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

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Background. Substantial additional efforts are needed to prevent, find and successfully treat tuberculosis (TB) in South Africa (SA). In the past decade, an increasing body of mathematical modelling research has investigated the population-level impact of TB prevention and care interventions. To date, this evidence has not been assessed in the SA context.
Objective. To systematically review mathematical modelling studies that estimated the impact of interventions towards the World Health Organization's End TB Strategy targets for TB incidence, TB deaths and catastrophic costs due to TB in SA.
Methods. We searched the PubMed, Web of Science and Scopus databases for studies that used transmission-dynamic models of TB in SA and reported on at least one of the End TB Strategy targets at population level. We described study populations, type of interventions and their target groups, and estimates of impact and other key findings. For studies of country-level interventions, we estimated average annual percentage declines (AAPDs) in TB incidence and mortality attributable to the intervention.
Results. We identified 29 studies that met our inclusion criteria, of which 7 modelled TB preventive interventions (vaccination, antiretroviral treatment (ART) for HIV, TB preventive treatment (TPT)), 12 considered interventions along the care cascade for TB (screening/case finding, reducing initial loss to follow-up, diagnostic and treatment interventions), and 10 modelled combinations of preventive and care-cascade interventions. Only one study focused on reducing catastrophic costs due to TB. The highest impact of a single intervention was estimated in studies of TB vaccination, TPT among people living with HIV, and scale-up of ART. For preventive interventions, AAPDs for TB incidence varied between 0.06% and 7.07%, and for care-cascade interventions between 0.05% and 3.27%.
Conclusion. We describe a body of mathematical modelling research with a focus on TB prevention and care in SA. We found higher estimates of impact reported in studies of preventive interventions, highlighting the need to invest in TB prevention in SA. However, study heterogeneity and inconsistent baseline scenarios limit the ability to compare impact estimates between studies. Combinations, rather than single interventions, are likely needed to reach the End TB Strategy targets in SA.

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South Africa (SA) remains one of the countries with the highest tuberculosis (TB) burden in the world.[1] In 2021, an estimated 304 000 people developed TB, and 55 000 died from the disease;[1] TB therefore remains the leading infectious disease cause of death in the country.[2] Recent measures to contain the spread of SARS-CoV-2[3] have led to considerable declines in individuals accessing healthcare services, TB testing and individuals diagnosed with TB,[4] resulting in an expected increase in TB prevalence and mortality. These developments have also seriously affected SA's progress towards the milestones and targets set for the World Health Organization (WHO)'s End TB Strategy[5] that aims to reduce the number of TB deaths by 95%, the TB incidence rate by 90% (relative to 2015) and the percentage of TB-affected families facing catastrophic costs due to TB to zero by 2035.

To mitigate these adverse consequences on TB epidemiology and to restore progress towards the End TB Strategy targets, substantial additional efforts are needed to prevent, find and successfully treat TB in SA. A comprehensive consultation process, co-ordinated by the TB Think Tank of the National Department of Health, has been initiated to define additional interventions to be implemented as part of SA's upcoming 2023 - 2028 National Tuberculosis Programme (NTP) Strategic Plan.

For policy-makers to identify and implement strategies for optimal outcomes towards the End TB Strategy targets, evidence must be collected to inform decisions.[6] Generating this evidence directly through empirical research poses considerable challenges. Cluster-randomised trials to estimate the population-level impact of interventions on TB incidence, mortality and catastrophic costs demand considerable resources and time. They often focus on a limited set (e.g. of one or two) interventions, yielding limited insights into how these interventions will compare with alternatives.[7]

Mathematical models for infectious diseases are valuable tools for evaluating the effect of intervention strategies and assisting policy-makers in making informed decisions.[8,9] Transmission-dynamic models of TB are increasingly used[10-12] to estimate the impact of interventions on population-level outcomes in high-burden countries, including SA. To date, the evidence from mathematical modelling research on interventions to reduce TB incidence, mortality and catastrophic costs in SA has not been systematically assessed.

Table 1. Outcomes reported for interventions modelled at country level by 18 studies

