The Union

WORLD CONFERENCE ON LUNG HEALTH 2022

COMBATING PANDEMICS: TODAY & TOMORROW

Virtual Event November 8-11

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Effects of integrating pediatric TB services into child health care on treatment outcomes: Results of the INPUT study

Lise Denoeud-Ndam, Boris Tchounga, Rose Masaba, Nicole Herrera, Millicent A Ouma, Saint Just Petnga, Stephen Siamba, Patrice Tchendjou, Anne Cecile Bisseck, Rhoderick Machekano, Martina Casenghi, Appolinaire Tiam, and the INPUT Study Team

CONFLICT OF INTEREST DISCLOSURE FORM

X I have no Conflict of Interest to report.

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INTRODUCTION

- In 2019, more than one million children (<15 years) fell ill with TB globally, and 230,000 died of TB disease **(1)**
- Underdiagnosis and underreporting of TB occurs frequently among children in sub-Saharan Africa **(2)**
- The importance of linking TB prevention and care to maternal and child health programs has been recognized **(3)**, however, very limited data are available on the feasibility and impact of such integrated approaches
- The Catalyzing Pediatric TB Innovations (CaP-TB) interventions package aims to increase TB case detection in children through facility-based interventions at hospital and primary health care levels
    - **Integration of TB screening into health care services for children**
    - Improved clinical, radiological, and bacteriological diagnosis capacity
- The INPUT stepped-wedge cluster-randomized study aims to **assess the effect of CaP-TB on TB case detection and treatment outcomes among children under the age of five**

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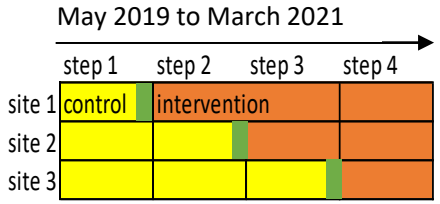
1) WHO Global TB Report, 2019
2) WHO Roadmap Towards Ending TB in Children and Adolescents, 2018
3) Marais BJ, Graham SM, et al, Lancet Infect Dis 2013

METHODS (1): STUDY SITES AND POPULATION

- Study sites: Six hospitals and eight attached primary health care facilities (PHCs) in Kenya
  Six hospitals and twelve attached PHCs in Cameroon
- Inclusion criteria:
  - **Children under five years of age**
  - **Presumptive of TB**: symptoms or clinical signs of active TB disease
  - TB diagnostic investigations initiated
  - Commitment to take treatment in the clinic of enrolment or another INPUT study site
  - Parental/caregiver consent for the child to participate in the study
- Exclusion criterion: children who are contacts but without symptoms or signs of active TB
- Follow-up until TB diagnosis is ruled out or until 2 months after TB treatment completion

METHODS (2): STUDY DESIGN AND STATISTICAL ANALYSIS

- Design: Stepped-wedge cluster-randomized with study sites starting intervention at different times
- Statistical analysis to compare outcomes in intervention versus control:
  - Generalized linear mixed models accounting for time and clustering
  - Rate ratio and 95% confidence interval (CI)
  - One-month transition period between steps: data removed from analysis



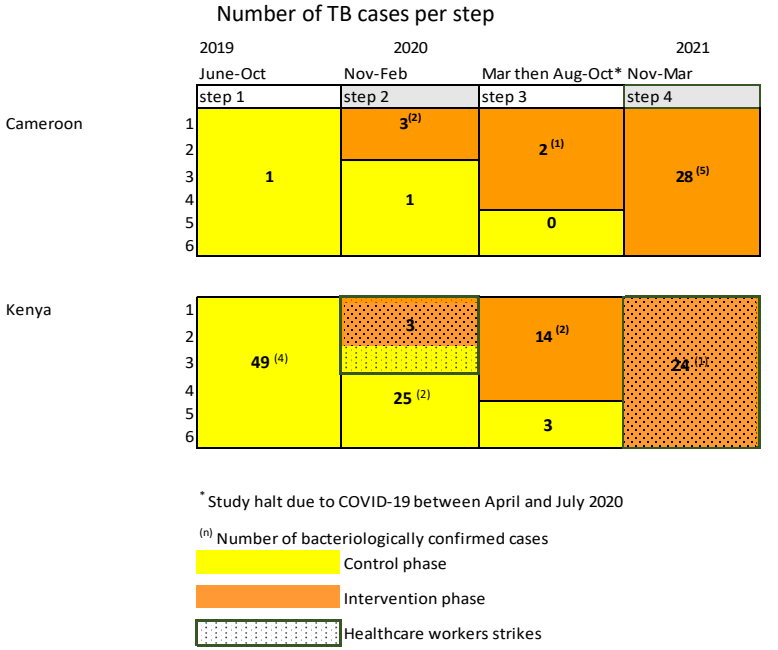
- Primary outcome: proportion of pediatric TB cases diagnosed among children under the age of five attending services (cluster level)
- Secondary outcomes (individual level):
  - **Proportion of TB cases with favorable treatment outcome (WHO definition of treatment completion)**
    - Collected 2 months after treatment completion
  - **Time from symptoms to TB diagnosis and to treatment initiation**
  - **Proportion of cases with a bacteriologically confirmed diagnosis**

