Results from the systematic review and individual patient data meta-analysis of children and adolescents 0-19 years of age treated for RR/MDR-TB

Anthony Garcia-Prats M.D., Ph.D., M.Sc.[1, 2]

On behalf of the BENEFIT Kids Team and the Collaborative Group for Meta-Analysis of Paediatric and Adolescent Individual Patient Data in Rifampicin-Resistant TB

November 30, 2021

[1]Desmond Tutu TB Centre, Stellenbosch University
[2]University of Wisconsin School of Medicine and Public Health

DESMOND TUTU TB CENTRE · SENTRUM · IZIKO — Every breath counts

UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY 100 1918 · 2018

Department of Pediatrics
Division of Global Pediatrics
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

BENEFIT Kids
Better Evidence & Formulations for Improved MDR-TB Treatment for Children

Background

- Prior systematic reviews in 2012 *(Ettehad Lancet ID 2012)* and 2014 *(Harausz PLoS Med 2018)* to characterize treatment outcomes in children treated for RR-TB
- 2014 review led to paediatric-specific guidance: 2016 DR-TB WHO guideline update
- Substantial evolution in field of RR-TB since 2016:
  - BDQ use age 6 years and older, DLM use age 3 years and older
  - Newer repurposed drugs
  - Shorter treatment durations, all-oral regimens
- BENEFIT Kids *(https://blogs.sun.ac.za/dttc/benefit-kids/)* consortium led by Desmond Tutu TB Centre, Stellenbosch University – funded by Unitaid
  - Output 1: systematic review and individual patient data meta-analysis of children and adolescents 0-19 years of age treated for RR-TB with final treatment outcomes (PK IPD pending)
  - In collaboration with University of California San Francisco and South African Medical Research Council Cochrane Centre and data collaborators

Objectives

Provide preliminary analysis of available data for:

PICO questions 4a/4b regarding outcomes of bedaquiline (BDQ) and delamanid (DLM) treated children less than 6 years and 3 years, respectively

- Among MDR/RR-TB patients aged < 6 years, does an all-oral treatment regimen containing BDQ versus an all-oral regimen without BDQ conforming to WHO guidelines result in improved outcomes?
- In MDR/RR-TB patients aged <3 years, does an all-oral treatment regimen containing DLM versus an all oral treatment regimen without DLM conforming to WHO guidelines, result in improved treatment outcomes?

Additional data, non-PICO format:

- Treatment outcomes of BDQ and DLM use in children and adolescents aged 6 to <12 years and 3 to <6 years, respectively (stratified by age)

Implementation question: Building optimal treatment regimens for children, based on evidence from the paediatric drug resistant TB individual patient dataset – Analysis still in progress

Methods Summary

- Eligibility criteria: children and adolescents 0-19 years treated for clinically diagnosed or bacteriologically confirmed RR-TB (PTB/EPTB), reported on treatment regimen and final outcomes
- Search strategy: published and unpublished data, October 2014 – 30 March 2020, any study design, from electronic search and broad network of contacts
- Data collection and extraction:
  - Standard study selection with reviewers, anonymized IPD transfer
  - Demographic, clinical, treatment, and outcome variables
  - Risk of bias assessed with Joanna Briggs appraisal tool for single cohorts

Results: Summary

Results: Characteristics of Included Studies

- **44 published and unpublished studies** from **52 countries** with broad geographic and income distribution
  - 19 countries among the 30 WHO high-burden MDR-TB countries
- Large number of individual records precluded the inclusion of smaller datasets for this analysis (~2% of all IPD data)
- **All data from observational studies or routine programmatic data**
- Incomplete/missing: adverse events, culture conversion
- **Risk of Bias assessed overall data as Low Quality**