Publication, time horizon	Intervention modelled and target population	Study outcome*	Percentage reduction compared with baseline at end of time horizon or number averted over time horizon
Vaccination			
Dye *et al.*,[21] 2025 - 2050	Hypothetical pre-infection vaccine introduced in 2025 protecting 70% of uninfected HIV-negative people by 2050	Number of TB cases and deaths would fall from 8 500 to ~1 700 and 1 220 to 360 per million, respectively.	Incidence: 80% Deaths: 70.5%
Harris *et al.*,[36] 2025 - 2050	Hypothetical vaccines with varied efficacy to prevent infection or disease (70/100%), effective in uninfected or infected individuals and duration of protection of 10 years	A pre-/post-infection vaccine (efficacious for PLWH) for protection against infection and disease resulted in an 84% IRR (81% - 87%) and an 83% reduction in mortality. A vaccine with the same specifications, but with 70% efficacy, resulted in an IRR of 71% (66% - 89%).	Incidence (100%): 84% Mortality (100%): 83% Incidence (70%): 71%
ART for TB prevention			
Chindelevitch *et al.*,[33] 2012 - 2032	Expanding ART eligibility by increasing ART initiation for each CD4 category for PLWH	Universal ART eligibility with 80% reached over 20 years reduced incidence and mortality by 70% and 75%, respectively.	Incidence: 70% Mortality: 75%
Dye *et al.*,[21] 2010 - 2050†	Increasing ART coverage from 40% - 80% (2010 - 2050) for PLWH on IPT	The efficacy of ART in preventing TB per unit time is 67%, which is offset by a 50% reduction in mortality, extending the number of life-years at risk of TB.	Incidence: 2.4% Mortality: 1.6%
Knight *et al.*,[24] 2014 - 2050	Expanding ART eligibility for PLWH	ART given universally (UTT) with 42% coverage reduced incidence and mortality by 18% and 27%, respectively.	Incidence: 18%‡ Mortality: 27%‡
Pretorius *et al.*,[26] 2014 - 2033	Improving pre-ART and ART services, and expanding ART eligibility for PLWH	Expanding ART access to all PLWH (universally), with 80% coverage, would reduce cumulative incidence and mortality by 28% - 37% and 36% - 44%, respectively.	Incidence: 28 - 37% Mortality: 36 - 44%
Williams *et al.*,[30] 2010 - 2050	Regular HIV testing and immediate ART for PLWH	HIV test-and-treat could avert 0.6 of 2.17 million cases of TB between 2010 and 2015 and 4.58 of 9.82 million cases between 2015 and 2050.	Cases (2010-2015): 28%‡§ Cases (2015-2050): 47%‡§
TB preventive treatment			
Dye *et al.*,[21] 2025 - 2050†	Increasing coverage of IPT (from 0% to 75%) among PLWH on ART between 2025 and 2035	IPT scale-up could reduce the number of cases and deaths from 8 500 to ~1 400 and 1 220 to 200 per million, respectively, by 2050.	Incidence (IPT): 83.5% Mortality (IPT): 83.6%
Houben *et al.*,[6] 2015 - 2025	Providing continuous ART-linked IPT to PLWH	In addition to the 2% - 5% annual decline in incidence, continuous IPT reduced incidence by a further 16% (range 8% - 51%).	Incidence: 16%
Knight *et al.*,[24] 2014 - 2050†	Providing IPT to HIV-negative people	By 2032, incidence and mortality were reduced by 13% and 20%, respectively, for the same intervention.	Incidence: 13%‡ Mortality: 20%‡
Rhines *et al.*,[27] 2012 - 2032	Scale-up of IPT to adolescents in secondary schools (from 5% to 90%)	90% IPT coverage in adolescents testing positive for infection reduces incidence in adolescents and adults by 55% and 36%, respectively.	Incidence (adolescents): 55% Incidence (adults): 36%
Case finding/ screening			
Azman *et al.*,[19] 2012 - 2022	Sustained ACF programmes in the general population	Sustaining an increase of 25% of cases diagnosed and treated in their first year could reduce incidence and mortality by 22% - 27% and 40% - 44%, respectively.	Incidence: 22% - 27% Mortality: 40% - 44%
Basu *et al.*,[32] Over 5 years	Early XDR-TB screening in hospitals and the community	In combination with improved treatment, early screening prevented ~50 deaths per 100 000 over 5 years.	Deaths: 50 per 100 000 over 5 years§

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Table 1. (continued) Outcomes reported for interventions modelled at country level by 18 studies

Publication ,time horizon	Intervention modelled and target population	Study outcome*	Percentage reduction compared with baseline at end of time horizon or number averted over time horizon
Houben *et al.*,[6] 2015 - 2025†	Screening of all attendees at primary-health clinics	In addition to the 2% - 5% annual decline in incidence, screening reduced incidence by a further 20% (7% - 35%).	Incidence: 20%
Knight *et al.*,[24] 2014 - 2050†	ACF in the general population measured in 2032	Periodic ACF with high sensitivity and high coverage reduced incidence and mortality by 58% and 67%, respectively, by 2032.	Incidence: 58%‡ Mortality: 67%‡
Sumner *et al.*,[42] 2016 - 2035	Intensified case finding (symptom-based screening) for PLWH	Symptom-based screening for PLWH reduced incidence by 14.5% (12.2% - 16.3%).	Incidence: 14.5%
Verguet *et al.*,[44] 2016 - 2035	Expanding access to care in outreach clinics and symptom screening in primary care facilities for households facing catastrophic costs due to TB	Decreasing population without access to care from 5% to 0% would avert 60 000 - 240 000 (5% - 20%) cases of catastrophic costs. Households in the lowest two income quintiles benefitted the most with 65% - 90% of cases of catastrophic costs averted.	Cases of catastrophic costs: 5% - 20% Cases of catastrophic costs (lowest two income quintiles): 65% - 90%
Diagnostic interventions			
Basu *et al.*,[32] over 5 years†	Rapid DST in hospitals and the community	To obtain XDR DST results in 1 week instead of the current 6-week delay, mortality was reduced from 230 to 215 deaths per 100 000 over 5 years.	Deaths: 15 per 100 000 over 5 years§
Chindelevitch *et al.*,[33] 2012 - 2032†	Using more sensitive diagnostics (replacing a proportion of smear microscopy with Xpert) in the general population	Improved diagnostics over 20 years reduced incidence and mortality by 6.7% and 21.6%, respectively.	Incidence: 6.7% Mortality: 21.6%
Dowdy *et al.*,[20] 2007 - 2017	Improving diagnosis for adults with access to expanded culture and DST	Performing culture and DST in 37% of new suspects and 85% of previously treated patients averted 17.2% of deaths (95% SI: 8.9% - 24.4%), 14.1% (5.3% - 23.8%) of incident MDR-TB cases and 46.6% (32.6% - 56%) of MDR-TB deaths.	Mortality: 17.2% MDR-TB cases: 14.1%§ MDR-TB deaths: 46.6%§
Menzies *et al.*,[10] 2012 - 2022	Improving diagnosis (scale-up of Xpert for initial diagnosis up to full coverage over 2012 - 2015) for individuals suspected to have TB	Xpert initiation reduced prevalence, incidence, and mortality by 28% (14% - 40%), 6% (2% - 13%), 21% (10% - 32%), respectively. The number of MDR-TB cases would be lowered by 25% (6% - 44%).	Incidence: 6% Mortality: 21% Incidence (MDR-TB): 25%
Ricks *et al.*,[41] 2020 - 2035	Improving testing (future LAM tests compared with current LAM tests) for people receiving HIV care and HIV-negative patients	Future LAM tests deployed to inpatients, outpatients and routine TB care reduced incidence and mortality by 17.7% (8.62% - 29%) and 29.6% (17.8% - 43.6%), respectively.	Incidence: 17.7% Mortality: 29.6%
Sumner *et al.*,[42] 2016 - 2035†	Increased usage of Xpert as a first-line test in the general population (80% - 100% coverage)	Using Xpert testing alone reduced incidence by 1.6% (2.5th - 97.5th PR, 0.9% - 2.4%).	Incidence: 1.6%
Reducing ILTFU			
Knight *et al.*,[24] 2014 - 2050†	Decreasing pre-treatment LTFU in the general population measured in 2032	A 50% decrease in pre-treatment LTFU reduced incidence and mortality by 33% and 54%, respectively, by 2032.	Incidence: 33%‡ Mortality: 54%‡
Treatment			
Basu *et al.*,[32] Over 5 years†	Improving treatment for XDR-TB at community- and hospital-based levels	In combination with early XDR-TB screening, improving XDR treatment prevented ~50 deaths per 100 000.	Deaths: 50 per 100 000§

