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

Lauren R Brown\*, Cari van Schalkwyk, Abigail K de Villiers, Florian M Marx

\*Corresponding author: laurenbrown@sun.ac.za

*Table S1: PICOS framework for the research question*

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| **Limit** | **Definition** | **Limit management** |
| **Population** | South Africa (country or subpopulations) | Search limit |
| **Intervention** | Any interventions reducing the impact of population-level outcomes (e.g., case finding, vaccination, TB preventive treatment, diagnosis, treatment) | No limit applied |
| **Comparator** | Current status quo of each modelled intervention | No limit applied |
| **Outcome** | Reduction in number of TB deaths, reduction in TB incidence rate, reduction in number of households facing catastrophic costs | Inclusion/exclusion criteria |
| **Study Design** | Transmission dynamic, mathematical models | Search terms and Inclusion/exclusion criteria |

*Table S2: Search strategies for each database*

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| **Database** | **Search Terms** |
| **PubMed** | (“South Africa\*”[Title/Abstract]) AND (Tuberculosis[Title/Abstract] OR TB[Title/Abstract]) AND ((mathem\* AND (model or models)) OR (mathem\* modell\*) OR (mathem\* modeling) OR (modelling OR modeling) OR “Population Dynamics”[MeSH Terms] OR “Population Dynamics” OR “System Dynamics” OR “Computer Simulation” OR “Computer Simulation”[MeSH Terms] OR “epidemiologic\* model” OR “tuberculosis model” or “TB model” OR “transmission model” OR “dynamic model” AND model) |
| **Scopus** | ( TITLE-ABS-KEY ( "South Africa\*" ) AND TITLE-ABS-KEY ( Tuberculosis OR TB ) AND ALL ( ( ( mathem\* AND ( model OR models ) ) OR ( mathem\* AND modell\* ) OR ( mathem\* AND modeling ) OR ( modeling OR modelling ) OR "Population Dynamics" OR "System Dynamics" OR "Computer Simulation" OR "epidemiologic\* model" OR "tuberculosis model" OR "TB model" OR "transmission model" OR "dynamic model" AND model ) ) ) |
| **Web of Science** | ((AB=tuberculosis OR TI=tuberculosis OR AB=TB OR TI=TB) AND (AB=("South Africa\*") OR TI = ("South Africa\*")) AND ALL=(((mathem\* AND (model OR models)) OR (mathem\* modell\*) OR (mathem\* modeling) OR (modeling OR modelling) OR "Population Dynamics" [MeSH Terms] OR "Population Dynamics" OR "System Dynamics" OR "Computer Simulation" OR "Computer Simulation" [MeSH Terms] OR "epidemiologic\* model" OR "tuberculosis model" OR "TB model" OR "transmission model" OR "dynamic model" AND model))) |

*Table S3: PRISMA 2020 Checklist[1]*

| **Section and Topic**  | **Item #** | **Checklist item**  | **Location where item is reported**  |
| --- | --- | --- | --- |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT**  |  |
| Abstract  | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 1 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 2 |
| Objectives  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 2, Table S1 |
| **METHODS**  |  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 3 |
| Information sources  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 3 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Table S2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 3 |
| Data collection process  | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 3 |
| Data items  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 3, Table 1,Table S4,Table S8 |
| 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 3,Table S4 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 4, Table S5 |
| Effect measures  | 12 | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. | Page 1, 2, 3 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 3 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | N/A |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 3 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | N/A |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression). | N/A |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | N/A |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | N/A |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | N/A |
| **RESULTS**  |  |
| Study selection  | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 5 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Table S9.1, Table S9.2 |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | Table 1, Table S4, Table S8, Page 6 |
| Risk of bias in studies  | 18 | Present assessments of risk of bias for each included study. | Page 5, Table S6  |
| Results of individual studies  | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. | Table 1, Table S4, Table S8 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Pages 6-10 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Page 16,Table S10 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | N/A |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | N/A |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | N/A |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | N/A |
| **DISCUSSION**  |  |
| Discussion  | 23a | Provide a general interpretation of the results in the context of other evidence. | Pages 17-19 |
| 23b | Discuss any limitations of the evidence included in the review. | Page 18 |
| 23c | Discuss any limitations of the review processes used. | Page 18 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Page 19 |
| **OTHER INFORMATION** |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 3 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 3 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | N/A |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 19 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 19 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 3 |