Figure 1: Analytic Approach

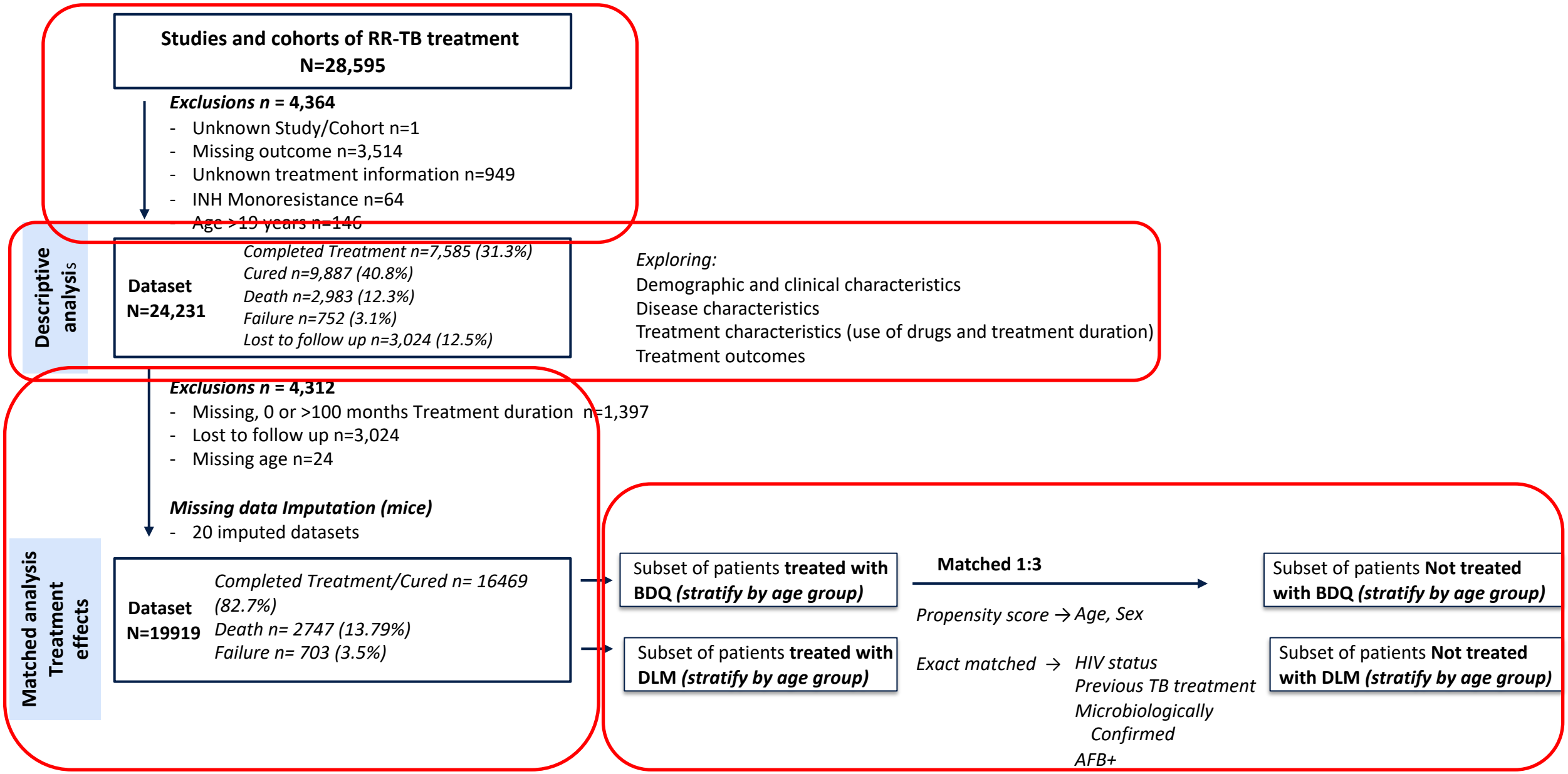

Table 1. Country of treatment by WHO Region of children and adolescent with RR-TB (n=24,231)

	Country by WHO Region	N (%)
African Region (AFR)	South Africa	7,684 (31.7%)
	Country not specified	24 (0.1%)
Region of the Americas (AMR)	Brazil	140 (0.6%)
	Peru	36 (0.1%)
	Country not specified	31 (0.1%)
South-East Asia Region (SEAR)	India	14,499 (59.8%)
	Country not specified	29 (0.1%)
European Region (EUR)	Belarus	5 (0.0%)
	Georgia	49 (0.2%)
	Latvia	53 (0.2%)
	Netherlands	3 (0.0%)
	Romania	16 (0.1%)
	Russia	39 (0.2%)
	Spain	17 (0.1%)
	Tajikistan	249 (1.0%)
	Ukraine	6 (0.0%)
	United Kingdom	22 (0.1%)
	Uzbekistan	414 (1.7%)
	Country not specified	45 (0.2%)
Eastern Mediterranean Region (EMR)	Pakistan	795 (3.3%)
	Country not specified	52 (0.2%)
Western Pacific Region (WPR)	South Korea	3 (0.0%)
	Taiwan	4 (0.0%)
	Country not specified	1 (0.0%)

