Tuberculosis from transmission in clinics in high HIV settings may be far higher than contact data suggest

Running title: TB from transmission in clinics

Nicky McCreesh[1], Alison D Grant[2,3,4], Tom A Yates[5,6], Aaron S Karat[2], and Richard G White[1]

[1]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

[2]TB Centre, London School of Hygiene & Tropical Medicine, London, UK

[3]Africa Health Research Institute, School of Nursing and Public Health, University of KwaZulu-Natal, South Africa

[4]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[5]Section of Infectious Diseases and Immunity, Imperial College London, London, UK

[6]Institute for Global Health, University College London, London, UK

*Corresponding author. Nicky.mccreesh@lshtm.ac.uk LSHTM, Keppel Street, London, WC1E 7HT, UK

Keywords

mathematical model; nosocomial; South Africa; social contact; healthcare facility

Abstract

Background: In South Africa, it is estimated that only 0.5-6% of people's contacts occur in clinics. Both people with infectious tuberculosis and people with increased susceptibility to disease progression may spend more time in clinics however, increasing the importance of clinic-based transmission to overall disease incidence.

Methods: We developed an illustrative mathematical model of Mycobacterium tuberculosis transmission in clinics and other settings. We assumed that 1% of contact time occurs in clinics. We varied the ratio of clinic contact time of HIV positive people compared to HIV negative people, and of people with infectious tuberculosis compared to people without tuberculosis, while keeping the overall proportion of contact time occurring in clinics, and each person's total contact time, constant.

Results: With clinic contact rates 10 and 5 times higher in HIV positive people and people with tuberculosis respectively, 10.7% (plausible range: 8.5%-13.4%) of tuberculosis resulted from transmission in clinics. With contact rates in HIV positive people and people with tuberculosis 5 and 2 times higher respectively, 5.3% (4.3%-6.3%) of all tuberculosis was due to transmission in clinics.

Conclusion: The small amounts of contact time that occur in clinics may greatly underestimate their contribution to tuberculosis disease in high tuberculosis/HIV burden settings.

Introduction

There is considerable evidence that *Mycobacterium tuberculosis* (*Mtb*) transmission occurs in clinics and other healthcare settings in South Africa and elsewhere. A recent systematic review of tuberculosis in healthcare workers found that, in eight high burden countries, tuberculosis disease incidence in healthcare workers was 2.0-11.9 times higher than tuberculosis disease incidence in the general population[1]. In KwaZulu-Natal, South Africa, the incidence of multi-drug-resistant tuberculosis hospitalisation in health-care workers was 5.5 times higher than that of non-HCW[2].

The elevated risk of tuberculosis in healthcare workers suggests that *Mtb* transmission occurs frequently in clinics. This transmission is unlikely to be confined to healthcare workers, with patients and other people attending clinics also likely to be at risk[3]. Members of the general population spend far less time in clinics than healthcare workers, however. One study of residents of a township near Cape Town, South Africa found that health clinics contributed 0.5% of indoor contacts (people present in the same indoor location or transport), and 0.7% of indoor time[4]. In another study (of adults only), 6.0% of indoor contacts and 5.1% of indoor contact hours occurring in locations outside respondents' own homes were in clinics in Western Cape, South Africa, and 6.4% and 5.2% respectively in Zambia.[5]

These low proportions of contacts and contact time in clinics suggest that clinic-based transmission may contribute little to overall community-wide transmission in these settings. This may underestimate the importance of clinic-based transmission to overall disease incidence, however, as both people with potentially infectious tuberculosis and people with

increased susceptibility to disease progression may have higher amounts of contact time in clinics.

One study in Eastern Cape Province, South Africa, estimated that 63%–79% of people with tuberculosis attending primary health clinics for tuberculosis-related symptoms, and 90%–100% of those attending a clinic for other reasons, were not diagnosed with tuberculosis during their visit, likely necessitating further clinic visits[6]. Another study in South Africa found a prevalence of tuberculosis of 3.0% among clinic patients attending for HIV care[7]. In a study in Tanzania, 48% of tuberculosis patients had sought care at a healthcare facility in relation to their tuberculosis symptoms three or more times before diagnosis[8]. These studies suggest that people with tuberculosis usually make multiple trips to clinics before being diagnosed and starting treatment, and that the prevalence of untreated, infectious tuberculosis in clinic attendees may be higher than that in the general population.