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| *Table S4: Summary of the 29 eligible studies* |
| **Author** | **Model Type** | **Modelling aim** | **Population stratification** | **Population Level Modelled** | **Intervention(s) modelled** | **Quantified results** | **Key findings** | **WHO End TB Strategy target** |
| Azman (2014) | DE | Impact and cost-effectiveness of generic ACF activities. | Smear status, HIV status | South Africa: Country Level  | Increased ACF by 25% over 2 and 10 years, beginning in 2012. | Short-term integration (2 years) could avert 2165 (95% UR 1504-3307) deaths and is cost-effective at $9400 (6957-13221) per case.10-year programs could reduce incidence and mortality by 22-27% and 40-44%, respectively. | ACF for TB may have an important impact, despite short-term integration underestimating full benefits. Both short-term and sustained ACF is cost-effective in South Africa.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Basu (2007) | DE | Impact of control measures on the epidemic trajectory of XDR TB.  | HIV status, drug resistance status, community vs. hospital transmission  | Tugela Ferry (rural area in KZN) and Church of Scotland Hospital (Msinga district in KZN) | Improved administrative measures, environmental measures, and personal protective measures between 2007 2012. | A combination of interventions could avert 48% (range 34-50%) of XDR-TB cases. | The optimal combination of available nosocomial interventions could reduce the number of XDR-TB cases by nearly half, even in settings where resources are scarce. | Reduction in TB incidence rate. (Specifically, XDR-TB) |
| Basu (2009) | SE | Impact of the emergence of nosocomial transmission dynamics of XDR-TB into community-based epidemics. | HIV status, community vs. hospital transmission | South Africa: Country level | Community-based case finding, treatment, detection, infection control, and follow-up protocols over 5 years.  | A combination of early screening and treatment prevented just > 50 deaths per 100,000 population. | A combination of early, community-based DST and treatment for XDR-TB could help prevent epidemics in territories neighbouring XDR-TB hot zones.  | Reduction in TB incidence rate.(Specifically, XDR-TB) |
| Chindelevitch (2015) | DE | Impact of various TB control approaches on population-level incidence, prevalence, and mortality. | HIV status, drug resistance status, smear status, DOTS/ Non-DOTS, treatment history | South Africa: Country Level | Broadening ART eligibility, improved coverage, diagnosis and treatment over 5 and 20 years, beginning in 2012. | A combination of interventions projected a decrease in incidence and mortality by 30% & 46%, and 45% & 69%, over 5 & 20 years, respectively. Incidence and mortality were projected to decrease by 22% & 45%, and 22% & 50%, over 5 & 20 years, respectively, due to expanded ART eligibility.  | Combining TB-specific control measures with expanded ART eligibility could potentially reduce incidence and mortality of the disease, therefore reducing TB burden greatly.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Dowdy (2008) | DE | Impact of expanded TB culture and DST on TB incidence and mortality. | HIV status, drug resistance status, TB infectivity | South Africa: Country level  | Expanded TB culture and drug susceptibility testing between 2007 and 2017. | A projected 17.2% (95% S.I. 8.9 -24.4%) reduction in TB mortality, 14.1% (5.3 -23.8%) reduction in MDR-TB cases and 46.6% (32.6-56%) reduction in MDR-TB could be the result of expanding culture and DST from 5% to 37% of new cases and from 37% to 85% of cases previously treated.  | Substantial reductions in TB incidence and mortality could be the result of combining expanded TB culture and DST. | Reduction in number of TB deaths.Reduction in TB incidence rate. (Specifically, MDR-TB, TB) |
| Dye(2013) a[Prospects for TB Elimination] | DE | Impact of interventions on prospects for TB elimination.  | Age, HIV status | South Africa, India, China, United States | ART (40% in 2010 to 80% in 2050), improving case management (early case detection, accurate diagnosis, and high cure rate), a scale up of IPT (0 -75% by 2035) and introduction of a hypothetical vaccine protecting 70% of uninfected people between 2010 and 2050. | Expanding ART coverage would reduce incidence, but not greatly, due to a reduction of 50% in mortality rate extending the number of life-years at risk of TB. Improved case management could result in a 3.7% and 5.1% reduction in incidence and mortality. The scale up of IPT for PWH could reduce incidence and mortality by 1400 cases and 200 deaths per million, respectively. Similar results are found when introducing a hypothetical vaccine. | Elimination of TB is possible, within 1-2 decades, when 1 death occurs per 100,000 population.Priorities in South Africa should be enhanced case management and prevention of TB infection among PWH. | Reduction in TB incidence rate.Reduction in number of TB deaths.  |
| Dye (2013) b[Making wider use of the world’s most widely used vaccine] | DE | Effectiveness and cost-effectiveness of BCG revaccination of adolescents in a high burden setting. | Not specified | Cape Town | Vaccination of adolescents. Impact measured over lifetime of people living in 2009.  | With an 80% efficacy, 17% of cases were averted with revaccination. The intervention with costs per DALY recovered as US$52-US$4540. | BCG revaccination, though not highly effective, is cost-effective in some settings.  | Reduction in TB incidence rate. |
| Gilbert (2015) | DE | Impact of community-based, integrated TB/HIV case finding and control strategies on the TB/HIV epidemics. | HIV status, drug resistance status | Msinga subdistrict of KwaZulu-Natal | Detection and treatment, CICF, Xpert MTB/RIF, MDR-TB treatment decentralization, improved first-line cure rate, IPT and expansion of ART coverage over 10 years. | The combination of recommended interventions with the addition of annual community-based case finding averted 44% of TB cases (95% CI 31–56%), 23% HIV (17–29%), 68% MDR-TB (40–88%), 73% XDR-TB (38–91%), and 24% TB/HIV deaths (16–39%).  | Simultaneous implementation of integrated community-based measures were most effective in reducing the impact of the TB/HIV epidemics. Strengthening of existing control measures is necessary.  | Reduction in TB incidence rate.Reduction in number of TB deaths. (Specifically, MDR-/ XDR-TB, TB) |
| Gilbert (2016) | DE | Cost-effectiveness and impact of TB/HIV screening and linkage to care on the epidemics in high-incidence settings.  | HIV status, drug resistance status | Msinga subdistrict of KwaZulu-Natal | Detection and treatment, screening, linkage to care and IPT between 2015 and 2025. | With implementation of the proposed measures, TB incidence was reduced to 233-274 cases per 100,000 population. With the addition of lifelong IPT among PWH, TB incidence was reduced by a further 153-208 cases per 100,000 population. Similarly, MDR-TB and XDR-TB incidence was reduced to 14-15 cases and 4-5 cases, respectively, per 100,000 population.  | In rural South Africa, the combination of screening and linkage to care is a very cost-effective approach to reduce the burden of both TB and HIV.  | Reduction in TB incidence rate. (Specifically, MDR-/ XDR-TB, TB) |