*Countries contributing 100 or more participants highlighted red; *Country not specified* indicates data reported WHO region but did not report specific country in order to maintain anonymity of the data

Table 2. Baseline demographic and clinical characteristics, and treatment duration for all children and adolescents 0-19 years of age treated for RR=TB (n=24,231)

	N (%) unless otherwise specified
Age (years), mean (SD)	14.7 (4.75)
0 to <6	2032 (8.4%)
6 to <12	2176 (9.0%)
12 to 19	19999 (82.6%)
Male sex, N (%)	13861 (57.2%)
HIV-positive	3092 (14.6%)
Bacteriologically confirmed	21,000 (90.5%)
AFB smear positive N (%)	4753 (55.7%)
Pulmonary TB, N (%)	20966 (96.4%)
Extrapulmonary TB, N (%)	2073 (20.4%)
Extended resistance profile, N (%)	
Additional FQN or SLI resistance	896 (56.9%)
Additional FQN and SLI resistance	679 (43.1%)
Year of treatment, mean (SD), [range]	2016 (3.2) [1991, 2020]
Treatment duration (months)	
Mean (SD)	14.9 (8.4)
Median (IQR)	13 (8.9, 23.6)

***Percentages are of those with available data**; Missing data by variable: Age, n=24 (0.0%); Sex, n=11 (0.0%); HIV-positive, n=3093 (12.8%); Bacteriologically confirmed, n=1030 (4.3%); AFB smear positive, n=15,700 (64.8%); Pulmonary TB, n=2475 (10.2%); Extrapulmonary TB, n=14, 056 (58%); Extended resistance, n=22,656 (93.5%); Year of treatment, 18 (0.1%); Treatment duration, 1397, (5.8%)

Table 3. Overall treatment outcomes in children and adolescents 0-19 years of age treated for RR-TB (N=24,231)

	N (%)
Completed or cured	17,472 (72.1%)
Died	2,983 (12.3%)
Treatment failure	752 (3.1%)
Lost-to-follow-up	3,024 (12.5%)

Results Bedaquiline

Table 4. Summary of overall treatment outcomes among children and adolescents 0-19 years of age with RR-TB, stratified by age and treatment with any bedaquiline-containing regimen

	<6 years of age		6 to <12 years of age		12 to 19 years of age	
	No BDQ (N=1,992)	BDQ (N=40)	No BDQ (N=2,108)	BDQ (N=68)	No BDQ (N=18,347)	BDQ (N=1,652)
Completed/ Cured	1,676 (84.1%)	30 (75.0%)	1,709 (81.1%)	59 (86.8%)	12,794 (69.7%)	1,190 (72.0%)
Died	117 (5.9%)	4 (10.0%)	210 (10.0%)	5 (7.4%)	2457 (13.4%)	189 (11.4%)
Treatment failure	12 (0.6%)	0 (0.0%)	43 (2.0%)	1 (1.5%)	638 (3.5%)	58 (3.5%)
Lost-to-follow-up	187 (9.4%)	6 (15.0%)	146 (6.9%)	3 (4.4%)	2,458 (13.4%)	215 (13.0%)

Table 5. Summary of key characteristics among children <6 years of age with RR-TB stratified by treatment with or without a bedaquiline-containing regimen

	No BDQ (N=1992)	BDQ (N=40)
Age in years, Mean (SD)	2.32 (1.55)	1.23 (1.66)
Male sex	977 (49.0%)	19 (47.5%)
HIV Positive	364 (20.0%)	12 (30.0%)
Bacteriologically confirmed	1237 (79.8%)	31 (96.9%)
AFB smear positive	273 (21.9%)	17 (48.6%)
Pulmonary TB	1669 (90.8%)	37 (92.5%)
Extrapulmonary TB	352 (20.1%)	2 (5.3%)
Extended resistance profile		
Additional FQN or SLI resistance	83 (41.9%)	4 (66.7%)
Additional FQN and SLI resistance	115 (58.1%)	2 (33.3%)
Drug used at any time in treatment		
Any injectable	1345 (67.5%)	6 (15%)
Moxifloxacin	390 (19.6%)	6 (15.0%)
Levofloxacin	959 (48.1%)	29 (72.5%)
Clofazimine	466 (23.4%)	33 (82.5%)
Linezolid	192 (9.6%)	25 (62.5%)
Delamanid	20 (1.0%)	1 (2.5%)

All percentages are of patients with available data. Missing data by variable: HIV positive, n=175 No Bdq; Bacteriologically confirmed, n=442 No Bdq, n=8 Bdq; AFB smear positive, n=747 no Bdq, n=5 Bdq; Pulmonary TB, n=158 No Bdq; Extrapulmonary TB, n=239 No Bdq, n=2 Bdq; Extended resistance profile, n=1794 No Bdq, n=34 Bdq.

