

Clinical & demographic predictors of tuberculosis in children – A multi-centre prospective study in Low- and Middle-Income Countries

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Objective

- To describe characteristics and determinants of TB disease in children in 5 high burden countries

Methods

- A prospective study of new diagnostics, of children (<15years) with suspected TB from 5 low-middle income countries
- Baseline demographic, clinical and CXR data, and specimens for microbiological testing collected
- Participants categorised as confirmed, unconfirmed or unlikely TB, by NIH consensus definitions
- Logistic regression analyses were performed to identify co-variates associated with TB disease

Results

- 975 of 5,313 (18.4%) screened were enrolled
- Microbiological confirmation in 35.9% (239/665) with TB disease, 41.3% (38/92) in <1 year, 30.9% (102/330) <5 years, 25.5% (24/94) in CLHIV, and 48.1% (37/77) with severe acute malnutrition (SAM)

Table 1: Baseline characteristics

| | All N = 975 | Confirmed TB n = 239 (24.5%) | Unconfirmed TB n = 426 (43.7%) | Unlikely TB n = 310 (31.8%) |
|---|------------------|---------------------------------|-----------------------------------|--------------------------------|
| Sex | | | | |
| Female | 470 (48.2) | 115 (48.1) | 203 (47.7) | 152 (49.0) |
| Age | | | | |
| Age in years, median (IQR) | 4.9 (1.8 to 8.8) | 6.2 (1.8 to 11.6) | 4.6 (1.8 to 8.1) | 4.7 (1.8 to 7.8) |
| Site | | | | |
| South Africa | 230 (23.6) | 77 (32.2) | 94 (22.1) | 59 (19.0) |
| Tanzania | 230 (23.6) | 46 (19.2) | 127 (29.8) | 57 (18.4) |
| Mozambique | 220 (22.6) | 22 (9.2) | 122 (28.6) | 76 (24.5) |
| Malawi | 201 (20.6) | 34 (14.2) | 74 (17.4) | 93 (30.0) |
| India | 94 (9.6) | 60 (25.1) | 9 (2.1) | 25 (8.1) |
| HIV status¹ | | | | |
| HIV infected | 157 (16.1) | 24 (10.0) | 70 (16.4) | 63 (20.3) |
| HIV-exposed uninfected | 128 (13.1) | 29 (12.1) | 57 (13.4) | 42 (13.5) |
| Nutrition² | | | | |
| Weight for age (z-score), mean (SD) | -1.2 (1.5) | -1.3 (1.5) | -1.1 (1.4) | -1.1 (1.5) |
| Severe acute malnutrition at baseline | 111 (11.4) | 37 (15.5) | 40 (9.4) | 34 (11.0) |
| Household exposures | | | | |
| Exposure to indoor smoking | 227 (23.4) | 56 (23.5) | 101 (23.9) | 70 (22.7) |
| Immunological testing | | | | |
| TST positive | 413 (47.3) | 131 (60.9) | 264 (66.2) | 18 (6.9) |
| CXR findings | | | | |
| CXR findings attributable to TB | 262 (26.9) | 108 (45.2) | 122 (28.6) | 32 (10.3) |
| TB disease manifestation | | | | |
| PTB only | 376 (38.6) | 139 (58.2) | 208 (48.8) | 29 (9.4) |
| EPTB only | 59 (6.1) | 37 (15.5) | 9 (2.1) | 13 (4.2) |
| PTB & EPTB | 99 (10.2) | 57 (23.8) | 34 (8.0) | 8 (2.6) |
| TB treatment initiation | | | | |
| Treatment for active TB, drug-sensitive | 474 (48.6) | 178 (74.5) | 249 (58.5) | 47 (15.2) |
| Treatment for active TB, drug-resistant | 55 (5.6) | 37 (15.5) | 15 (3.5) | 3 (1.0) |
| Preventive treatment | 52 (5.3) | 0 (0.0) | 36 (8.5) | 16 (5.2) |

Data are n (%), except where noted otherwise. IQR: Interquartile range, SD: Standard deviation, TST: Tuberculin skin test, CXR: chest X-ray, PTB: Pulmonary TB, EPTB: Extra-pulmonary TB. ¹ HIV status not available for 25 participants; ² Nutritional status assigned according to WHO 2006 child growth standards.