| Harris (2020) | DE | Impact of hypothetical TB vaccines in high-burden countries. | HIV status, vaccination status | South Africa, China, India | Hypothetical vaccination between 2025 and 2035.  | A pre-/post-infection vaccine efficacious for protection against infection and disease (including PWH) had an IRR of 84% (81-87%), with 4.3 million (2.5-7.0 million) cases averted and 0.9 million (0.5-1.6 million) deaths averted. | Vaccination development has the potential to reduce TB burden substantially. It should focus on disease prevention in infected populations, and infection prevention in uninfected populations where transmission is high.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Hippner (2019) | DE (TIME) | Impact of the TIME modelling tool on TB burden of reaching the 90-(90)-90 Stop TB Partnership Global Plan to End TB.  | Treatment history, smear status, HIV status, drug resistance status | KZN, LP and WC: Provincial Level | Screening, linkage to care and treatment success from 2017 to 2035. | A combination of ACF, linkage to care and treatment success reduced incidence and mortality by approximately 19%, 17.5%, and 35% and 36.2%, 38.8%, and 59.8% for KZN, LP and WC, respectively.  | A combination of the three interventions modelled results in the largest reduction in TB incidence and mortality rates by 2035 compared to baseline scenarios. To improve predictions for sub-country models, TB burden estimates and coverage levels must be addressed.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Houben (2016) | 7 DE, 1 IBM(DE: Hopkins, IRD, SIPTM, UGA, Harvard, AuTuMN, TIME,IBM: IDM) | Assess whether the 2025 End TB Strategy targets are feasible in different high-burden countries. | Varies by model | South Africa, China, India | Access to high quality care, diagnosis, post-diagnostic care, ACF, treatment of latent TB and combination of IPT and ART between 2015 and 2025. | A combination of prevention, case finding and improvements in care reduced incidence and mortality by 55% (31–62%) and 72% (65–82%), respectively, and averted a cumulative 1.2 million (0.7-1.8 million) cases and 298 000 (193 000–453 000) deaths. | Substantial reductions in TB burden are possible with interventions currently in place, however, to reach End TB Targets by 2025, country-specific interventions must be put in place. | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Kendall (2017) | DE | Prioritize different treatment regimen characteristics based on their potential to prevent new TB cases and deaths.  | Drug resistance status, HIV status, treatment history | South Africa, India, Brazil, Philippines  | Various novel RS TB /RR TB treatment regimens over 25 years. (Optimal regimens for RS & RR TB: efficacies of 99% & 94%, barriers to resistance of 0% & 0.8%, no pre-existing resistances to regimen, no medical contra-indications, durations of 2 mo & 6 mo, and ease of adherence of 50% & 50%). | Optimal 10-year RS TB treatment projected a 9.7% (95% UR: 5.8-16.5%) and 9.3% (5.0-16.2%) reduction in RS incidence and mortality, respectively, compared to current projections. Optimal RR TB treatment projected a 30.1% (15.4-47.7%) and 30.3% (17.1-45.4%) reduction in incidence and mortality, respectively.  | Maintenance of the efficacy of novel regimens is important, however, improvements could enable infected populations to receive timely treatment to reduce the number of deaths.  | Reduction in TB incidence rate.Reduction in number of TB deaths.  |
| Kendall (2019) | DE | Population impact of providing an implementation of an IPT regimen to ART recipients in a high burden area. | HIV status, IPT status, drug resistance status  | Khayelitsha: Urban area on the outskirts of Cape Town | Combined IPT and ART between 2008 and 2013. | IPT among patients receiving ART prevented 1 TB case per 18 (95% CrI 11-29) individuals treated and reduced incidence by 23% (14-30%). IPT lowered incidence by 5.2% (2.9-8.7%) in the general population.  | IPT in combination with ART reduces TB incidence and has an additional impact on transmission within the population.  | Reduction in TB incidence rate. |
| Knight(2015) a[Tuberculosis prevention in South Africa] | Stochastic IBM | Investigate if NSP targets could be reached if scale up of control measures had happened in 2014. | Age, HIV status | South Africa: Country Level | ART, IPT and improved TB case management (ACF, LTFU) between 2014 and 2050. | The interventions modelled had the following impact of incidence and mortality, respectively: ACF (48%, 58%), LTFU ($\~$30%, 52%), ART & UTT ($\~$20%, NA), IPT among HIV negative patients (13%, 20%).  | TB burden could be decreased with current measures and the addition of increased finding and treatment of infected individuals. Despite this, NSP targets are unlikely to be achieved even if portfolios were scaled up early.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Knight(2015) b[The Impact and Cost-Effectiveness of a Four- Month Regimen...] | Stochastic IBM | Impact and cost-effectiveness of a shortened regimen for first-line active TB treatment.  | Age, HIV status, treatment history  | South Africa: Country Level | Treatment between 2015 and 2035. | A 4-month first-line active TB regimen would avert < 1% of the predicted 6 million pyrs infected. Similarly, the impact on averted deaths and DALYs was small.The regimen is cost-effective at $436(NA, 5983) per month.  | It is unlikely that a 4-month regimen would stop the spread of TB in a high burden region, however it would be highly cost-effective for individuals enrolled.  | Reduction in TB incidence rate. |
| Marx (2018) | SE | Effect of interventions targeted to previously treated people in a high burden setting.  | HIV status, treatment history | Two adjacent suburban communities  | ACF and secondary IPT between 2016 and 2025. | In addition to interventions already in place, specifically targeting previously treated people would avert 40% (95% UI 21-56%) of incident cases and 41% (16-55%) of deaths. | A combination ACF and secondary IPT for people previously treated for TB could accelerate reductions in morbidity and mortality. Studies on cost and resource implications for the measures are needed.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Marx (2020) | SE | Estimate costs and health benefits of interventions targeted to previously treated people in a high incidence setting.  | HIV status, treatment history | Two adjacent suburban communities | Follow-up examinations and secondary IPT between 2019 and 2028. | Single follow up examination with 12 months of secondary IPT would avert 2472 DALYs (95% UI -888 - 7801) and, at a cost of US$18.2 per DALY averted, sustained annual examinations with continuous secondary IPT would avert an additional 1179 DALYs (-1796 – 4377).Cases and deaths averted were estimated at 14.3% (0.1-28%) and 12.2% (-3.9 – 27%), respectively.  | Sustained examinations and continuous secondary IPT is the optimal strategy to reduce incidence and potentially save resources for TB control.  | Reduction in TB incidence rate. |
| Menzies (2012) | DE | Impact and cost-effectiveness of Xpert MTB/RIF diagnosis.  | HIV status, drug resistance status, smear status, DOTS/ Non-DOTS, treatment history | South Africa, Botswana, Lesotho, Namibia, Swaziland | Xpert MTB/RIF beginning in 2012 for 10- and 20-yr periods. | Xpert implementation would decrease TB prevalence by 28% (95% CI: 14-40%), incidence by 6% (2-13%) and mortality by 21% (10-32%) over a 10-yr period. MDR-TB cases would be lower by 25% (6-44%).More aggressive SA Xpert algorithm increased costs by 60% and DALYs averted by 27% resulting in an ICER of US$2,128 [1,215-3,954] per DALY averted. | Xpert roll-out is likely to reduce TB illness and death through improved case finding and treatment, but the long-term impact on transmission dynamics is limited.Although likely to cause financial burden, Xpert diagnosis is valuable at its cost.  | Reduction in TB incidence rate.Reduction in number of TB deaths. (Specifically, MDR-TB, TB) |
| Pretorius (2014) | Two models (DE, stochastic IBM) were considered. | Effects of changing HIV treatment policy on TB outcomes. | HIV status, drug resistance status, smear status, DOTS/ Non-DOTS, treatment history | South Africa: Country Level | ART between 2014 and 2033. | TB incidence was reduced by 6-30% if all PWH were given ART access, and by 28-37% if effective ART coverage was increased to 80%.An estimated one TB case per 10-13 additional pyrs on ART was averted.  | ART expansion could halt HIV-associated TB while effectively reducing TB incidence and mortality.  | Reduction in TB incidence rate.Reduction in number of TB deaths. |