Table 7. Results of matched multivariate model regression evaluating the effect of bedaquiline treatment vs. no bedaquiline treatment on success (treatment completion and cure) vs. unsuccessful outcome (death or treatment failure)

	Bdq given (success/total*)	Bdq NOT given (success/total**)	Matched multivariate model regression	
			Adjusted OR (95%CI)	P-value
Primary Comparison				
Intervention: All-oral regimen with BDQ; *Comparator:* All-oral regimen without BDQ				
Bdq <6 years	24/27 (89%)	485/498 (97%)	0.94 (0.09, 10.3)	0.9
Bdq 6 to <12 years	50/55 (91%)	202/215 (94%)	0.31 (0.03, 2.96)	0.3
Secondary Comparisons				
Intervention: Any regimen with BDQ; *Comparator:* Any regimen without BDQ				
Bdq <6 years	30/33 (91%)	1486/1573 (94%)	0.87 (0.13, 5.96)	0.9
Bdq 6 to <12 years	53/58 (91%)	1523/1716 (89%)	1.17 (0.41, 3.32)	0.8
Intervention: All-oral regimen with BDQ ; *Comparator:* Any regimen without BDQ				
Bdq <6 years	24/27 (89%)	1486/1573 (94%)	0.7 (0.1, 4.6)	0.7
Bdq 6 to <12 years	50/55 (91%)	1523/1716 (89%)	1.01 (0.36, 2.9)	0.9

*Total: total number of children, including those with treatment success, treatment failures and death outcomes.

Table 8. Results of matched multivariate model regression evaluating regimen duration in months among children with successful outcome treated with bedaquiline vs. no bedaquiline

	Bdq given N Duration in months mean, (SD)	Bdq NOT given N Duration in months mean, (SD)	Matched linear model regression	
			Estimate Drug effect (months) (95%CI)	P-value
Primary comparison				
Intervention: All-oral regimen WITH BDQ; *Comparator:* All-oral regimen WITHOUT BDQ				
Bdq <6 years	N=24 **12** (5)	N=485 **13.7** (5.4)	-2.19 (-5.1, 0.69)	0.13
Bdq 6 to <12 years	N=50 **12.2** (4.1)	N=202 **16.1** (6)	-3.60 (-5.2, -1.9)	<0.001
Secondary comparisons				
Intervention: Any regimen WITH BDQ; *Comparator:* Any regimen WITHOUT BDQ				
Bdq <6 years	N=30 **13.3** (5.9)	N=1486 **16.4** (5.8)	-3.47 (-6.0, -0.91)	0.008
Bdq 6 to <12 years	N=53 **12.4** (4.1)	N=1523 **17.8** (6.7)	-3.97 (-5.7, -2.2)	<0.001
Intervention: All-oral regimen WITH BDQ; *Comparator:* Any regimen WITHOUT BDQ				
Bdq <6 years	N=24 **12** (5)	N=1486 **16.4** (5.8)	-4.56 (-7.2, -1.9)	<0.001
Bdq 6 to <12 years	N=50 **12.2** (4.1)	N=1523 **17.8** (6.7)	-3.95 (-5.8, -2.1)	<0.001

Treatment with Bdq significantly associated with a reduced duration of treatment among children 6 to <12 years of age treated for RR-TB

Table 9. Results of matched multivariate model regression evaluating receipt of any injectable drug among children <6 years and 6 to <12 years of age with RR-TB treated with regimens containing bedaquiline vs. no bedaquiline

	Bdq given N [Inj given/total*]	Bdq NOT given N [Inj given/total*]	Matched multivariate model regression Adjusted OR (95%CI)	P-value
Intervention: Any regimen with BDQ; *Comparator:* Any regimen without BDQ				
Bdq <6 years	6/33 (18%)	1075/1573 (68%)	0.12 (0.05,0.32)	<0.001
Bdq 6 to <12 years	3/58 (5%)	1501/1716 (87%)	0.01 (0.003,0.04)	<0.001

* Total: total number of children, including those with treatment success, treatment failures and death outcomes.