Table 2: Multivariable logistic regression of demographic and clinical characteristics with confirmed PTB

| Covariate | n | Confirmed PTB vs Unlikely PTB | | | | |
|--|-----|-------------------------------|--------|-------|-------------------|---------|
| | | n-pos. | %-pos. | aOR | 95% CI | p-value |
| Site | | | | | | |
| South Africa* | 74 | 43 | 58,1 | 1 | - - | - |
| Tanzania | 93 | 41 | 44,1 | 2,76 | (0.74 to 10.29) | 0.1293 |
| Mozambique | 32 | 7 | 21,9 | 0,99 | (0.17 to 5.72) | 0.9878 |
| Malawi | 106 | 27 | 25,5 | 1,53 | (0.43 to 5.39) | 0.5094 |
| India | 42 | 28 | 66,7 | 5,47 | (1.35 to 22.14) | 0.0172 |
| Sex | | | | | | |
| Male | 173 | 72 | 41,6 | 1,71 | (0.85 to 3.46) | 0.1340 |
| HIV status | | | | | | |
| HIV infected | 54 | 14 | 25,9 | 0,89 | (0.32 to 2.46) | 0.8267 |
| TST Result | | | | | | |
| Positive | 108 | 96 | 88,9 | 45,16 | (18.43 to 110.66) | 0.0000 |
| BCG received | | | | | | |
| Yes | 332 | 133 | 40,1 | 0,14 | (0.02 to 1.35) | 0.0893 |
| Severe acute malnutrition at baseline¹ | | | | | | |
| Yes | 44 | 21 | 47,7 | 0,71 | (0.24 to 2.12) | 0.5428 |
| Number of TB symptoms | | | | | | |
| 1-2 | 96 | 31 | 32,3 | 0,94 | (0.14 to 6.15) | 0.9506 |
| 2-4 | 173 | 67 | 38,7 | 1,49 | (0.19 to 11.63) | 0.7051 |
| >4 | 63 | 39 | 61,9 | 4,23 | (0.36 to 49.23) | 0.2492 |
| Chest radiograph findings | | | | | | |
| Abnormal – Likely TB | 94 | 75 | 79,8 | 7,98 | (3.04 to 20.92) | 0.0000 |
| Abnormal – Equivocal | 89 | 32 | 36 | 1,18 | (0.50 to 2.79) | 0.7047 |

* reference stratum; N = number of observations; N-pos. = number of positives; %-pos. = percent positive; OR = odds ratio; 95% CI = 95% confidence interval, TST = Tuberculin skin test, CXR = Chest X-ray. ¹ Nutritional status assigned according to WHO 2006 child growth standards.

- PTB disease associated with a positive TST (aOR: 68.48 [33.23-141.10], p<0.0001) or CXR likely TB (aOR: 9.12 [4.75-17.5], p<0.0001)
- For **CLHIV**, confirmed PTB and PTB disease associated with CXR likely TB (aOR: 23.11[1.33-401.43], p=0.0311 and aOR: 8.05[2.41-26.94], p=0.0007)
- For **SAM**, confirmed PTB and PTB disease associated with CXR likely TB (aOR: 34.72[2.73-441.94], p=0.0063 and aOR: 12.63[2.511-63.54], p=0.0021)
- In **<2 years**, confirmed PTB associated with a positive TST (aOR: 15.32[5.45-43.08], p<0.0001) and, CXR likely TB (aOR: 7.26[2.88-18.27], p<0.0001)

Conclusions

- One of the largest childhood cohorts, across 5 countries
- Over half with TB disease diagnosed based on clinical and radiological features
- High rates of microbiological confirmation
- Clinical determinants differ among vulnerable subgroups, highlighting need for adapted diagnostic approaches

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