| Rhines (2018) | DE | Impact of providing IPT to adolescents on TB control in a high HIV-prevalence setting. | HIV status, treatment status, age | South Africa: Country Level | IPT between 2012 and 2032. | In adolescents, increasing IPT coverage by 50% and 90% reduces active TB incidence by 5-34% and 9-40%, respectively. In the general population, increasing IPT coverage by 50% and 90% reduces active TB incidence by 29% and 36%, respectively.  | Targeting IPT to adolescents with high TB prevalence and low HIV prevalence reduces TB disease incidence, and spillover IPT coverage to the general population causes a decline in TB incidence.  | Reduction in TB incidence rate. |
| Ricks (2020) | DE | Impact of current and future urine-LAM on TB incidence and mortality. | HIV status, extra/pulmonary TB, community vs. hospital transmission  | South Africa: Country Level | Future urine-LAM tests with varying sensitivities for HIV-, HIV+ and virally suppressed people between 2020 and 2035. | Compared to current tests, future LAM tests for all TB patients, regardless of HIV status, could avert 29.6% (95% CrI 17.8-43.6%) of deaths and 17.7% (8.62-29%) of cases. Compared to scaling up of Xpert use, future LAM tests could avert 16.4% (10.4-22.2%) of deaths and 5.68% (3.18-7.52%) of cases. | Increased use of future urine-LAM tests, with sufficient performance, could achieve population-level impact on the TB epidemic.  | Reduction in number of TB deaths.Reduction in TB incidence rate. |
| Shrestha (2017) | StochasticIBM | Impact of targeted vaccination among a mining population. | HIV status, vaccination status, community vs. mining transmission | South Africa: Country Level | Hypothetical vaccination over 20 years. | Relative to vaccinating labor-sending districts, targeting miners provided 1.46-fold (95% range: 1.13-1.91) improvement. Overall, vaccination averted 0.374 (0.274-0.527) cases per dose with mine-targeted vaccination averting 8,090 cases (95% range, 3,750–13,300) cases per 100,000 persons. | Vaccination targeted to high-risk groups may reduce TB burden. Mines may highlight demographic groups at high risk for TB to allow a logistically accessible population to target.  | Reduction in TB incidence rate. |
| Sumner(2019) a[Estimating the impact of TB case detection...] | DE | Impact of case detection in constrained health systems. | HIV status, drug resistance status, smear status, treatment history | South Africa: Country Level | Intensified case finding (Xpert MTB/RIF, cough-based screening, symptom screening) between 2016 and 2035. | Increasing screening in PHCs and PWH from 50-95% and 40-100% reduced TB incidence by 9.5% (2.5th-97.5th PR, 8.6-12.2) and 14.5% (12.2-16.3), respectively. Increasing use of Xpert from 80-100% reduced incidence by 2.7% (1.6-4.1). Increasing cough-based screening in PHCs from 50-90% reduced incidence by 5% (3.8-7.1). | Models should consider resource constraints. If ignored, the impact of the interventions may be overestimated and lead to incorrect policy decisions. | Reduction in TB incidence rate. |
| Sumner(2019) b[Potential population impact…] | DE | Impact of using an mRNA expression signature COR test to target preventive treatment.  | Age, HIV status, smear status | South Africa: Country Level | COR test (with progression sensitivity and specificity of 0.71 (95% CI 0.57-0.82) and 0.84 (0.79-0.88), respectively, and sensitivity for prevalent TB of 0.91 (0.78-0.97)) and preventive treatment between 2020 and 2035. | Reductions in incidence by 20% (95% CI 15–27) and 39% (31–48) could be achieved with annual screening coverage of 30% COR-targeted PT and IGRA-targeted PT, respectively. IGRA would require greater PT resulting in more cases to treat per case averted (COR: 49 (29–77); IGRA: 84 (59–123)).  | Allowing more efficient targeting of treatment using COR-targeted PT could reduce TB burden in high incidence settings. COR-like tests should be used in high burden areas to maximize impact. | Reduction in TB incidence rate. |
| Uys (2009) | DE | Potential of rapid diagnosis for DR-TB and DS-TB in areas of high prevalence. | Drug resistance status | WC: Provincial Level  | Diagnosis over 20 years. | For diagnosis methods with sensitivities of 90% and 97%, DR-TB incidence will decrease from 11 cases per 100,000 per month to 9.6 and 2.4 cases, respectively. DS-TB incidence decreases from 60 cases per 100,000 per month to 57 cases regardless of sensitivity of the diagnosis method. | Current control strategies are not sufficient to halt the spread of MDR-TB. Coupled with screening within the community, rapid diagnosis of DR-TB can reduce incidence. | Reduction in TB incidence rate.(Specifically, DS-/ DR-TB) |
| Verguet (2017) | DE(Harvard, TIME: both DE) | Potential costs averted by TB control. | HIV status, drug resistance status, treatment history, healthcare sector | South Africa: Country Level | Expanding access to care and improving treatment quality between 2016 and 2035. | Utilizing outreach clinics and symptom screening in primary care decreases population without access to care from 5% to 0%.Mobile health care, treatment follow-up, counselling on adherence and improved MDR-TB staffing increases treatment adherence from 76% to 85% for DS-TB and from 52% to 67% for MDR-TB.  | Implementing expansion of TB services could lessen, but not eliminate, the financial burden of TB affected households. | Reduction in TB affected households facing catastrophic costs.(Specifically, DS-/ MDR-TB, TB) |
| Vynnycky (2015) | DE | Exploring the lack of a detectable impact of interventions in a trial of gold miners.  | HIV status, smear status, culture status, treatment status | South African gold mines | IPT, LTFU, treatment delay, ART scale-up and Xpert MTB/RIF between 2003 and 2017. | A combination of increasing ART coverage for PWH from 0% to 80% by 2009, treatment delay reduction, and Xpert screening resulted in a 60% decrease in incidence. The addition of IPT in combination with ART reduced incidence for the general population and PWH by 70% and 80%, respectively.  | TB prevention requires an optimal combination of interventions including strengthening of health systems and improving diagnosis, ART treatment coverage, and effective preventive measures.  | Reduction in TB incidence rate. |
| Williams (2010) | DE | Impacts of short- and long-term ART on the incidence of TB. | HIV status | South Africa, Gabon, Ghana, Tanzania, Botswana, Lesotho, Malawi, Swaziland, Zambia | ART between 2010 and 2050. | ART 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.  | Frequent HIV testing and immediate ART in high prevalence HIV settings could rapidly reduce and, potentially, eliminate HIV-associated TB. | Reduction in TB incidence rate. |
| ACF: Active case findingART: Antiretroviral treatmentBCG: Bacille Calmette Guérin TB vaccine(C)ICF: (Community-based) intensified case finding COR: correlate-of-riskDE: Deterministic, compartmental, differential equations modelDR/DS: Drug-resistant/ drug-sensitiveHAART: Highly active antiretroviral activityIBM: Individual-based model ICER: Incremental cost-effectiveness ratioIGRA: Interferon-$γ$ release assayIPT: Isoniazid preventive therapyIRR: incidence reduction rateKZN: KwaZulu-NatalLP: Limpopo LTFU: Loss to follow up | MDR-/XDR-TB: multi-drug-resistant/ extensively drug-resistant tuberculosisNA: invalid value not determined due to little impact or a negative valueNSP: National Strategic PlanPHC: Public health clinicPWH: People with HIVPyrs: person-yearsRS/RR: rifampicin-susceptible/ rifampicin-resistantSE: Stochastic, compartmental, differential equations modelSI: Simulation intervalST: state-time model using ordinary and partial differential equations TIME: Tuberculosis Impact Module and EstimatesTLTI: treatment of latent TB infectionUI: Uncertainty intervalUR: Uncertainty rangeUTT: Universal Test and TreatWC: Western Cape |