Treatment with Bdq is significantly associated with a lower adjusted odds of receipt of an injectable drug among children <6 years ($p<0.001$) and children from 6 to <12 years of age ($p<0.001$) treated for RR-TB

Results: Delamanid

Table 10. Summary of treatment outcomes among children and adolescents 0-19 years of age with RR-TB stratified by age and treatment with delamanid

	<3 years of age		3 to <6 years of age		6 to <12 years of age		12 to 19 years of age	
	No DLM (N=1,227)	DLM (N=7)	No DLM (N=784)	DLM (N=14)	No DLM (N=2107)	DLM (N=69)	No DLM (N=19541)	DLM (N=458)
Completed/ Cured	1,018 (83.0%)	7 (100.0%)	667 (85.1%)	14 (100.0%)	1709 (81.1%)	59 (85.5%)	13691 (70.1%)	293 (64.0%)
Died	73 (5.9%)	0 (0.0%)	48 (6.1%)	0 (0.0%)	207 (9.8%)	8 (11.6%)	2553 (13.1%)	93 (20.3%)
Treatment failure	5 (0.4%)	0 (0.0%)	7 (0.9%)	0 (0.0%)	42 (2%)	2 (2.9%)	668 (3.4%)	28 (6.1%)
Lost-to-follow-up	131 (10.7%)	0 (0.0%)	62 (7.9%)	0 (0.0%)	149 (7.1%)	0 (0.0%)	2629 (13.5%)	44 (9.6%)

Insufficient numbers of children <3 years (n=7) or 3 to <6 years of age (n=14) who received delamanid to complete matched analysis.

Limitations

- Observational data, including routine programmatic data
- High proportion bacteriologically confirmed
- Missing data for some key variables, such as weight
- Small sample size for intervention group for PICO 4a/b
- Have not adjusted for treatment factors and likely still residual confounding, including confounding by indication
- Data on duration of treatment overall, not of individual drugs
- No data on drug doses, limited data on safety (analysis pending)
- Lack of conclusive information on drug susceptibility to FQN or INJ; may lead to confounding that could not be controlled for by matching

Conclusions

- Very large dataset of children routinely treated for RR-TB, good geographic diversity, includes newer data with new drugs, shorter regimens
- Overall outcomes good despite relatively severe disease with high bacteriological confirmation
- In matched analysis, Bdq was not associated with outcome, but was significantly associated with shorter treatment duration and lower odds of injectable use
- Few children < 6 years received bedaquiline globally (not recommended)
- Very few children received delamanid globally, especially <6 years of age (not recommended for <3 years of age)
- Analyses ongoing to address question about optimal regimen construction in children

Acknowledgements

Desmond Tutu TB Centre, Stellenbosch University

- BENEFIT Kids Project
  - Co-PIs: Anthony Garcia-Prats, Anneke Hesseling
  - Lead: evidence synthesis: Vivian Cox
  - Project Manager: Tina Sachs
- Data Team: Rory Dunbar, Rose Brown, Jessica Workman

University of California San Francisco

- Rada Savic, Kendra Radtke, Maria Garcia-Cremades Mira, Alexander Floren

South African Medical Research Council/Cochrane South Africa

- Tamara Kredo, Funeka Bango

Unitaid

Data contributors and Collaborative Group for Meta-Analysis of Paediatric and Adolescent Individual Patient Data in RR- TB

- Bobojon Pirmahmadzoda, Jarmila Kliescikova, Shifoeva Iskandarovna
- Richard Menzies, Jonathon Campbell
- Norbert Ndjeka, Mathapelo Mafohla
- Mazhar Khan
- Silvia Chiang
- Parpieva Nargiza, Tasnim Hasan, Jatinder Singh
- Petros Isaakidis, Gabriella Ferlazzo, Erika Mohr-Holland
- Kuldeep Singh Sachdeva, Malik Parmar
- Ira Shah
- Anneke Hesseling, Anthony Garcia-Prats, Rada Savic, Elisa Lopez, Simon Schaaf, Heather Draper, James Seddon, Jana Winckler, Louvina van der Laan
- Giovanni Migliori, Margareth Dalcolmo
- Cathy Hewison, Molly Franke
- Farhana Amanullah
- Liz Harausz

THANK YOU

Photo taken with permission, Sue Purchase, DTTC