Impact of interventions for tuberculosis prevention and care in South Africa - a systematic review of mathematical modelling studies

Lauren Brown

Cari van Schalkwyk Florian Marx Abigail de Villiers

Stellenbosch University &

South African Centre for Epidemiological Modelling and Analysis (SACEMA)



forward together sonke siya phambili saam vorentoe





National Research Foundation

Overview









In 2021~**304,000** people developed TB and ~**55,000** people died from the disease HIV ~60% TB deaths were PLWH in 2021



* **COVID-19**

Diversion of key resources & lack of patient access to care



WHO's End TB Strategy







Reduction in TB incidence.



Reduction in number of TB deaths.



0%

Threshold for TBaffected households facing catastrophic costs.

* Source: WHO End TB Strategy Framework

Introduction



- South Africa reduced the TB incidence rate by 20% in 2020, but the country is **unlikely to reach the 2035** goals.
- Substantial efforts are needed to prevent, find and successfully treat TB in South Africa
- Evidence from mathematical modelling research on interventions to reduce TB incidence, mortality and TB-related costs in South Africa had not been systematically assessed prior to this paper.





2

Systematically review **TB transmissiondynamic modelling** studies that estimated the **impact of interventions** on population-level TB **incidence and/or mortality** in **South Africa**. Determine which interventions had the most promising estimated impact on population-level outcomes linked to the WHO's End TB Strategy. 3

Highlight gaps in TB modelling research.

Key objectives

Methods



Inclusion criteria

- Transmission dynamic model of TB
- Population-based model
- South African population at country or subcountry level
- Model the impact of an intervention(s)
- Estimate reductions in TB incidence and/or mortality
- Estimate impact towards WHO's End TB strategy targets

Exclusion criteria

- Model type other than transmission dynamic
- Non-South African population
- No intervention
- Review/ commentary



Methods



Literature search

- Web of Science
- PubMed
- Scopus
- TB MAC
- Global Index Medicus
- African Index Medicus

Abstract and full-text screening Two reviewers

Data extraction Narrative synthesis of findings Summarize and compare results from final studies

RoB Assessment



Data extraction summary



Risk of Bias Assessment

Study						J	Risk of]	Bias it	em						Final Score	Quality Grading
	Aims & Objectives	Setting & Population	Interventions & Comparators	Outcome measures	Model structure & Time horizon	Modelling methods	Parameters, Ranges & Data sources	Assumptions	Quality of data & Exploration of uncertainty	Methods of fitting	Model validation	Results	Interpretation & Discussion of results	Funding sources & Conflicts of interest		
Azman et al. (58)	2	1	1	2	2	2	1	1	2	1	0	2	2	2	21	High
Basu et al. (59)	2	1	1	2	2	2	2	2	2	2	2	2	2	2	26	Very High
Basu et al. (60)	2	2	2	2	2	1	2	2	2	2	0	2	1	1	23	Very High
Chindelevitch <i>et al.</i> (61)	2	2	2	2	2	2	2	1	2	2	1	2	2	2	26	Very High
Dowdy et al. (62)	2	2	2	2	2	1	1	2	2	1	0	2	2	1	22	High
Dye et al. (63)	2	2	2	1	2	1	1	1	1	2	0	1	1	2	19	High
Dye et al. (64)	2	2	2	2	1	2	2	2	1	2	0	2	1	1	22	High
Gilbert et al. (65)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28	Very High
Gilbert et al. (66)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28	Very High
Harris et al. (67)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Hippner et al. (45)	2	2	2	2	2	2	2	1	1	1	0	1	1	2	21	High
Houben et al. (40)	2	2	2	1	2	2	1	1	1	1	0	1	2	2	20	High
Kendall et al. (68)	2	2	2	2	2	2	2	2	2	2	0	2	2	2	26	Very High
Kendall et al. (69)	2	2	2	2	2	2	2	2	2	2	0	2	2	1	25	Very High

16 studies were of very high quality, and 13 of high quality.

...



Calculating AAPDs for comparison of intervention impact



Impact of interventions on TB outcomes at country-level

Scale-up of IPT among PLWH on ART(20) Vaccination with a pre-/post-infection vaccine (100% coverage)(35) Expanding ART eligibility to all PLWH(32) Vaccination with pre-infection vaccine (70% coverage)(20) ACF in the general population(18) Improving TB healthcare coverage(32) Increasing ART coverage among PLWH(25) Scale-up of IPT among adolescents*(26) IPT among people with a positive COR test(42) Enhancing TB case management*(20) Introduction of Xpert for TB diagnosis(9) Symptom-based screening among PHC attendees⁽⁶⁾ Expanding the use of culture and DST in people with DR-TB*(19) ACF using a high sensitivity test in the general population(23) Continuous IPT among PLWH on ART*(6) Decreasing initial (pre-treatment) LTFU⁽²³⁾ Improving TB treatment outcomes(32) Increasing the efficacy of RR-TB treatment regimen(36) Xpert for routine TB diagnosis(32) Improving linkage to care and TB treatment success*(6) Symptom-based screening among PLWH*(41) Lipoaribomannan for TB diagnosis(40) Increasing TB treatment success(23) Extending ART eligibility to all PLWH(23) Extending IPT to HIV-negative people at high risk for TB(23) Increasing coverage of Xpert-based testing*(41) Increasing ART coverage among PLWH at risk for TB(20) Reducing LTFU through shortening TB treatment(24)