**

Fig. S1. (A) Illustrative example of how AAPDs are calculated for different interventions in this review – Assumed scenario compared to baseline. (B) Illustrative example of how this assumption may fail – Realistic scenario compared to baseline.

If a hypothetical intervention is introduced into a population, TB incidence is estimated to decline by an additional 30% compared to baseline at the end of the time horizon (15 years). The period percentage decline (PPD) is thus 30% compared to baseline. Using our AAPD formula for the assumed scenario (Figure S1(A)), we get:

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

Where t denotes the time horizon (15 years), and PPD is 30%. Thus, the AAPD for this hypothetical intervention is estimated as 2.35%.

Figure S1(A) illustrates the assumption behind the calculation of AAPDs in the review. The baseline scenario is defined as a continuation of current TB control measures in the country. We assume the difference between baseline and intervention increases linearly over the time horizon as shown in Figure S1(A). We include an example of a typical realistic scenario of the reduction in incidence in Figure S1(B) to illustrate a scenario in which our assumption may fail.

*S5: Risk of bias tool for assessment of eligible modelling studies\**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Criterion**  | **Considerations**  | **Score considerations (0, poor to 2, good)** |  |
| 1 | **Are the aims and objectives clear?** | Are the research questions and modelling objectives clearly defined? | 0 Not stated1 Stated but vague2 Stated and focussed | Definitions: max 8 points |
| 2 | **Is the setting and population clearly defined?** | Does the paper clearly state the setting (e.g. geographical location, high/low TB burden)? | 0 Not stated1 Stated but vague or details missing2 Stated and focussed |
| Does the paper clearly state the modelled population? (e.g. patient or population group characteristics) |
| Have sub-populations necessary for the research question and setting been modelled? |
| 3 | **Are the intervention and comparators adequately defined?** | Does the paper clearly state the population(s) targeted for specific interventions? | 0 Not stated or very unclear1 Stated but details missing2 Stated and all necessary details stated |
| Does the paper clearly define the intervention characteristics (e.g. specificity/ sensitivity of a test, vaccine efficacy, duration of treatment)? |
| If there is a comparator (current status quo), is it clearly defined? |
| 4 | **Are the outcome measures defined and answer the research question?** | Does the paper clearly define the outcomes of interest? | 0 Not stated, very unclear or not suited to research question1 Stated but details missing or not directly aligned with research question2 Stated, all necessary details stated, and aligned with research question |
| Do the outcomes correspond to the research question? |
| 5 | **Are the model structure and time horizon clearly described and appropriate for the research question?** | Is the model structure clearly reported and appropriate for the research question? | 0 Not appropriate model structure, or poor/no description of model1 Incomplete description, and/or appropriate in part for research question2 Complete and reproducible, appropriate structure and time horizon | Model methods: max 4 points |
| Does the model reflect current knowledge of disease natural history? Does the model consider subclinical disease? |
| Is the time horizon and time step of the model clearly stated and appropriate to the research question (i.e. is it long enough to capture health effects)? |
| 6 | **Are the modelling methods appropriate for the research question and adequately described?** | Were the modelling methods clearly described, and suited to the research question? | 0 Not appropriate model structure, or poor/no description of methods1 Incomplete description, and/or appropriate in part for research question2 Complete and reproducible, appropriate method |
| 7 | **Are the parameters, ranges and data sources specified?** | Are all parameters and their ranges reported? | 0 Poorly reported1 Some information missing2 Complete reporting of parameters, ranges and data sources | Model inputs: max 6 points |
| Are the data sources for parameters reported? |
| 8 | **Are any assumptions explicit and justified?** | Are all assumptions explicit and justified? | 0 Not reported1 Explicit2 Explicit and justified |
| 9 | **Is the quality of data considered and is uncertainty explored through uncertainty and/or sensitivity analyses?** | Are data limitations discussed? Are any of the sources known to the reviewer to be inappropriate (e.g. do not match the parameter, are outdated, or known to be poor quality)?  | 0 No sources or uncertainty1 Partially addressed, and/or some data inappropriate2 Fully addressed |
| Is uncertainty in model structure, parameters and/or assumptions explored through uncertainty and/or sensitivity analyses? |
| 10 | **Is the method of fitting described and suitable?** | Is the method of fitting/calibrating the model clearly described? | 0 Not done, unsuitable method or poor/no description1 Incomplete description or method not optimal2 Complete description and suitable methods  | Fitting/ validation: max 4 points |
| Is the method of model fitting/calibration suitable? |
| 11 | **Has the model been validated?** | Has an assessment of validity of the results been made by comparing across one or more different model structures, or against a validation data set? | 0 Not considered1 States criteria for validation2 Validation undertaken |
| 12 | **Have the results been clearly and completely presented, with a range of uncertainty?** | Have the outcome values and their uncertainty ranges for each intervention/scenario been reported? | 0 Not reported, very unclear or not suited to research question1 Stated, but ranges or planned sensitivity analyses missing and/or not directly aligned with research question2 Values and ranges and planned sensitivity analyses reported and aligned with research question. | Results: max 4 points |
| Do the results match the objectives? |
| Are sensitivity analyses clearly reported? |
| 13 | **Are the results appropriately interpreted and discussed in context?** | Does the discussion reflect a fair and balanced interpretation of the results?  | 0 No/poor discussion1 Some discussion but key points, limitations or context missed2 Full discussion of key points in context, generalisability considered, limitations discussed |
| Are the results of the study discussed in context and is generalisability considered? |
| Are possible biases and limitations discussed? |
| 14 | **Are the funding source and conflicts of interest reported?** | Is the funding and the role of the funder clearly stated? | 0 No statement of funding or conflicts1 Funding or conflicts reported2 Funding and conflict statement | Conflicts:Max 2 points |
| Is there a conflict of interest statement? |

|  |
| --- |
| Overall Scoring: Max 28 points |
| Very high | >22 |
| High | 19-22 |
| Medium | .14-18 |
| Low | <14 |

\* Adapted from Fone *et al*,[2] Caro *et al*,[3] and Harris *et al.[4]*

*Table S6: Risk of bias assessment of included studies*

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Risk of Bias item** | **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 (2014) | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 0 | 2 | 2 | 2 | 21 | High |
| Basu (2007) | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 26 | Very High |
| Basu (2009) | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 1 | 1 | 23 | Very High |
| Chindelevitch (2015) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 26 | Very High  |
| Dowdy (2008) | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 22 | High |
| Dye (2013) a  | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 19 | High |
| Dye (2013) b  | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 0 | 2 | 1 | 1 | 22 | High |
| Gilbert (2015) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 28 | Very High |
| Gilbert (2016) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 28 | Very High |
| Harris (2020) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Hippner (2019) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 1 | 1 | 2 | 21 | High |
| Houben (2016) | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 1 | 2 | 2 | 20 | High |
| Kendall (2017) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Kendall (2019) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 25 | Very High |
| Knight (2015) a | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 1 | 2 | 2 | 22 | High |
| Knight (2015) b | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 0 | 1 | 2 | 2 | 22 | High |
| Marx (2018) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Marx (2020) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Menzies (2012) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 0 | 2 | 2 | 2 | 25 | Very High |
| Pretorius (2014) | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 21 | High |
| Rhines (2018) | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 2 | 21 | High |
| Ricks (2020) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Shrestha (2017)  | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 20 | High |
| Sumner (2019) a  | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 2 | 24 | Very High |
| Sumner (2019) b  | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 26 | Very High |
| Uys (2009) | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 0 | 2 | 1 | 0 | 19 | High |
| Verguet (2017) | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 0 | 2 | 2 | 2 | 24 | Very High |
| Vynnecky (2015) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 2 | 24 | Very High |
| Williams (2010) | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 22 | High |

