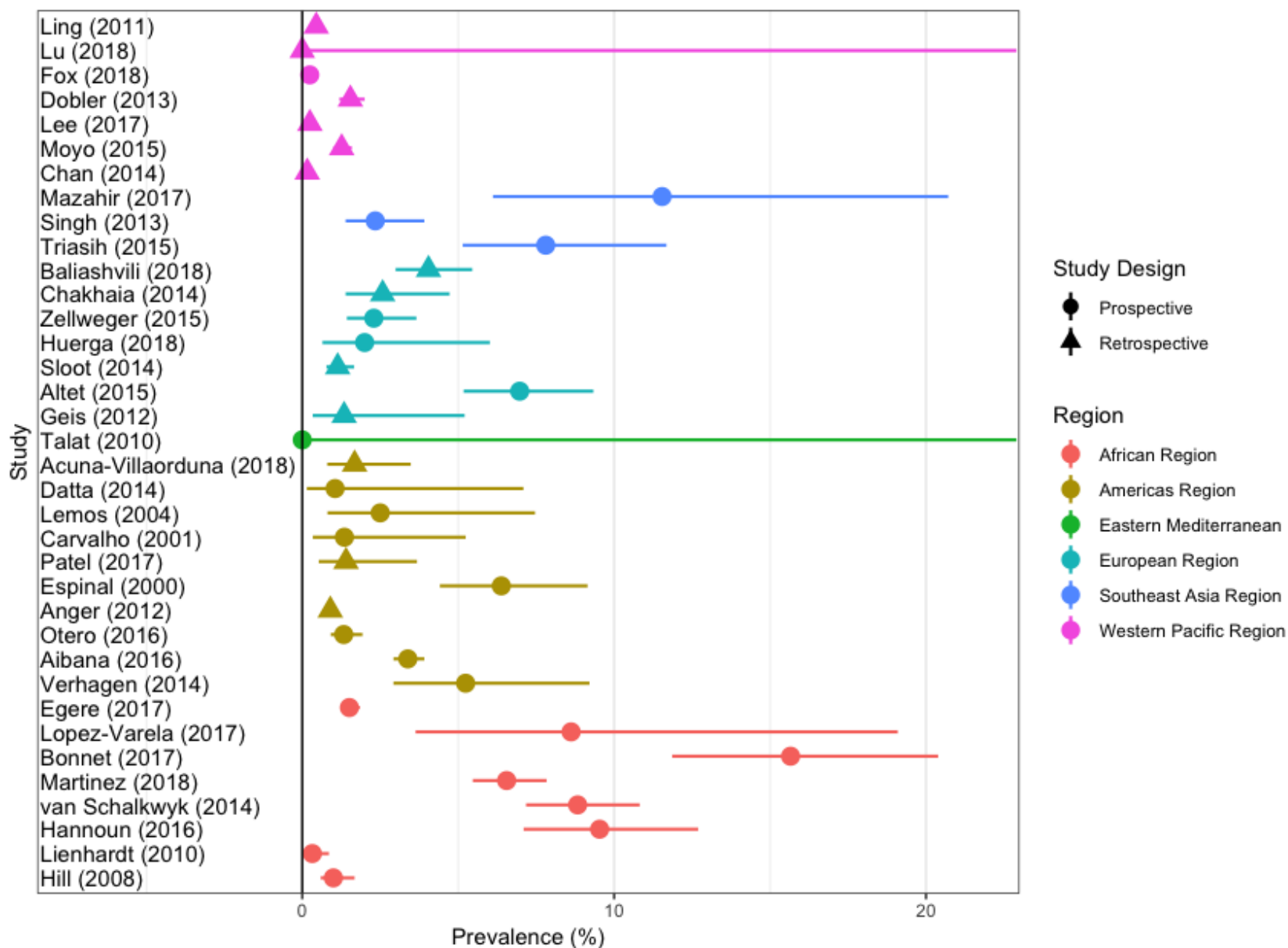
The Prevalence of Tuberculosis
Infection Increased with Age