Clinic attendance is also higher in people living with HIV, who have increased susceptibility to tuberculosis disease progression. South African 2017 national HIV management guidelines recommend three-monthly adherence counselling visits[9], necessitating frequent clinic visits by people living with HIV who are receiving antiretroviral therapy. In Zambia, antiretroviral therapy (ART) patients had a median appointment interval of only 59 days[10].

Increased rates of clinic visiting and/or time spent in clinics by people with infectious tuberculosis and people living with HIV (or other risk factors for tuberculosis disease progression) will amplify rates of transmission in clinics and, in particular, rates of transmission that result in disease. In this paper, we use mathematical modelling to determine the potential effects of that amplification on the proportion of disease that results from clinic-based transmission, using South Africa as a case study. Our model is not

designed to give an estimate of the proportion of tuberculosis that results from clinic-based transmission in any particular setting in South Africa, but instead gives an indication of the extent of the effects that increased contact time in clinics in people with HIV and/or infectious tuberculosis may have on the contribution of clinic-based transmission to tuberculosis incidence.

Methods

Model

We used an individual-based model, written in Netlogo 6.0.1[11]. Full details of the model structure and parameter values are given in the supplementary material Model description and Figure S1.

Simulated individuals could be uninfected with *Mtb*, have a latent infection, have smear-negative disease, have smear-positive disease, or be receiving tuberculosis treatment. Treatment was assumed to always be successful.

HIV was included in the model as a binary variable, with simulated individuals either being HIV positive or HIV negative. 12.7% of individuals were assumed to be HIV positive, in line with the estimated HIV prevalence in South Africa in 2017[12].

Overall, 1% of contact time in the model occurs in clinics, with the other 99% occurring in a homogenous 'other locations', representing all other settings. Contacts are defined as any people 'sharing air' in an indoor location or transport, as these are the contacts thought to be most relevant for *Mtb* transmission[13, 14]. Random mixing was assumed between people in

clinics and in other locations. Each simulated individual had the same contact rate. The ratio of contact time in clinics of HIV-positive individuals compared to HIV-negative individuals, and of people with tuberculosis compared to people without tuberculosis, could be varied, while keeping the overall proportion of contact time that occurred in clinics and the contact rate of each simulated individual constant.

A paediatric population, with different risks of disease progression and different contact patterns, was not simulated.

Increased clinic visiting in HIV-positive people and people with tuberculosis

629 parameter combinations were created where the rate ratio of clinic visiting in HIV-positive people compared to HIV-negative people (RR_{HIV}) varied from 1 to 10 in increments of 0.25, and where the rate ratio of clinic visiting in people with infectious tuberculosis compared to people without infectious tuberculosis (RR_{TB}) varied from 1 to 5 in increments of 0.25. Maximum rate ratios of 10 and 5 were chosen based on expert opinion, as plausible upper bounds for the majority of settings. All combinations of the two ratios were simulated. The rate ratio of clinic visiting in people with both HIV and tuberculosis relative to people with neither HIV nor tuberculosis was assumed to be equal to $max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$. In other words, it was assumed having both HIV and untreated tuberculosis would require some extra clinic visits (or longer clinic visits) compared to having just one of the conditions, but it would not require as many as the sum of those required by someone who has HIV only and those required by someone who has untreated tuberculosis only.

For each parameter combination, the model was run for 50 years to allow equilibrium to be reached. The model was then run for a further 950 years, and the results averaged over the 950 years and 10 model runs.

Calibration

The model was fitted to estimates of overall tuberculosis incidence in South Africa and the proportion of incident tuberculosis that occurred in HIV-positive people in 2017[15].

Scenarios

Low and high clinic-based transmission scenarios were generated, to determine plausible ranges for the proportion of transmission that occurs in clinics for each parameter combination.