*Table S7: Intervention specifications grouped according to the TB care cascade*

|  |  |
| --- | --- |
| **Publication** | **Intervention specification** |
| **Vaccination** |
| Dye (2013) a | Hypothetical pre-infection vaccine introduced in 2025 protecting 70% of uninfected people by 2050 |
| Dye (2013) b | BCG revaccination of adolescents (efficacy of between 10-80% with protection or 10 years) |
| Harris (2020) | Hypothetical vaccines with varied efficacy to prevent infection or disease (70% and 100%), effective in uninfected or infected individuals and duration of protection (2 to 10 years) |
| Shrestha (2017) | Hypothetical post-infection vaccine with 60% efficacy over 10 years |
| **ART for TB prevention** |
| Basu (2007) | Offering ART with voluntary counselling and testing at community-level |
| Chindelevitch (2015) | Expanding ART eligibility |
| Dye (2013) a | ART-linked IPT for PWH  |
| Gilbert (2015) | ART-linked IPT for PWH  |
| Kendall (2019) | ART-linked IPT for PWH (expanding levels of ART coverage) |
| Knight (2015) a | ART-linked IPT for PWH (varying ART levels) |
| Pretorius (2014) | Improving pre-ART and ART services, and expanding ART eligibility |
| Vynnecky (2015) | Scale up of ART to 80% for all PWH |
| Williams (2010) | ART provided at different stages after HIV infection |
| **TB preventive treatment** |
| Dye (2013) a | ART-linked IPT for PWH (IPT coverage from 0% in 2025 to 75% in 2035) |
| Gilbert (2015) | ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive) |
| Gilbert (2016) | ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive and lifetime for PWH) |
| Houben (2016) | ART-linked IPT for PWH and TLTI |
| Kendall (2019) | ART-linked IPT for PWH (12-month regimen of IPT, continuous IPT, and expanding levels of ART) |
| Knight (2015) a | ART-linked IPT for PWH (continuous, 6-, and 36-month IPT for PWH and 6 months for HIV negatives, varying ART levels) |
| Marx (2018) | Secondary IPT (offered IPT after complete treatment) |
| Marx (2020) | Secondary IPT (offered IPT after complete treatment) |
| Rhines (2018) | Continuous IPT to adolescents (scale up from 5% coverage to 50% and 90%) |
| Vynnecky (2015) | Uptake and retention of IPT (continuous 9-month regimen for community-wide and 50% of population), 3-month curative PT (isoniazid and rifapentine) |
| **Case Finding/ screening**  |
| Azman (2014) | Active case finding in general population |
| Basu (2009) | Community-based intensified case finding, community-based XDR screening and implementing rapid case detection |
| Gilbert (2015) | TB/ HIV community-based intensified case finding and improving case detection |
| Gilbert (2016) | Community-based TB/ HIV screening |
| Hippner (2019) | Increasing screening coverage |
| Houben (2016) | Active case finding in general population |
| Knight (2015) a | Active case finding in general population |
| Marx (2018) | Case finding targeted to previously treated individuals |
| Sumner (2019) a | Intensified case finding (cough-based screening and symptom-based screening) for PWH and in PHCs |
| Uys (2009) | Screening in the community |
| Verguet (2017) | Expanding access to care (outreach clinics and symptom screening in primary care) |
| **Diagnostic interventions** |
| Basu (2007) | DST (phage-based, line probe, GTMD and MODS assays) |
| Basu (2009) | Rapid DST |
| Chindelevitch (2015) | Using more sensitive diagnostics (replacing a proportion of smear microscopy with Xpert) |
| Dowdy (2008) | Improving diagnosis (expanded culture, DST, hypothetical test with 100% sensitivity) |
| Gilbert (2015) | Improving diagnosis (Xpert) |
| Menzies (2012) | Improving diagnosis (incorporating Xpert for initial diagnosis, DST) |
| Ricks (2020) | Improving testing (future LAM tests compared current LAM tests and Xpert testing) |
| Sumner (2019) a | Improving testing (increasing usage of Xpert as first-line test from 80% to 100%) |
| Uys (2009) | Improving diagnosis (earlier diagnosis of DR-TB) |
| Vynnecky (2015) | Improving diagnosis (using Xpert) |
| **Reducing initial LTFU** |
| Hippner (2019) | Improving linkage to care (assumed ILTFU was reduced by 80% by 2021) |
| Knight (2015) a | Decreasing pre-treatment LTFU |
| Vynnecky (2015) | Reducing ILTFU |
| **Treatment** |
| Basu (2009) | Improving treatment for XDR-TB at community- and hospital-based levels |
| Chindelevitch (2015) | Improving treatment (identifying treatment failure and improving cure rates) |
| Gilbert (2015) | Improving TB/MDR-TB treatment and first-line treatment cure rates |
| Hippner (2019) | Improving DS-/DR-TB treatment |
| Houben (2016) | Improving first-line/ MDR-TB treatment success |
| Kendall (2017) | Improving RR-/RS-TB treatment with novel regimens |
| Knight (2015) a | Increasing treatment success (better adherence and improved health services) |
| Knight (2015) b | Shortening TB treatment length with novel 4-month regimen |
| Verguet (2017) | Improving treatment quality (mobile health, patient follow-up, adherence counselling, improved staffing for MDR-TB) |
| Vynnecky (2015) | Decreasing treatment delay |
| **Other** |
| Basu (2007) | Reducing length of stay, detention of confirmed XDR-TB cases, mechanical/ natural ventilation, using HEPA/ UVGI, using isolation facilities, reducing clusters of patients, and ensuring staff and patients wear N95 masks |
| Chindelevitch (2015) | Improving healthcare coverage (reducing delay of disease development to clinic attendance) |
| Dye (2013) a | Enhanced case management (early case detection, accurate diagnosis and high cure rate) |
| Marx (2020) | Post-treatment follow-up examinations |
| Sumner (2019) b | Improving testing (use of an mRNA expression signature COR test to target PT) |