Mortality Incidence 6.95 7.07 7.07 6.84 5.84 6.70 6.23 4.77 3.10 5.63 2.86 4.72 4.34 4.46 3.91 (-) 1.51 3.32 3.27 (-) 0.62 2.33 2.21 (-) 2.21 -1.75 2.13 1.73 (-) 1.55 0.87 0.93 1.43 1.42 1.42 0.36 1.23 0.83 0.82 0.48 0.68 0.20 0.32 0.26 0.26 0.14 0.02 0.08 (-) 0.06 0.04 0.05 0.05 6.00 4.002.000.002.004.006.00 8.00

Average annual percentage decline (%)

8.00

Most impactful interventions estimated

Scale-up of IPT among PLWH on ART ⁽²⁰						6.95	7.07					
/accination with a pre-/post-infection vaccine (100% coverage)(35						7.07	6.84					
Expanding ART eligibility to all PLWH(32						5.84	6.70					
Vaccination with pre-infection vaccine (70% coverage)(20						6.23	4.77					
ACF in the general population ⁽¹⁸⁾	-					3.10	5.63					
Improving TB healthcare coverage ⁽³²	1					2.86	4.72					
Increasing ART coverage among PLWH ⁽²⁵⁾						4.34	4.46					
Scale-up of IPT among adolescents*(26	-					3.91	-					
IPT among people with a positive COR test ⁽⁴²	-					1.51	3.32					
Enhancing TB case management*(20						3.27	-					
Introduction of Xpert for TB diagnosis ⁽⁹⁾	-					0.62	2.33					
Symptom-based screening among PHC attendees ⁽⁶⁾	-					2.21	-					
Expanding the use of culture and DST in people with DR-TB*(19						-	2.21					
ACF using a high sensitivity test in the general population ⁽²³⁾						2.13	1.75					
Continuous IPT among PLWH on ART*(6						1.73	-					
Decreasing initial (pre-treatment) LTFU ⁽²³⁾						0.87	1.55					
Improving TB treatment outcomes(32						0.93	1.43	ī 🗌				
Increasing the efficacy of RR-TB treatment regimen ⁽³⁶						1.42	1.42					
Xpert for routine TB diagnosis ⁽³²						0.36	1.23					
Improving linkage to care and TB treatment success*(6						0.83	-					
Symptom-based screening among PLWH*(41						0.82	-					
Lipoaribomannan for TB diagnosis ⁽⁴⁰						0.48	0.68					
Increasing TB treatment success ⁽²³						0.20	0.32					
Extending ART eligibility to all PLWH ⁽²³⁾						0.26	0.26					
Extending IPT to HIV-negative people at high risk for TB ⁽²³⁾						0.14	0.02					
Increasing coverage of Xpert-based testing*(41						0.08	-					
Increasing ART coverage among PLWH at risk for TB ⁽²⁰⁾						0.06	0.04					
Reducing LTFU through shortening TB treatment ⁽²⁴						0.05	0.05					
	8.00	6.00	4.0	00	2.00	0.0)0	2.00	4	.00	6.00	

Mortality Incidence

Preventive interventions vs care cascade interventions

Scale-up of IPT among PLWH on ART(20) Vaccination with a pre-/post-infection vaccine (100% coverage)(35) Expanding ART eligibility to all PLWH(32) Vaccination with pre-infection vaccine (70% coverage)(20) ACF in the general population⁽¹⁸⁾ Improving TB healthcare coverage(32) Increasing ART coverage among PLWH(25) Scale-up of IPT among adolescents*(26) IPT among people with a positive COR test(42) Enhancing TB case management*(20) Introduction of Xpert for TB diagnosis(9) Symptom-based screening among PHC attendees⁽⁶⁾ Expanding the use of culture and DST in people with DR-TB*(19) ACF using a high sensitivity test in the general population⁽²³⁾ Continuous IPT among PLWH on ART*(6) Decreasing initial (pre-treatment) LTFU⁽²³⁾ Improving TB treatment outcomes(32) Increasing the efficacy of RR-TB treatment regimen(36) Xpert for routine TB diagnosis(32) Improving linkage to care and TB treatment success*(6) Symptom-based screening among PLWH*(41) Lipoaribomannan for TB diagnosis(40) Increasing TB treatment success(23) Extending ART eligibility to all PLWH(23) Extending IPT to HIV-negative people at high risk for TB⁽²³⁾ Increasing coverage of Xpert-based testing*(41) Increasing ART coverage among PLWH at risk for TB(20) Reducing LTFU through shortening TB treatment(24) Mortality Incidence