Three characteristics of the model were changed in the scenarios:

1. The proportion of incident tuberculosis that was in HIV-positive people was changed from 60% in the main scenarios to 55% and 64% in the low and high clinic-based transmission scenarios respectively (proportions equal to the best estimate and low and high bounds from World Health Organization (WHO) incidence estimates[15]).
2. In the main scenario, the proportion of HIV-positive and HIV-negative people with tuberculosis who had smear-positive disease was 35% and 45%, respectively; these were changed to 30% and 50%, and to 40% and 40%, in the low and high clinic-based transmission scenarios, respectively[16].
3. The rate ratio of clinic visiting in people with both HIV and tuberculosis relative to people with neither HIV nor tuberculosis ($RR_{HIV\_tuberculosis}$) was assumed to be equal to $max(RR_{HIV}, RR_{TB})$ and $RR_{HIV} + RR_{TB} - 1$ in the low and high clinic-based transmission scenarios, respectively.

Univariate sensitivity analyses where each factor was varied individually were also conducted; these results are given in the supplementary material.

All data used came from published sources, and no ethical approval was required.

Results

Fit to data

Figure 1 shows the model fit to the tuberculosis incidence estimates and the estimated proportion of incident disease that is in HIV positive people in each scenario. Figure S2 shows the model fit in the sensitivity analyses. For all scenarios and parameter combinations, the modelled tuberculosis incidence was well within the lower and upper bounds of the estimated empirical incidence, and the proportion of incident disease that was in HIV-positive people was within ±2% (absolute difference) of the desired value. The proportion of contact that occurs in clinics for people without and without HIV and tuberculosis is shown in Figures S3-S5

Proportion of transmission in clinics

Figure 2 shows the estimated proportion of disease that resulted from transmission occurring in clinics overall, in HIV-positive people, and in HIV-negative people, in the best, low, and high clinic-based transmission scenarios. With $RR_{HIV} = 10$ and $RR_{TB} = 5$, an estimated 10.7% (8.5%–13.4% in low and high scenarios) of disease resulted from clinic-based transmission overall, 16.3% (14.0%–19.2%) in HIV-positive people, and 1.9% (1.5%–2.2%) in HIV-negative people. With $RR_{HIV} = 5$ and $RR_{TB} = 2$, an estimated 5.3% (4.3%–6.3%) of disease resulted from clinic-based transmission overall, 7.7% (6.7%–8.8%) in HIV-positive people, and 1.6% (1.4%–1.8%) in HIV-negative people.

Discussion

Our results show that the small proportions of contact time that occur in clinics may greatly underrate their importance to tuberculosis incidence in high burden settings with high HIV prevalences. Despite only 1% of contact time occurring in clinics in our model, 10.7% of disease overall and 16.3% in HIV-positive people resulted from transmission in clinics when we simulated clinic contact 10 times higher in HIV-positive people compared with HIV-negative people, and five times higher in people with infectious tuberculosis compared to people without. With clinic contact five times higher in HIV-positive people and two times higher in people with infectious tuberculosis, 5.3% of disease overall and 7.7% of disease in HIV-positive people resulted from transmission in clinics.

We did not explicitly simulate drug sensitive and drug resistant tuberculosis. It is plausible however, that clinic-based transmission may be higher for drug resistant disease than for drug susceptible disease, due to more clinic visits being required before the patient starts effective treatment and becomes uninfectious.

Our findings demonstrate the importance of minimising the potential for clinic-based *Mtb* transmission. Ensuring that adequate infection control measures are implemented in clinics is critical to this, but our results also suggest two other strategies for reducing clinic-based transmission. The first is reducing the number of visits that people with tuberculosis make to clinics before diagnosis and starting effective treatment. The second is reducing the amount of contact that HIV-positive people have at clinics, through reducing the mean number of people present at clinics and/or reducing time spent at clinics. This could be achieved through increasing the time between clinics visits for people on stable ART, or reducing clinic waiting times for people attending HIV clinics.