3HP: isoniazid and rifapentine for 3 months

ART: antiretroviral therapy

BCG: Bacille Calmette Guérin

COR: correlate-of-risk

DST: drug susceptibility testing

GTMD: GenoType Mycobacteria Direct

MDR-/XDR-TB: multi-drug-resistant/ extensively drug-resistant tuberculosis

MODS: microscopic-observation drug-susceptibility

HAART: highly active antiretroviral therapy

IGRA: interferon-$γ$ release assay

(I)LTFU: (initial) loss to follow-up

IPT: isoniazid preventive therapy

PHC: public health clinics

PT: TB preventive treatment

PWH: people with HIV

TLTI: treatment of latent TB infection

TST: tuberculin skin test

*Table S8: Impact of interventions for studies modelling TB at sub-country level in South Africa including provincial level, city level, rural community/ district level, township or sub-/urban level, and occupational setting level.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Publication**Time horizon | **Intervention modelled and target population** | **Study outcomes** | **% Reduction compared to baseline at end of time horizon or number averted over time horizon** |
| **Provincial level** | **Case finding/ screening** |
| Hippner (2019)2017-2035 | Increasing screening coverage in the general population | Screening reduced incidence and mortality in KZN, LP and WC by 11.5% and 18.8%, 3.4% and 8.8%, and 25% and 41.4%, respectively. | Incidence (KZN, LP, WC): 11.5%, 3.4%, 25%Mortality (KZN, LP, WC): 18.8%, 8.8%, 41.4% |
| Uys (2009)Over 20 years | Screening in the community | Screening in combination with rapid diagnosis of DR-TB reduced incidence from 11.2 cases per month (per 100,000) to 1.6 cases. | Cases: 85.7% |
| **Diagnostic interventions** |
| Uys (2009)Over 20 years | Improving diagnosis (earlier diagnosis of DR-TB) in the community | Rapid diagnosis of resistance with 97% sensitivity reduced incidence from 11.2 cases per month (per 100,000) to 2.4 cases.  | MDR-TB cases: 78.6% |
| **Reducing initial loss to follow-up** |
| Hippner (2019)2017-2035 | Improving linkage to care (ILTFU reduced by 80% by 2021) in the general population | Improving linkage to care reduced incidence and mortality in KZN, LP and WC by 4.9% and 10.2%, 5.2% and 13.2%, and 13.8% and 22.8%, respectively. | Incidence (KZN, LP, WC): 4.9%, 5.2%, 13.8%Mortality (KZN, LP, WC): 10.2%, 13.2%, 22.8% |
| **Treatment** |
| Hippner (2019)2017-2035 | Improving DS-/DR-TB treatment (DS-TB to 85% and DR-TB to 67%) in the general population | Improving treatment reduced incidence and mortality in KZN, LP and WC by 5.6% and 14.8%, 11.5% and 26.2%, and 4.6% and 11.6%, respectively. | Incidence (KZN, LP, WC): 5.6%, 11.5%, 4.6%Mortality (KZN, LP, WC): 14.8%, 26.2%, 11.6% |
| **City level** | **Vaccination** |
| Dye (2013) b2009 | BCG revaccination of HIV-negative adolescents and teenagers (efficacy of 80% with protection of 10 years) | With a revaccination efficacy of 80%, the percentage of cases averted reaches 17% (1,554 of 9,290 cases) and the annual risk of infection is reduced from 5.7% to 4.8% per year. | Cases: 17% |

|  |  |
| --- | --- |
| **Rural community/ district level** | **TB preventive treatment** |
| Gilbert (2015)2001-2011 | ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive)  | IPT averted 7% (95% CI 4-9%) of total TB and 8% (5-10%) of DS-TB cases. Minimally impacted MDR-/XDR-TB and TB/HIV mortality. | Cases (TB, DS): 7%, 8%  |
| Gilbert (2016) 2015-2025 | ART-linked IPT for PWH (12 months for TST negative, 36 months for TST positive and lifetime for PWH)  | Expanding IPT from 36/12 months to lifetime (without screening) reduced incidence from 298 to 254 cases per 100,000. Negligible impact on MDR-/XDR-TB. | Incidence: 14.8%  |
| **Case finding/ screening** |
| Gilbert (2015) 2001-2011 | TB/ HIV CICF and improving case detection for individuals interested in voluntary TB or HIV testing | Cases averted for total TB, DS-TB, MDR-TB, and XDR-TB were 23% (95% CI 13-27%), 24% (15-31%), 10% (6-20%), and 9% (18-23%), respectively. TB/HIV mortality was reduced by 13% (9-18%).  | Cases (TB, DS, MDR, XDR): 23%, 24%, 10%, 9% Deaths (TB/HIV): 13% |
| Gilbert (2016) 2015-2025 | Community-based TB/ HIV screening for individuals interested in voluntary TB or HIV screening | Introducing community-based screening reduced total TB, MDR-TB, and XDR-TB incidence from 298 to 274-233, from 54 to 15-14, and from 12 to 5-4 cases per 100,000, respectively.  | Incidence (TB, MDR, XDR): 8-22%, 72%-74%, 58-67% |
| **Diagnostic interventions** |
| Basu (2007)2007-2012 | Drug susceptibility testing (phage-based, line probe, GTMD and MODS assays) in hospital wards and the catchment community population | Rapid DST prevented between 2 and 4% of XDR-TB cases (26-52 cases).  | Cases: 2-4% |
| Gilbert (2015) 2001-2011 | Improving diagnosis (Xpert) in the general population | Xpert averted 31% (95% CI 11-65%) and 41% (10-72%) of MDR-TB and XDR-TB cases, respectively. Minimally impacted TB and DS-TB incidence, and TB/HIV mortality.  | Cases (MDR, XDR): 31%, 41% |
| **Treatment** |
| Gilbert (2015) 2001-2011 | Improving TB/MDR-TB treatment and first-line treatment cure rates for patients presenting for diagnosis at hospitals or clinics | Increasing cure rates to 80% reduced DS-TB and MDR-TB cases by 6% (95% CI 2-11%) and 9% (3-20%), respectively, and TB/HIV mortality was reduced by 3% (1-4%). Improving MDR-TB treatment reduced MDR-TB and XDR-TB cases by 43% (18-71%) and 72% (35-92%).  | Cases (CR: DS, MDR): 6%, 9%Deaths (CR): 3%Cases (Treatment: MDR, XDR): 43%, 72% |
| **ART for TB prevention** |
| Gilbert (2015) 2001-2011 | ART-linked IPT for PWH (expanding ART coverage) | Expanding coverage averted 10% (95% CI 2-14%) of total TB cases.  | Cases: 10% |
| Basu (2007)2007-2012 | Offering ART with voluntary counselling and testing at community-level for PWH | ART averted 312 (221-391) XDR-TB cases  | Cases: 24%  |
| **Other** |
| Basu (2007)2007-2012 | Reducing length of stay, detention of confirmed XDR-TB cases, mechanical ventilation, natural ventilation, using HEPA/ UVGI, using individual isolation facilities, reducing clusters of patients (5pt/10pt), and ensuring staff/ patients wear N95 masks for diagnosed XDR-TB patients or hospital staff | In order of intervention specification, XDR-TB cases prevented: 78 (39-117), -39 (-26- -52), 430 (104-456), 156 (130-326)/ 286 (260-456), 417 (391-586), 742 (664-820), 482 (417-586)/ 391 (352-456), and 26 (13-39)/ 65 (26-130).  | Cases: 6%, -3%, 33%, 12%, 22%/ 32%, 57%, 37%/ 30%, 2%/ 5%  |
| **Township or sub-/urban level** | **TB preventive treatment** |
| Kendall (2019) 2008-2013 | Continuous ART-linked IPT for PWH | Continuous IPT regimen reduced incidence and mortality by 10.5% (6.9-14.8) and 6.7% (3.8-10.7%), respectively.  | Incidence: 10.5% Mortality: 6.7%  |
| Marx (2018)2016-2025 | Secondary IPT for previously treated TB patients  | Secondary IPT in addition to ACF would avert 40% (21-56%) of all incident cases and 41% (16-55%) of deaths. | Incidence: 40% Mortality: 41%  |
| Marx (2020)2019-2028 | Secondary IPT for previously treated TB patients | Continuous follow up in combination with secondary IPT would avert 20.4% (5.9-35.9%) of cases and 18.2% (0.7-34.2%) of deaths. | Incidence: 20.4% Mortality: 18.2%  |
| **Case finding/ screening** |
| Marx (2018) 2016-2025 | Active case finding for previously treated TB patients | ACF alone would avert 14% (0.4-28%) of all incident cases and 21% (2.5-39%) of deaths.  | Incidence: 14% Mortality: 21%  |
| **ART for TB prevention** |
| Kendall (2019) 2008-2013 | ART-linked IPT for PWH (expanding levels of ART) | Increasing ART coverage in the presence of IPT reduced incidence by 7.2% (4.3-12.6%). In the presence of IPT, ART reduced mortality by 5.4% (2.8-9.6%). | Incidence: 7.2% Mortality: 5.4%  |
| **Other**  |
| Marx (2020) 2019-2028 | Post-treatment follow-up examinations for previously treated TB patients | Continuous follow up in combination with IPT would avert 20.4% (5.9-35.9%) of cases and 18.2% (0.7-34.2%) of deaths. | Incidence: 20.4% Mortality: 18.2%  |