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Table 1. (continued) Outcomes reported for interventions modelled at country level by 18 studies

Publication, time horizon	Intervention modelled and target population	Study outcome*	Percentage reduction compared with baseline at end of time horizon or number averted over time horizon
Chindelevitch *et al.*,[33] 2012 - 2032†	Improving treatment (identifying treatment failure and improving cure rates) in the general population	Improved treatment over 20 years reduced incidence and mortality by 16.7% and 24.5%, respectively.	Incidence: 16.7% Mortality: 24.5%
Houben *et al.*,[6] 2015 - 2025†	Improving first-line/MDR-TB treatment success by monitoring patients and outreach programmes in communities	In addition to the 2% - 5% annual decline in incidence, improving treatment reduced incidence by a further 8% (0% - 25%).	Incidence: 8%
Kendall *et al.*,[37] over 25 years	Improving novel treatment regimens, for RR-TB in this case, in the general population	An optimal RR-TB regimen reduced incidence and mortality by 30.1% (15.4% - 47.7%) and 30.3% (17.1% - 45.4%), respectively.	Incidence (RR-TB): 30.1% Mortality (RR-TB): 30.3%
Knight *et al.*,[24] 2014 - 2050†	Increasing treatment success in the general population	A 50% increase in treatment success reduced incidence and mortality by 15% and 28%, respectively.	Incidence: 15%‡ Mortality: 28%‡
Knight *et al.*,[25] 2015 - 2035	Shortening TB treatment length with novel 4-month regimen in the general population	Novel 4-month treatment regimen reduced incidence and mortality by 1% compared to the standard 6-month regimen.	Incidence: 1% Mortality: 1%
Verguet *et al.*,[44] 2016 - 2035†	Improving treatment quality (mobile healthcare, patient follow-up, adherence counselling, improved staffing for MDR-TB) for households facing catastrophic costs due to TB	Improving treatment for DS-TB and MDR-TB would avert 90 000 - 220 000 and 70 000 - 220 000 cases of catastrophic costs, respectively. Households in the lowest two income quintiles would avert 90% of cases of catastrophic costs in both scenarios.	Cases of catastrophic costs (DS-TB): 90 000 - 220 000 Cases of catastrophic costs (MDR-TB): 70 000 - 220 000 Cases of catastrophic costs (lowest two income quintiles): 90%
Other interventions			
Chindelevitch *et al.*,[33] 2012 - 2032†	Improving healthcare coverage (reducing delay of disease development to clinic attendance) in the general population	Improved coverage over 20 years reduced incidence and mortality by 44% and 61.7%, respectively.	Incidence: 44% Mortality: 61.7%
Dye *et al.*,[21] 2025 - 2050†	Enhancing case management (early case detection, accurate diagnosis and high cure rate)	Halving the ARI over 20 years reduced the number of cases and deaths from 8 500 to ~3 700 and 1 220 to 530 per million, respectively.	Incidence: 56.5% Mortality: 56.6%
Sumner *et al.*,[43] 2020 - 2035	Improving testing (use of mRNA expression signature COR test to target PT) for HIV-uninfected adults	COR reaches a reduction in incidence of 20.4% (15.2% - 26.9%) and IGRA a reduction of 38.8% (31.2% - 48%) after 15 years.	Incidence (COR): 20.4% Incidence (IGRA): 38.8%

TB = tuberculosis; PLWH = people living with HIV; IRR = incidence reduction rate; ART = antiretroviral therapy; IPT = isoniazid preventive therapy; UTT = universal test and treat programme; ACF = active case finding; XDR-TB = extensively drug-resistant TB; DST = drug susceptibility testing; SI = simulation interval; MDR-TB = multidrug-resistant TB; LAM = lipoarabinomannan; PR = percentile range; (I)LTFU = (initial) loss to follow-up; RR-TB = rifampicin-resistant TB; DS-TB = drug-susceptible TB; ARI = annual risk of infection; COR = correlate of risk; PT = TB preventive treatment; IGRA = interferon gamma release assay.
*Uncertainty intervals are reported where provided in the article.
†Studies that modelled the impact of multiple interventions.
‡Studies that reported % declines in incidence/mortality over the time frame, and studies that reported cases and deaths averted compared to baseline.
§The World Health Organization estimated 1 230, 988, and 554 cases and 360, 116, and 103 deaths, per 100 000 population, for 2010, 2015 and 2020.[48]

In an effort to support decision-making for TB in SA, we reviewed mathematical modelling studies that estimated the population-level impact of interventions towards the End TB Strategy targets for TB incidence and mortality, and catastrophic costs associated with TB. We aimed to describe the types of interventions, intervention designs and target populations considered, and the impact estimated through modelling. We also aimed to highlight gaps in TB modelling research that could be addressed in future research to inform TB policy-making in the country.