We fitted our model to data from South Africa, which has a high prevalence of HIV. A similar amplification of disease resulting from transmission in clinics may also be found in settings with much lower HIV prevalences, due to the presence of other risk factors for tuberculosis, such as diabetes and undernutrition. The magnitude of the amplification is likely to be smaller, however, as the effect of most other risk factors on the risk of tuberculosis disease development is lower than that of HIV[17].

Our results are intended to give an indication of the extent of the effects that increased contact in clinics in people with tuberculosis and HIV positive people are likely to have on tuberculosis from transmission in clinics, rather than an estimate of the proportion of tuberculosis that results from clinic-based transmission in South Africa. For that reason, we simulated an arbitrary 1% of contact time occurring in clinics, to allow comparisons to be easily made between the proportion of contact and the proportion of disease, and present results over a wide range of different values of RR_{HIV} and RR_{TB}. We also kept the overall amount of contact constant for people with and without tuberculosis and HIV, and did not model contact patterns by age.

We simulated random mixing in both clinics and in all other locations. This assumption is likely to be reasonable for clinics, with different people being present each time a person visits a clinic. It will be less reasonable for some other locations however, in particular homes, workplaces, and schools, where high proportions of contact time occur. Contact saturation may reduce transmission in these locations, increasing the proportion of transmission that occurs in clinics[18]. We may therefore have underestimated the contribution of clinics to tuberculosis incidence. Conversely, clustering of people with HIV

and TB in locations other than clinics may have meant that we overestimated the contribution of clinics.

We made the assumption in our model that there was no difference between clinics and other types of congregate settings in indoor ventilation levels. There is limited empirical data on ventilation levels in congregate settings in South Africa. One study found that the proportion of room air that had previously been exhaled by other room occupants was similar in a clinic waiting room and in other indoor congregate settings in KwaZulu-Natal, South Africa; this measure is impacted both by occupancy and ventilation levels[19]. If ventilation levels are higher or lower in clinics, then we will have over- or under-estimated the importance of clinics to transmission.

We did not explicitly simulate HIV disease progression or ART, and therefore did not model how clinic visiting behaviour may vary between HIV-positive people. If susceptibility to developing tuberculosis is higher for HIV-positive people who frequently attend clinics than for HIV-positive people who do not (e.g. people with lower CD4 counts spend more time at clinics than people with higher CD4 counts), then we will have underestimated the proportion of disease that results from clinic-based transmission for a given RR_{HIV}. Alternatively, if the susceptibility to developing tuberculosis is lower for HIV-positive people who frequently attend clinics than for HIV-positive people who do not (e.g. HIV-positive people on ART visit clinics more frequently than those not on ART), then we will have overestimated the proportion of disease that results from clinic-based transmission for a given RR_{HIV}. We also did not simulate variation in infectiousness for people with tuberculosis (beyond smear status). If clinic visiting increases as the disease progresses and people become more infectious, then we may have underestimated transmission in clinics.

The proportion of incident tuberculosis that was in HIV-positive people in the model varied slightly between different parameter combinations within the same scenario (Figure 1), increasing as the value of RR_{HIV} increased. This will have resulting in us slightly overestimating the extent to which the proportion of disease that results from clinic-based transmission increases as RR_{HIV} increases. The effect of this bias will be small however, as the increase in the proportion of incident tuberculosis in HIV-positive people was small. In addition to this, in the low and high clinic-based transmission scenarios, for some values of RR_{HIV} and RR_{TB}, the proportion of incident tuberculosis that was in HIV-positive people was slightly outside the range of WHO estimates[15]. This was an inevitable consequence of fitting to the lower and upper bounds of the range in the low and high clinic-based transmission scenarios respectively and, while it may have changed the results slightly, it will have had no effect on the overall conclusions of this paper.

To conclude, we demonstrate in this paper that although only small amounts of contact time may occur in clinics, this may greatly underestimate the contribution of clinics to tuberculosis disease in high tuberculosis/HIV burden settings. Future work to generate empirical estimates of how much HIV and infectious tuberculosis increase clinic visiting in different settings would allow improved estimates to be made of the contribution of clinic-based transmission to tuberculosis burden, and of the potential impact on community-wide tuberculosis incidence of interventions to reduce transmission in clinics.