6.00	4.00	2.00	0.0	00	2.00	4.00	6.00	8.00
			0.05	0.05				
			0.06	0.04				
			0.08	-				
			0.14	0.02				
			0.26	0.26				
			0.20	0.32				
			0.48	0.68				
			0.82	-				
			0.83	-				
			0.36	1.23				
			1.42	1.42				
			0.93	1.43				
			0.87	1.55	1			
			1.73	-				
			2 13	1.75				
			2.21	2 21				
			0.62	2.33				
			3.27	-	_			
			1.51	3.32				
			3.91	-		_		
			4.34	4.46				
			2.86	4.72				
			3.10	5.63				
			6.23	4.77				
			5.84	6.70				
			7.07	6.84				
			0.95	1.07				

Average annual percentage decline (%)

8.00

AAPDs required to meet incidence and mortality targets for South Africa

	Scale-up of IPT among PLWH on ART ⁽²⁰⁾	6.95 7.07
	Vaccination with a pre-/post-infection vaccine (100% coverage)(35)	7.07 6.84
	Expanding ART eligibility to all PLWH ⁽³²⁾	5.84 6.70
	Vaccination with pre-infection vaccine (70% coverage) ⁽²⁰⁾	6.23 4.77
	ACF in the general population ⁽¹⁸⁾	3.10 5.63
Incidanca	Improving TB healthcare coverage ⁽³²⁾	2.86 4.72
IIICIUEIICE	Increasing ART coverage among PLWH ⁽²⁵⁾	4.34 4.46
	Scale-up of IPT among adolescents*(26)	3.91 -
	IPT among people with a positive COR test ⁽⁴²⁾	1.51 3.32
1.2%	Enhancing TB case management*(20)	3.27 -
1 2 / 0	Introduction of Xpert for TB diagnosis ⁽⁹⁾	0.62 2.33
	Symptom-based screening among PHC attendees ⁽⁶⁾	2.21 -
	Expanding the use of culture and DST in people with DR-TB*(19)	- 2.21
	ACF using a high sensitivity test in the general population ⁽²³⁾	2.13 1.75
Mortality	Continuous IPT among PLWH on ART*(6)	1.73 -
	Decreasing initial (pre-treatment) LTFU ⁽²³⁾	0.87 1.55
	Improving TB treatment outcomes ⁽³²⁾	0.93 1.43
100/	Increasing the efficacy of RR-TB treatment regimen ⁽³⁶⁾	1.42 1.42
19%	Xpert for routine TB diagnosis ⁽³²⁾	0.36 1.23
	Improving linkage to care and TB treatment success*(6)	0.83 -
	Symptom-based screening among PLWH*(41)	0.82 -
	Lipoaribomannan for TB diagnosis ⁽⁴⁰⁾	0.48 0.68
	Increasing TB treatment success ⁽²³⁾	0.20 0.32
	Extending ART eligibility to all PLWH ⁽²³⁾	0.26 0.26
	Extending IPT to HIV-negative people at high risk for TB ⁽²³⁾	0.14 0.02
	Increasing coverage of Xpert-based testing*(41)	0.08 -
	Increasing ART coverage among PLWH at risk for TB ⁽²⁰⁾	0.06 0.04
	Reducing LTFU through shortening TB treatment ⁽²⁴⁾	0.05 0.05

8.00

6.00

Average annual percentage decline (%)

0.00

2.00

4.00

6.00

8.00

2.00

4.00

Mortality Incidence



Modelling gaps identified





Limitations

- Restricted to **South African** population
- Findings from sub-country level studies may not be readily generalizable to the national level
- Heterogeneity in model structure, study design and reported outcomes
- Reported impact with **crude measures of AAPDs for single interventions**, many studies considered **combinations**
- If multiple scenarios were modelled, we chose the scenario resulting in the **highest impact**



Interventions to tackle TB in South Africa

Strategic focus on preventive interventions

Vaccination, TPT among PLWH and scaling-up ART were **most promising** to reduce TB incidence and mortality. Consideration of **care cascade interventions**

Case finding initiatives and improving testing and treatment estimated to be of **lower impact** but does not negate significance. Combinations of interventions

Needed to meet **WHO's End TB Strategy targets** in South Africa.

Thank you!

Acknowledgements:

- Cari van Schalkwyk
- Florian Marx
- Abigail de Villiers
- Ted Cohen •
- David Dowdy
- Christopher Dye •
- Rein Houben
- National Research Foundation
- Yuri Munsamy

Contact: Lauren Brown laurenbrown@sun.ac.za

https://doi.org/10.7196/SAMJ.2023.v113i3.16812





Forward together sonke siya phambili saam vorentoe





We acknowledge the support of the South African DSI-NRF Centre of Excellence in Epidemiological Modelling and Analysis towards this research. Opinions expressed, and conclusions arrived at, are those of the authors and do not represent the official views of SACEMA.