Methods

We employed the PICOS (Population, Intervention, Control, Outcomes and Study design) tool[13] to define the research question and the design of this systematic review. The review protocol is registered with the international prospective register for systematic reviews (PROSPERO; CRD42021276526). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for 2020.[14] The review design and PRISMA checklist (Table S1 - S3) are available in the appendix (https://www.samedical.org/file/1985).

Search strategy and selection criteria

We conducted a systematic search of the published literature using the PubMed, Web of Science, and Scopus databases. Search strings are provided in Table S2 in the appendix. Additionally, we searched the TB Modelling and Analysis Consortium (TB MAC)'s list of mathematical and economic TB modelling studies,[15] Global Index Medicus, African Index Medicus and reference lists of eligible studies. We also consulted four leading global experts in TB modelling to identify additional publications not included in the initial search from their personal databases. The search was conducted up to 28 September 2021. We included articles that used population-based transmission dynamic models of TB in SA at country or sub-country level, and reported population-level reductions in TB incidence, TB mortality and/or catastrophic costs associated with TB. We excluded articles that reported statistical models of empirical data or cohort models that were not transmission dynamic. We further excluded reviews of modelling studies and articles describing mathematical models that did not refer to the SA population (or a population in SA).

Data extraction and analysis

Titles and/or abstracts of articles identified during the initial search were screened by two reviewers. The full texts of these studies were then retrieved and independently assessed for eligibility. Data extracted from eligible studies included the type of model, study population, intervention details, key study outcomes and model projections. For studies that modelled multiple scenarios of the same intervention, we extracted the scenario that resulted in the greatest impact. We described modelling results by type of intervention and target population with respect to estimated gains towards the End TB strategy targets. In addition, for studies describing country-level TB models, we compared average annual percentage declines (AAPDs) in TB incidence and mortality estimated for different interventions relative to base-case (no intervention). For articles reporting percentage declines over the entire model time horizon, we calculated AAPD using the formula:

$$AAPD = (1 - \sqrt[t]{1 - PPD/100}) \times 100$$

where t denotes the time horizon of the model, and PPD the period percentage decline attributable to the intervention investigated (i.e. the percentage difference between the baseline scenario and intervention scenario at the end of the time horizon) reported in a study. An example of calculating AAPDs is illustrated in Fig. S1 in the appendix.

Risk of bias assessment

An adapted risk-of-bias tool[16-18] was used to assess the methodological quality of eligible modelling studies. The tool uses a set of questions regarding the study aims and objectives, model structure, setting and population, methods of fitting, assumptions and others. An overall score consideration of 0 for each criterion was given if no required information was provided, 1 if some aspects of the study were incomplete, and 2 if the necessary information was clear and appropriate for the research question. A full description of the questions and score considerations is available in the appendix (Table S5). A risk-of-bias score (0 - 28) was given to each study by adding itemised scores for each criterion. The quality of eligible studies was deemed very high (>22), high (19 - 22), medium (14 - 18) or low (<14) according to the risk of bias score.

Results

Search process and selection of articles

Our initial search yielded 2 128 records, of which 1 243 were unique. The majority of articles that were excluded at title and abstract screening (n=1 168) described statistical models, descriptive analyses or static cost-effectiveness models. Following full-text review of 75 articles, we identified a total of 29 that met the inclusion criteria. A full breakdown of articles identified for this review is shown in Fig. 1. Detailed reasons for exclusion at full-text review are provided in the appendix (Table S9.1 - 9.2).

Risk-of-bias assessment

Of the 29 articles included in this review, 13 received a risk-of-bias score of 19 - 22, and were considered of high quality,[6,19-30] and 16 received a score of >22, considered very high quality.[10,31-45] A median score of 23 (out of 28) was recorded, equivalent to very high quality. Reductions in the score were due to lack of model validation, incomplete parameter descriptions, lack of justification of assumptions made, and missing information about limitations and study context. Detailed scores of the assessment are provided in the appendix (Table S6).

Characteristics of included studies

Studies varied considerably in terms of model design, time horizon over which interventions were modelled, study population, type of intervention and outcomes measured (Fig. 2; appendix Tables S4 and S7). Of the 29 articles included, 20 described deterministic compartmental models,[10,19-23,27,29-31,33-38,41-43,45] three stochastic compartmental models[32,39-40] and three stochastic individual-based models (IBMs).[24,25,28] The remaining three studies used a combination of different types of transmission-dynamic models.[6,26,44] All but one study included stratifications by HIV status to account for the modifying effect of HIV infection on TB natural history.[29] With respect to the End TB Strategy targets, all but two studies[32,44] reported outcomes for reductions in TB incidence, 17 reported reductions in TB mortality,[10,19,20,23-26,32-34,36-41] and only one[44] considered catastrophic costs averted due to TB interventions.

Interventions modelled

Of the 29 studies identified, 22 modelled hypothetical interventions, while 7 modelled scenarios for scale-up of existing interventions.[10,22,26,30,33,38,42] Seven studies modelled preventive interventions,[22,26-28,30,36,38] 12 considered interventions along the care cascade for TB[10,19,20,23,25,29,32,37,41-44] and 10 considered a combination of both.[6,21,24,31,33-35,39,40,45] Table 1 provides an overview of key characteristics and study outcomes by type of intervention for the 18 country-level studies included in this review. Details of studies modelling the impact of interventions at sub-country level are provided in the appendix (Table S8). Estimates of impact measured in the studies are provided below.