Acknowledgements

This work was supported by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement that is also part of the EDCTP2 programme supported by the European Union MR/N014693/1 and MR/P002404/1. The support of the Economic and Social Research Council (UK) to ADG and ASK is gratefully acknowledged (ES/P008011/1). This project is partly-funded by The Antimicrobial Resistance Cross Council Initiative supported by the seven UK research councils in partnership with other funders. TAY is supported by an NIHR Academic Clinical Fellowship and acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC). RGW is additionally funded by the Bill and Melinda Gates Foundation (Tuberculosis Modelling and Analysis Consortium: OPP1084276/OPP1135288, SA Modelling for Policy: OPP1110334, CORTIS: OPP1137034, Vaccines: OPP1160830) and UNITAID (4214-LSHTM-Sept15; PO 8477-0-600).

NM conceived the idea for the work, designed the model, analysed the results, and wrote the first draft of the paper. RGW, ADG, TAY, ASK, and RGW commented on drafts of the manuscript, and approved the final version. The authors report no conflicts of interest.

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Figures

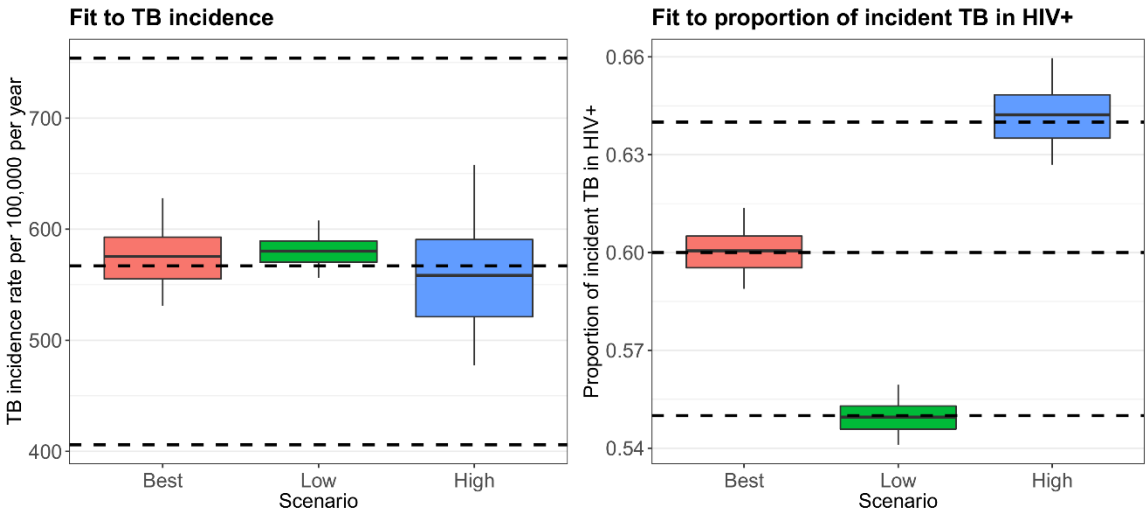

Figure 1. Model fit to a) tuberculosis incidence and b) the proportion of incident tuberculosis in HIV positive people, in the best, low, and high scenarios. Box hinges indicate the upper, middle and lower quartiles of the values in each parameter set, and whiskers extend to the upper and lower ranges of the values. The horizontal dashed lines show the best estimate and lower and upper ranges of the empirical data.