|  |  |
| --- | --- |
| **Occupational setting level** | **Vaccination** |
| Shrestha (2017) Over 20 years | Hypothetical post-infection vaccine with 60% efficacy over 10 years for miners or people in associated labour-sending communities | Vaccines targeted to labor-sending community averted a median of 5,510 (95% range 2,360-10,000) cases. Vaccines targeted to miners averted a median of 8,090 (3,750-13,300) cases. | Cases (labor): 5,510 Cases (mine): 8,090  |
| **TB preventive treatment** |
| Vynnecky (2015)2003-2017 | IPT scenario with 100% cure and 100% protection for gold miners  | Incidence was reduced by 24.5% (95% CI: 24.2-25%) using an IPT regimen with 100% cure and 100% protection against infection.  | Incidence: 24.5% |
| **Diagnostic interventions** |
| Vynnecky (2015)2003-2017 | Improving diagnosis (using Xpert) for gold miners | An approximate 30% reduction in predicted true incidence. | Incidence: 30% |
| **Reducing initial loss to follow-up** |
| Vynnecky (2015)2003-2017 | Reducing ILTFU for gold miners | Decrease in ILTFU and treatment delay reduced incidence by approximately 40%. | Incidence: 40%  |
| **Treatment** |
| Vynnecky (2015)2003-2017 | Decreasing treatment delay for gold miners | Decrease in LTFU and treatment delay reduced incidence by approximately 40%. | Incidence: 40% |
| **ART for TB prevention** |
| Vynnecky (2015)2003-2017 | Scale up of ART to 80% for gold miners with HIV | An approximate 50% reduction in predicted true incidence. | Incidence: 50% |

|  |  |
| --- | --- |
| CI: confidence interval | ILTFU: Initial loss to follow-up |
| CR: cure rates  | MODS: microscopic-observation drug-susceptibility |
| CICF: community-intensified case finding | pt: patients |
| GTMD: GenoType Mycobacteria Direct | TST: tuberculin skin test |
| HEPA: high-efficiency particulate air | UVGI: ultraviolet germicidal irradiation |

*Table S9.1: Studies using transmission dynamic models and reason for exclusion in review*

|  |  |
| --- | --- |
| **Publication (year)** | **Reason for exclusion** |
| Bacaer (2008)  | None of the End TB targets quantified |
| Basu (2008) | Review of modelling studies |
| Blaser (2016) | No intervention modelled |
| Cohen (2009) | Review of modelling studies |
| Chang (2018) | No intervention modelled  |
| Currie (2003) | Not modelled for South Africa: modelled for Kenya |
| Du Toit (2007) | Not a population-based study: The number of cells over time (T4, infected cells, CTLs, APC’s, viral load, and bacterial load) represent the state variables that are modelled dynamically.  |
| Enagi (2017)  | Not modelled for South Africa: modelled for Nigeria |
| Houben (2014) | Not representative of the population: model reflects a closed cohort of individuals during and after TB preventive treatment |
| Houben (2016)  | No intervention modelled |
| McCreesh (2018) | No intervention modelled |
| McCreesh (2020) | No intervention modelled |
| Menzies (2016) | None of the End TB targets quantified |
| Pretorius (2011) | No intervention modelled |
| Reid (2015) | Secondary report of modelling studies |
| Salvatore (2019) | No intervention modelled |
| Sharma (2017) | No intervention modelled |
| Sumner (2016) | Not representative of the population: model reflects a closed cohort of individuals during and after TB preventive treatment & none of population-level outcomes measured |
| Viljoen (2012) | Not modelled for South Africa: not calibrated to South African data |
| Witbooi (2017) | No intervention modelled |
| Wood (2011) | Intervention not modelled (explicitly – do show a model and discuss ART intervention, but focus on evidence gained from literature) |

|  |  |
| --- | --- |
| **Author**  | **Year** |
| Agnarson | 2020 |
| Andrews | 2012 |
| Andrews | 2013 |
| Andrews | 2014\* |
| Channing  | 2014 |
| Dodd | 2015 |
| Dowdy | 2008 |
| Foster | 2021 |
| Gomez | 2016 |
| Jo | 2021 |
| Johnstone-Robertson | 2011\* |
| Nelson | 2020 |
| Nyabadza (external incidence used) | 2013 |
| Reddy | 2019 |

*Table S9.2: 27 studies excluded at full text that did not use transmission dynamic models*

|  |  |
| --- | --- |
| **Author**  | **Year** |
| Reddy  | 2020 |
| Reddy  | 2020 |
| Schluter  | 2021 |
| Schnippel | 2013 |
| Schnippel | 2013 |
| Schnippel | 2015 |
| Tawfik | 2008 |
| Uys | 2011\* |
| Vassall | 2011 |
| Vassall | 2017 |
| Williams (HIV dynamic, TB not) | 2017 |
| Wood  | 2010 |
| Zelner (editorial) | 2020 |

*Table S10.1: Incidence and mortality data from the WHO used to estimate the required AAPD to meet the End TB Strategy targets for 2035*

|  |
| --- |
| **Incidence (90% reduction compared to 2015 levels)** |
| **Year** | **Incidence (per 100k)** | **PPD (time horizon)** | **AAPD** |
| 2015 | 988 | 44% (5 years) | 11% |
| 2020 | 554 |
| 2022 | 554 (Assumed) | 82% (13 years) | 12% |
| 2035 | 98.8 (Target) |
| **Mortality (90% reduction compared to 2015 levels)** |
| **Year** | **Mortality (per 100k)** | **PPD (time horizon)** | **AAPD** |
| 2015 | 116 | 11% (5 years) | 2.3% |
| 2020 | 103 |
| 2022 | 103 (Assumed) | 94% (13 years) | 19% |
| 2035 | 5.8 (Target) |

**Estimated impact by type of intervention**

****Fig. S2 shows AAPDs for incidence (A) and mortality (B), calculated from reported model outcomes and time horizons. AAPDs varied between 0.05% and 7.1% for incidence, and between 0.04% and 7.1% for mortality. Interventions that were estimated to have the largest impact on TB incidence were of the vaccination and preventive treatment categories, with AAPDs estimated above 6% for incidence. Interventions of improved diagnosis, and improved treatment were estimated to be of lower impact (AAPDs below 3%).

*Fig. S2.* *(A) & (B). The number of studies corresponding to average annual percentage declines which were ascertained using reported percentage declines in incidence (A) and mortality (B) from eligible studies in addition to the baseline scenario, and time horizons over which interventions were modelled at country level.*

# References

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