(*i*) Vaccination

Three studies estimated the impact of vaccination against TB. Two studies modelled novel vaccines,[21,36] and one considered revaccination using the bacillus Calmette-Guérin (BCG) vaccine.[22] Considerable reductions in TB incidence and mortality were projected for a hypothetical novel vaccine with 70% efficacy in preventing TB infection,[21] and a different hypothetical vaccine with 100% efficacy, equally effective in people living with HIV (PLWH) and HIV-negative people, TB-infected and TB-uninfected populations.[36] The latter study considered various vaccination strategies including early-adolescent and 10-yearly mass vaccination campaigns.[36] Re-vaccinating HIV-negative adolescents in an urban high-transmission setting using the BCG vaccine (efficacy: 10 - 80%) was estimated to be of limited impact but potentially cost-effective[22] (appendix Table S8).

(*ii*) ART for TB prevention

Five studies estimated the impact of antiretroviral therapy (ART) scale-up for TB prevention in SA. Two[24,33] were published in 2015 and one in 2014,[26] at a time when ART eligibility in SA was limited to PLWH with a CD4 count of ≤500 cells per mm^3,[46] and focused on expanding ART towards universal treatment (regardless of CD4 count). Reaching 80% coverage among PLWH was estimated to reduce TB incidence and mortality substantially,[26,33] while a coverage of 42% was estimated to be of lower impact.[24] Other studies focused on combinations of ART and isoniazid preventive therapy,[21] and the introduction of universal HIV testing with immediate ART following a positive test.[30]

(*iii*) TB preventive treatment

Six studies estimated the impact of TB preventive treatment (TPT), which all considered isoniazid monotherapy.[6,21,24,27,33,40] Target groups considered included adolescents, PLWH and people previously treated for TB. Screening adolescents attending secondary schools for latent TB infection followed by TPT for those testing positive was found to be beneficial to both the adolescent and adult populations.[27] Scaling up TPT among PLWH on ART after screening for TB disease was estimated to lead to considerable reductions in population-level TB incidence and mortality in one study,[21] but was of lower impact in another.[6] Limited impact was estimated when extending TPT to HIV-negative individuals.[24] Two subsequent studies of TB in a suburban high-incidence setting concluded that TPT combined with case finding/follow-up examinations among people who previously completed TB treatment could accelerate declines in TB incidence and mortality at population level and potentially reduce costs[38,39] (appendix Table S8).

(*iv*) Case finding/screening

Seven studies modelled TB screening/active case finding (ACF) interventions. Target populations considered included the general population, PLWH on ART, people previously treated for TB and public health clinic attendees. Three studies considered case-finding interventions in the general population.[24,35,42] Periodic ACF reaching 60% of the general population using a hypothetical, high-sensitivity screening test was estimated to moderately reduce TB incidence with greater impact seen on mortality.[24] In a rural setting, symptom-based screening followed by Xpert, culture and/or drug susceptibility testing (DST) was estimated to simultaneously reduce incident multidrug-resistant (MDR-) and extensively drug-resistant (XDR-)TB[35] (appendix Table S8). Increasing the use of a symptom-based screening tool from 40% to 100% among people on ART was estimated to have limited impact on TB incidence.[42] Expanded access to care using outreach clinics and symptom-based screening in primary care was estimated to reduce cases of catastrophic costs due to TB substantially, with larger impact seen after 5 - 10 years.[44] One study in a high-incidence setting focused on ACF among people who had previously completed TB treatment.[39] The study showed considerable declines in TB incidence for targeted ACF, alone or in combination with TPT[39] (appendix Table S8). Two studies modelled the impact of TB screening among individuals attending public healthcare clinics.[6,23] Verbal TB symptom screening at public health clinic entrances, assuming 100% screening coverage, was estimated to reduce TB incidence countrywide.[6] In the Western Cape Province, increasing cough-based screening coverage followed by smear microscopy for those positive was estimated to have a considerable impact on TB incidence and mortality[23] (appendix Table S8).

(*v*) Diagnostic interventions

Five modelling studies focused on Xpert-based algorithms as the standard diagnostic test for TB in SA, prior to[10,33,34,45] and during[42] its roll-out in 2013. A diagnostic modelling study of TB in five African countries including SA suggested that the introduction and scale-up of Xpert could reduce morbidity and mortality, with less impact seen on long-term epidemiological outcomes.[10] Replacing all smear-microscopy tests with Xpert,[33] increasing the coverage of Xpert-based diagnoses from 80% in 2016 to 100% in 2035[42] and supplementing DST with Xpert[34] (appendix Table S8) were suggested to have limited impact on TB incidence and mortality. Diagnosing gold miners, an occupational group at high risk for TB in SA, with Xpert instead of radiographical screening was estimated to reduce TB incidence in mining settings substantially[45] (appendix Table S8). One study[41] estimated the impact of novel lateral flow urine lipoarabinomannan (LAM) tests for the early detection of TB in SA and found that, while future LAM tests could be important for averting TB deaths among PLWH with advanced disease, population-level impact would depend on diagnostic accuracy. All three studies that investigated the impact of DST on drug-resistant (DR)-TB concluded that, although transmission could be reduced, additional interventions would be necessary to effectively reduce the burden of DR-TB in the population.[20,29,32]

(*vi*) Reducing initial loss to follow-up

One study focused on interventions for reducing initial loss to follow-up (ILTFU), defined as the loss of individuals with confirmed TB from care before initiating treatment.[24] It concluded that decreasing ILTFU by 50% through higher efficiency in the diagnostic process, increased education and improved follow-up by healthcare professionals could lead to moderate reductions in TB incidence.[24]