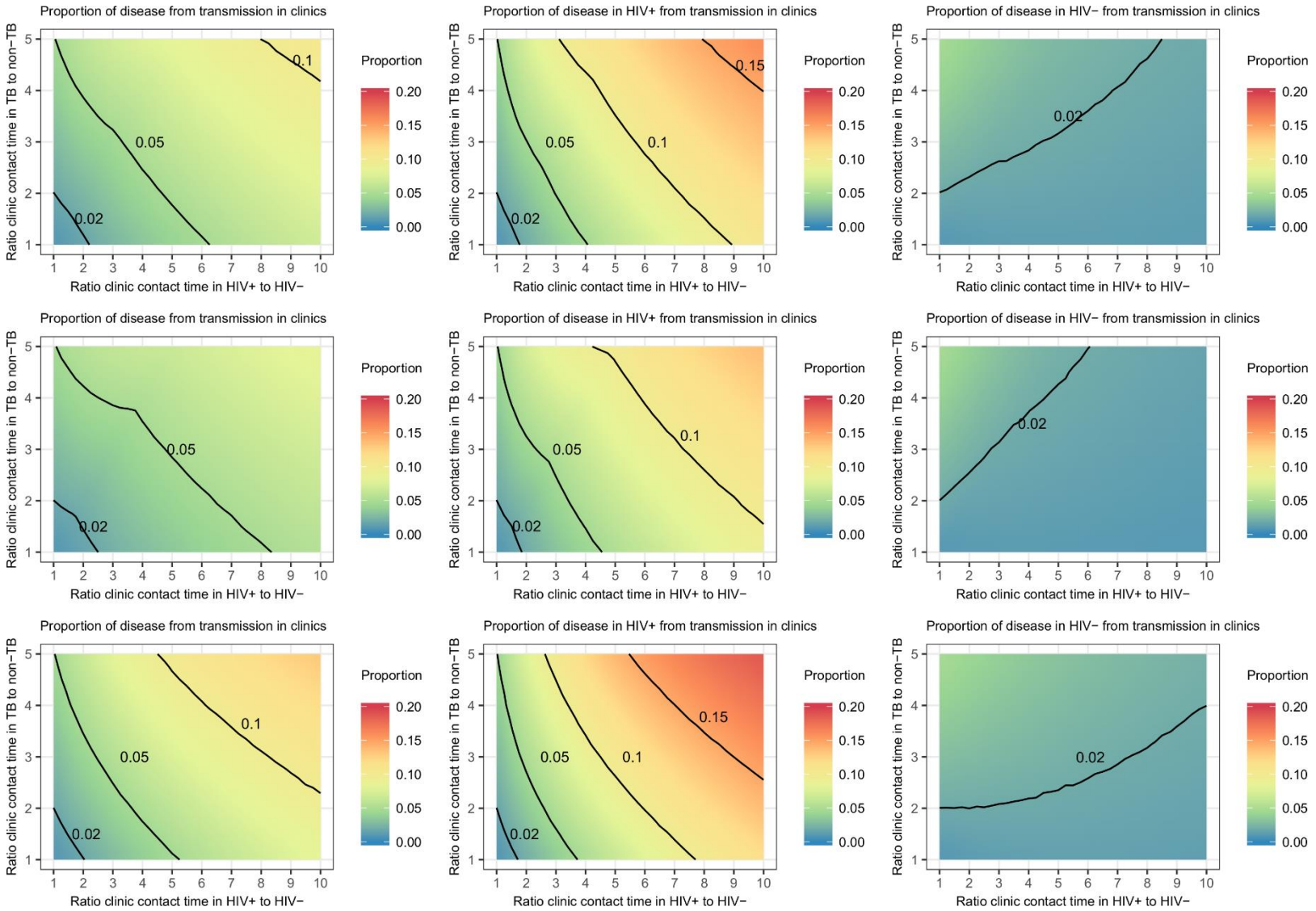
Proportion of disease from transmission in clinics
Proportion of disease in HIV+ from transmission in clinics
Proportion of disease in HIV− from transmission in clinics
Ratio clinic contact time in TB to non−TB
Ratio clinic contact time in HIV+ to HIV−
Proportion
0.00
0.05
0.10
0.15
0.20
0.02
0.05
0.1
0.15

Figure 2. Proportion of disease resulting from transmission in clinics overall (1st column), in HIV positive people (2nd column) and in HIV negative people (3rd column) in the best (1st row), low (2nd row), and high (3rd row) clinic-based transmission scenarios

Supplementary information

supplementary_information.pdf