RESULTS (1): FLOW CHART AND BASELINE CHARACTERISTICS

790 enrolled TB presumptive

	Control 133 enrolled	Transition 51 enrolled	CaP-TB 606 enrolled
Country (N,%)			
Cameroon	27 (20.3)	36 (70.6)	465 (76.7)
Kenya	106 (79.7)	15 (29.4)	141 (23.3)
Age in months (median, IQR)	19.3 (12.0-38.1)	23.0 (12.9-40.9)	18.7 (9.8-35.0)
HIV-positive (N, %)	14 (10.5)	6 (11.8)	33 (5.4)
Moderate or severe acute malnutrition (N, %)	34 (25.6)	5 (9.8)	61 (10.1)
Household contact diagnosed with TB (N, %)	35 (26.3)	5 (9.8)	89 (14.7)
	79 diagnosed with TB (59% of those enrolled)	4 diagnosed with TB (8% of those enrolled)	74 diagnosed with TB (12% of those enrolled)
	74 evaluated for treatment outcome (94% of the diagnosed)	4 evaluated for treatment outcome (100% of the diagnosed)	73 evaluated for treatment outcome (99% of those enrolled)

RESULTS (2): PRIMARY OUTCOME: CASE DETECTION



	Control		Intervention			
	TB cases	Attendees	TB cases	Attendees	Risk Ratio** (95% CI)	P value
Total	79	121,909	74	109,614	**1.32 (0.66-2.61)**	**0.43**
Cameroon	2	43,775	33	52,241	**9.75 (1.04-91.84)**	**0.046**
Kenya	77	78,134	41	57,373	**0.94 (0.44-2.01)**	**0.88**

**** Risk ratio of a child to be diagnosed with TB under Cap TB compared to SOC, estimated from mixed Poisson modelling accounting for time and clustering**

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RESULTS (3): SECONDARY OUTCOMES BY STUDY PHASE AND COUNTRY

	TOTAL (N=153)		Cameroon (N=35)		Kenya (N=118)	
	Control N=79	Intervention N=74	Control N=2	Intervention N=33	Control N=77	Intervention N=41
Treatment outcome* n (%)						
Cured	6 (7.6%)	4 (5.4%)	0	4 (12.1%)	6 (7.8%)	0
Treatment completed	59 (74.7%)	64 (86.5%)	2 (100%)	24 (72.7%)	57 (74.0%)	40 (97.6%)
Died	6 **(7.6%)**	2 **(2.7%)**	0	2 (6.1%)	6 (7.8%)	0
Lost to follow-up	4 (5.1%)	3 (4.1%)	0	2 (6.1%)	4 (5.2%)	1 (2.4%)
Not evaluated	4 (5.1%)	1 (1.4%)	0	1 (3.0%)	4 (5.2%)	0
WHO favorable treatment outcome n (%) (cured or treatment completed)	65 (82.3%)	68 (91.9%)	2 (100%)	28 (84.8%)	63 (81.8%)	40 **(97.6%)**
Time between symptom onset and TB Diagnosis (months) * *N=149*						
Median (IQR)	2.0 (1.0-6.5)	1.0 (1.0-3.0)	**6.5 (5.0-8.0)**	1.0 (1.0-3.0)	2.0 (1.0-6.0)	2.0 (1.0-5.5)
≤1 n (%)	34 (43.0%)	38 (51.4%)	0	19 (57.6%)	34 (44.2%)	19 (46.3%)
]1-2] n (%)	7 (8.9%)	12 (6.2%)	0	5 (15.2%)	7 (9.1%)	7 (17.1%)
]2-5] n (%)	12 (15.2%)	13 (17.6%)	1 (50.0%)	9 (27.3%)	11 (14.3%)	4 (9.8%)
>5 n (%)	23 (29.1%)	10 (13.5%)	1 (50.0%)	0	22 (28.6%)	10 (24.4%)
Proportion of bacteriologically confirmed cases n %	6 (7.6%)	11 (14.9%)	0 (0.0%)	8 **(24.2%)**	6 (7.8%)	3 (7.3%)

*** Months from symptom onset to treatment initiation was equal to months from symptom onset to TB diagnosis**

RESULTS (4): MULTIVARIATE MODELLING OF SECONDARY OUTCOMES

Outcome	RR (95% CI) *	P value
WHO favorable treatment outcome (cured or treatment completed)	1.32 (0.01-210.12)	0.61
Time between symptom onset and diagnosis (months) 1 months or less vs greater than 1 month	1.20 (0.02-66.39)	0.67
Proportion of bacteriologically confirmed cases	0.77 (0.07-8.19)	0.83

* Risk ratio associated with Cap-TB compared to SOC, estimated from mixed Poisson modelling; accounting for time and clustering; and adjusting for country

After adjusting for country, clustering, and time, none of the risk ratios were significant

DISCUSSION

- Primary outcome results show a 10-fold increase in case detection during CaP-TB in Cameroon
- The time to TB diagnosis, proportion of bacteriologically confirmed cases, and proportion with favorable treatment outcome (including case fatality) all evolved positively with the introduction of CaP-TB
- Limitations
  - Secondary outcomes results are not significant after adjusting for study design
  - Limited number of TB cases (153, where we expected to have 288) resulted in reduced power
  - In Kenya, strikes of health care worker impacted the intervention phase
  - The COVID-19 pandemic directly impacted the third and fourth steps of randomization

SUMMARY

- We observed a clinically relevant improvement in treatment outcomes during CaP-TB, with almost a two-third reduction in case fatality
- These results may be a consequence of the timelier TB diagnosis and earlier treatment initiation allowed by the intensified pediatric TB case finding
- Limited power, however, does not allow to show a statistically significant association with CaP-TB

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