(*vii*) Treatment

Eight modelling studies focused on TB treatment-related interventions of three types: reducing poor treatment outcomes; introducing novel drugs and treatment regimens; and improving DR-TB treatment. Three studies considered reducing poor outcomes of routine TB treatment in SA.[24,33,44] Identifying treatment failure, improving cure rates[33] and increasing treatment success through improved adherence[24] were estimated to yield limited impact on TB incidence and mortality. However, another study suggested that improving treatment quality by using mobile healthcare, patient follow-up, adherence counselling and improved staffing for MDR-TB could greatly reduce catastrophic costs in TB-affected households.[44] Two studies focused on the introduction of hypothetical novel TB treatment regimens at country level.[25,37] Focusing on treatment efficacy in clinical trials of novel treatment regimens, in this case a rifampicin-resistant regimen, was estimated to yield significant impact on TB incidence and mortality.[37] Rapid scale-up of a 4-month TB treatment regimen that was as effective as the standard 6-month regimen, but would reduce loss to follow-up during treatment, was estimated to be of low impact.[25] Three studies focused on treatment interventions to reduce MDR- and XDR-TB.[6,32,34] A study published in 2009, when XDR-TB treatment was only offered in tertiary hospitals in SA, estimated that early DST in combination with providing treatment at outpatient health clinics (as opposed to inpatient treatment) could substantially reduce the probability of XDR-TB epidemics.[32] Improving first-line and MDR-TB treatment success using patient monitoring and community outreach programmes[6] and MDR-TB treatment decentralisation, initialised by shortened hospitalisation and home-based treatment for individuals presenting for treatment,[34] were estimated to accelerate reductions in TB incidence and mortality (appendix Table S8).

(*viii*) Other interventions

Reducing delay in care-seeking among people experiencing TB-characteristic symptoms was found to have substantial impact on TB incidence and mortality.[33] Halving the annual risk of infection through a combination of interventions to enhance case management was estimated to reduce TB incidence and mortality four-fold and eight-fold, respectively.[21] One modelling study considered the use of a novel mRNA correlate-of-risk (COR) test[48] to target TPT towards high-risk HIV-negative adults. Use of this new test for effective targeting of TPT was estimated to reduce TB incidence considerably.[43]

Estimated impact by type of intervention

Fig. 3 shows AAPDs in TB incidence and mortality for different interventions, calculated from reported model outcomes and time horizons. AAPDs varied between 0.05% and 7.1% for TB incidence, and between 0.02% and 7.1% for TB mortality. Larger impacts were estimated for preventive interventions (TB vaccination, TPT among PLWH on ART, and ART with high coverage) than for improved diagnosis and treatment. Interventions along the care cascade (e.g. case finding, diagnosis, treatment) were estimated to have greater AAPDs in TB-associated mortality than in TB incidence. AAPDs in TB incidence and mortality stratified by intervention are illustrated in Fig. S2 (appendix).

Discussion

We conducted this systematic review to synthesise the evidence for TB prevention and care in SA from studies using transmission-dynamic mathematical models.

We identified 29 eligible modelling studies, the majority of which were published in the past 6 - 7 years. Studies focused on a variety of interventions for preventing TB and strengthening the care cascade for TB. Most studies (22 of 29) investigated the impact of hypothetical novel interventions, with the remainder focusing on the scale-up of existing interventions. All but one study projected the impact of interventions on the End TB Strategy target indicators of TB incidence, TB mortality, or both. The remaining study[44] extended earlier modelling studies[9,12] to estimate the impact of interventions on the number of households experiencing TB-related catastrophic costs.

We calculated crude estimates of AAPDs in TB incidence and mortality from study outcomes of impact over different time horizons. We found that preventive interventions, including TB vaccination, TPT among PLWH and scaling up ART, were most promising to reduce TB incidence and mortality in SA. The use of novel vaccines to prevent *Mycobacterium tuberculosis* infection and/or TB disease was estimated to lead to substantial reductions, >5% per annum, in TB incidence at country level, highlighting the importance of vaccine research and development in the fight against TB in SA. These findings are consistent with a recent systematic review that emphasised the important role of novel vaccines towards achieving TB elimination globally.[18] Specific and data-driven strategies for delivering vaccines to key populations in SA will be important prior to the arrival of novel vaccines.[50] Varying levels of impact were projected for TPT implementation and scale-up. This variation is explained by different target populations for TPT considered and different model assumptions, including about intervention coverage and time horizons. All studies of TPT focused on isoniazid monotherapy, and none considered the impact of novel shorter regimens for TB prevention such as 3RH (a 3-month rifampicin-isoniazid course).[51] Prior to the roll-out of universal ART to PLWH in 2016, extending ART eligibility for TB prevention with high coverage was predicted to have a substantial impact on TB incidence and mortality. This is also consistent with a retrospective study conducted in 2019 that showed that recent declines in TB incidence and mortality in SA were associated with expanding access to and coverage of ART among PLWH.[52]

The majority of studies focused on interventions along the care cascade for TB. Interventions considered included screening/active case finding, scale-up of current and introduction of novel TB diagnostic tests, reducing ILTFU and improving TB treatment. While interventions of case finding and strengthening the care cascade for TB are essential to reduce suffering from TB and improve individual-level health outcomes, their impact on reducing transmission and TB incidence may be lower compared with preventive interventions. Consistently, we found that most care-cascade interventions were estimated to have a greater effect on TB mortality than on TB incidence (Fig. 3). One exception might be interventions to reduce ILTFU, i.e. people who are bacteriologically confirmed but are lost before initiating TB treatment, a serious challenge in SA.[53] Furthermore, a large fraction of people with subclinical TB have recently been reported in SA's first national TB prevalence survey,[54] raising concerns about onward transmission from this group.[55] As people with subclinical TB are less likely to self-present for TB diagnosis, interventions to detect subclinical TB may be important in SA. Several studies in the review estimated that Xpert-based algorithms had only moderate impact on TB incidence and mortality at country level.[10,33,34,42,45] These findings align with recent studies that found

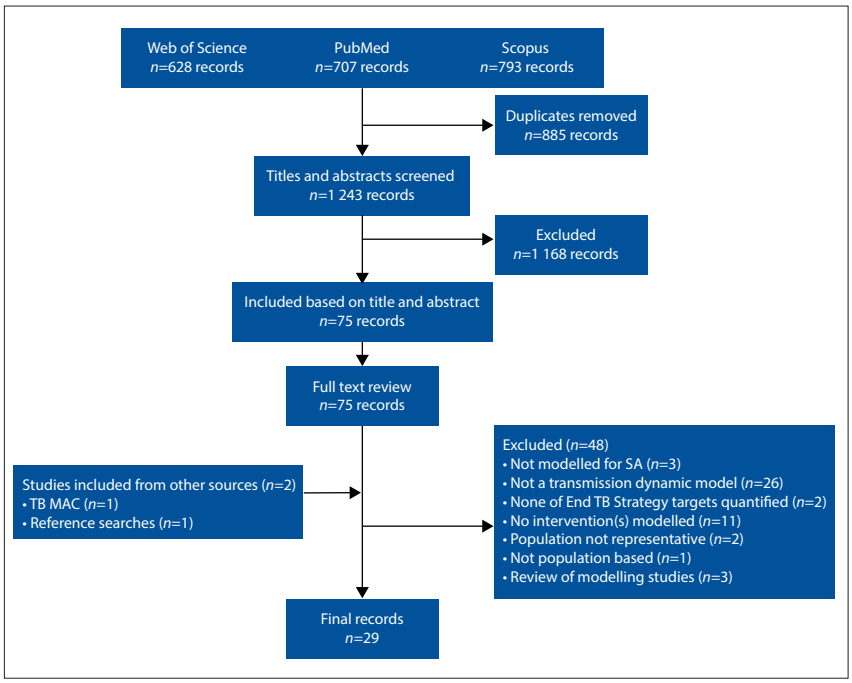

Fig. 1. Flow diagram of the study selection process. (TB MAC = TB (tuberculosis) Modelling and Analysis Consortium; SA = South Africa.)

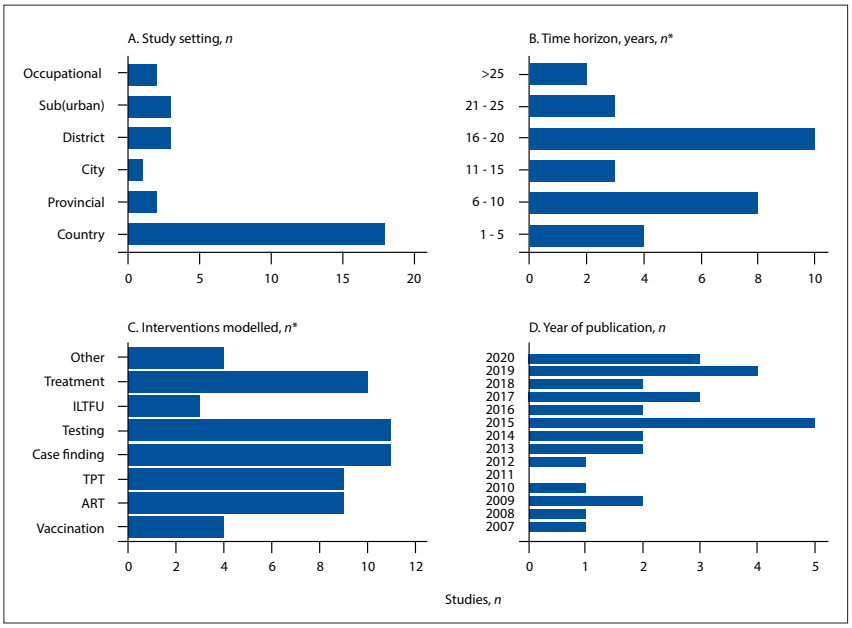

Fig. 2A-D. Key characteristics of studies included in this review, n. **Models may use multiple interventions and/or time horizons. (ILTFU = initial loss to follow-up; TPT = tuberculosis preventive therapy; ART = antiretroviral therapy.)*

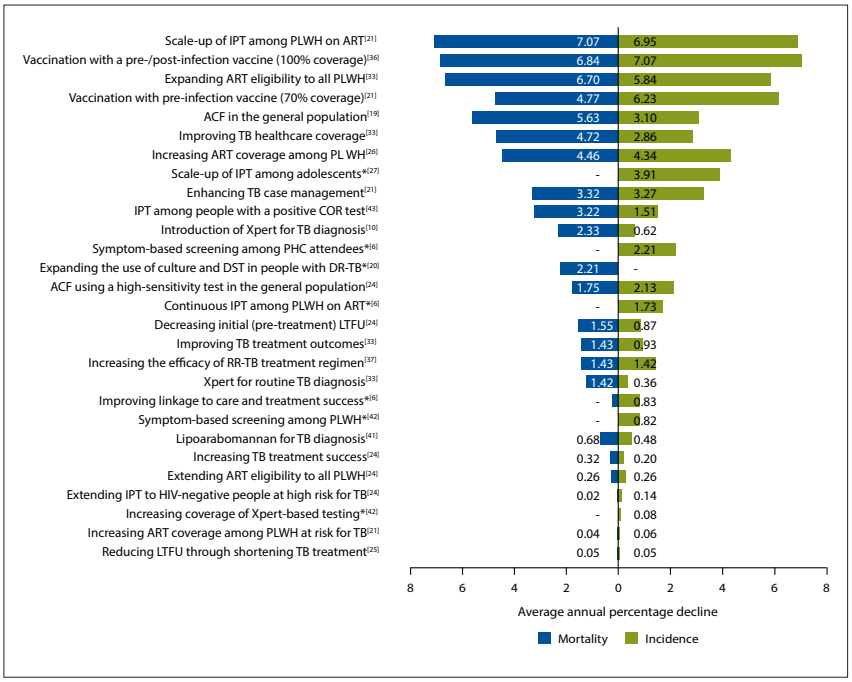

*Fig. 3. Average annual percentage declines (AAPDs) for different interventions modelled at country level. AAPDs were calculated from reported percentage declines in incidence and mortality relative to the baseline scenario at the end of model time horizons.*Missing result as impact was not estimated for the indicator. (IPT = isoniazid preventive therapy; PLWH = people living with HIV; ART = antiretroviral therapy; ACF = active case finding; TB = tuberculosis; COR = correlate of risk; PHC = primary healthcare facility; DST = drug susceptibility testing; LTFU = loss to follow-up; DR-TB = drug-resistant TB; RR-TB = rifampicin-resistant TB.)*

that the introduction of Xpert did not result in a significant effect on TB mortality[56] and diagnostic yield.[57]

While we report impact with crude measures of annual reductions in TB incidence and mortality for single interventions, many studies considered combinations of interventions. We estimated that a 12% and 19% decline in incidence and mortality, respectively, is required between 2022 and 2035 to meet the End TB Strategy targets for SA (appendix Table S10). Of note, none of the single interventions was estimated to yield sufficient reductions over time, consistent with the idea that a combination rather than single interventions will be necessary to achieve the End TB targets.[6]

Our review identified gaps for TB modelling research in SA that, if addressed, could provide valuable additional information for decision-making. More vulnerable groups, such as people with alcohol abuse, people living with diabetes and those living in poverty, should be considered for future case-finding initiatives, as was highlighted in a recent systematic review.[58] New developments in TB diagnosis and treatment are currently underway.[59] Modelling the effect of these novel diagnostic tests and treatment regimens for active TB could assist in understanding how they should be optimally implemented in the population. Shortening the length of preventive treatment regimens is associated with higher rates of treatment success and lower loss to follow-up.[60] Modelling the impact of TPT in different target populations, such as PLWH and exposed household contacts, will be important. Additional modelling of interventions to reduce ILTFU in SA could help understand how these interventions could help reduce transmission and TB deaths in SA.[61] Beyond impact, future modelling research should also address the affordability and cost-effectiveness of interventions to inform decision-making. Only 9[10,19,22,25,29,35,40,42,44] of the 29 modelling studies identified addressed cost-effectiveness. Reducing TB-affected households facing catastrophic costs due to TB to zero represents one of the three targets of WHO's End TB Strategy. We found that only one modelling study estimated the effect of interventions on reducing households facing catastrophic costs in SA.[44] More modelling research is needed to estimate the financial impact of TB on families in SA, and to estimate the impact of TB interventions on reducing catastrophic costs. This gap is of particular relevance for SA, where over one-quarter of people face barriers such as unemployment, limited access to transport for clinic attendance and household overcrowding,[62] and where these challenges amplify TB.

This review has limitations. We restricted our analysis to modelling studies of TB in the SA population. Findings from other TB modelling studies focusing on populations outside of SA may still be relevant to the SA context, and should be taken into consideration for policy-making. While we report findings from modelling studies at different population levels, findings from studies at sub-country level might not be

readily generalisable to the national level. Likewise, generalisability of country-level analyses to different local areas in SA may be limited given the considerable heterogeneity in TB burden and epidemiology in the country.[63] Our study focused on impact with respect to the End TB Strategy target indicators. We did not focus on affordability and cost-effectiveness of interventions, which are also relevant for decision-making. We intended to compare the impact of different interventions on TB incidence and mortality. Estimated AAPDs and their differences between studies have to be interpreted with caution as they are dependent on the baseline to which intervention scenarios are being compared; these baselines are not consistent between the modelling studies. Furthermore, rates of decline in TB incidence and mortality are expected to vary during the course of an intervention. Finally, heterogeneity in model structure, study design and reported outcomes further limit our ability to compare interventions with respect to their potential to generate progress towards the End TB Strategy targets.

Conclusion

We highlight an extensive body of modelling research with relevance for TB decision-making in SA. We present these findings at a time where additional guidance is urgently needed to confront recent setbacks in the fight against TB caused by health service disruptions during the COVID-19 pandemic, and to ensure progress towards the 2035 End TB Strategy targets in SA. We found that interventions focusing on prevention, including vaccination, TPT among PLWH and scaling-up ART, would have the greatest potential to reduce TB incidence and mortality. However, relating estimates of impact to the progress that would be needed in SA to achieve the End TB strategy targets revealed that single interventions will be unlikely to generate sufficient progress. Combinations of interventions rather than single interventions are therefore needed to effectively reduce TB incidence and mortality in SA. Our review discusses important knowledge gaps in modelling research, including studies of novel diagnostic tests for TB, interventions in vulnerable and high-risk populations and interventions towards reducing TB-related catastrophic costs. Closing these gaps through additional modelling research could help prioritise novel interventions and accompany already implemented interventions to better understand how they will aid progress towards TB elimination in SA.

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Conflicts of interest. None.

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