RESEARCH ARTICLE (2649 words)

TITLE (73 characters)

Mathematical modelling of the ZAMSTAR household intervention against tuberculosis.

AUTHORS

Peter J. Dodd[1*]

Richard Hayes[2]

Sian Floyd[2]

Ab Schaap[2,3]

Nulda Beyers[4]

Peter Godfrey-Faussett[2]

Elizabeth L. Corbett[2,5]

Helen Ayles[2,3]

Richard G. White[2]

AFFILIATIONS

1. Health Economics and Decision Science, School of Health and Related Research, The University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK

2. London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

3. ZAMBART, University of Zambia, School of Medicine, Ridgeway Campus, Lusaka, Zambia

4. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa

6. HIV and TB Group, Malawi- Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi

* corresponding author

ABSTRACT (192/350 words)

Background: Case-finding interventions have high potential for rapidly improving tuberculosis control, and were widely used historically. However the evidence-base from which to design interventions is extremely limited. The cluster-randomized Zambia, South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) intervention trial in communities with high HIV and TB burdens in the Western Cape, South Africa and Zambia had multiple components targeting TB and HIV, including TB/HIV education, HIV counseling and testing, TB case-finding and referral for treatment, referral for ART, isoniazid preventive therapy and. One trial arm reduced tuberculosis (TB) prevalence and transmission with an intervention focused on the households of newly detected TB cases.

Methods: We developed a novel household-structured individual-based TB transmission model of these communities, calibrated it to data from the trial, and modelled the impact of the household intervention.

Results: Even assuming extreme levels of behavior change around care-seeking for TB among those reached directly by the intervention, we found the probability of the model generating the trial impact to be small unless diffusion of behavior change beyond the household was considered.

Conclusions: The indirect health promotion effects of TB case-finding may have been substantial in the ZAMSTAR household intervention.

Keywords: Tuberculosis; HIV; mathematical modelling; TB case-finding; behavior change.

BACKGROUND

Tuberculosis (TB) remains a major public health concern, with an estimated 8.6 million TB cases and 1.3 million deaths from TB globally in 2012 (1). Slow and incomplete case detection remains one of the critical bottlenecks to improving control, with an estimated 12 million undiagnosed active TB cases prevalent globally (1), and high burdens of undiagnosed TB identified in community-based prevalence surveys (2–4). Poor control of infectious TB in the community is a major contributor to the high risk of TB transmission, and the high subsequent morbidity and mortality from TB in sub-Saharan Africa, notably Southern Africa. Despite limited evidence for case-finding interventions impacting on TB epidemiology (5), recent WHO guidelines included populations with incidences of more than 100/100,000 population per year among the high-risk populations where systematic screening for TB should be considered (6).

ZAMSTAR (7) was a two-country factorial cluster randomized trial (8 communities in the Western Cape of South Africa, 16 in Zambia, all with TB notification rates higher than 400/100,000 per year) that investigated the effectiveness of two potentially sustainable interventions coordinated from health care facilities: a community based case finding intervention that showed no impact on the burden of TB, and a household intervention, which showed some reduction in both prevalence of adult TB disease and incidence of childhood TB infection, of borderline statistical significance ($p= 0.06$ for both outcomes).

The household intervention, included at least 3 visits to the households of all newly detected TB patients during the 6 months following diagnosis (7). Over a 3 year period, this arm achieved an

18% (95% CI: -4% - 36%) reduction in the population-level prevalence of undiagnosed culture positive TB prevalence, and a 55% (95%CI: -5% - 80%) reduction in the annual risk of infection with *Mycobacterium tuberculosis* (*M.tb.*) among young school children compared to non-intervention clusters (8). The household arm of ZAMSTAR consisted of household visits to the house of a newly diagnosed TB case and included additional household TB case-finding, isoniazid preventive therapy (IPT) for children under 5 year of age and people living with HIV (PLHIV), HIV counseling and testing, and ongoing health promotion encouraging early diagnosis and treatment of HIV and TB and increased support for individuals affected by either disease. The study was informed by prior qualitative research (9–12).

Understanding the impact of complex community interventions requires resolution of the likely contribution of each component, which may require mathematical modelling as well as statistical analysis (13). Mathematical modelling has been successfully used before to support the interpretation of cluster randomized trials of HIV interventions (14,15), but this is the first use of mathematical modelling for a controlled trial of a TB intervention in the general population. Here, we bring together biomedical evidence, epidemiological data from the trial and comparisons with observed effects using a household-structured individual-based model of TB transmission calibrated to epidemiological data from ZAMSTAR, in order to explore the mechanisms of action for the household intervention.

METHODS

The model was developed in the C++ programming language and had a TB natural history based on previous models. (Further information and parameter values are available in the Additional file 1.) Individuals have a higher rate of progressing to active TB disease for the first 2 years following infection than in subsequent years. Infection with *M.tb.* confers a partial protection against reinfection (24,25), which behaves like primary infection if it occurs. Individuals may be smear positive or smear negative and are correspondingly infectious to different extents (26,27). Risks of progression and of being smear-positive depend on age (24).

HIV infection was modelled, together with CD4 count and ART status. A continuous CD4 variable was modelled to decline as in (28): an initial drop followed by a linear decline over a Weilbull-distributed period between HIV infection and HIV-related death. The effect of HIV on the risk of progression to TB depended exponentially on CD4 loss (28). The dynamics of HIV infection risk through calendar time were captured by a statistical model of incidence as in (29), with infections distributed according to individuals' age as in (30). To generate household clustering of HIV infection, sharing a household with an individual infected with HIV was a risk factor for infection. ART scale-up was modelled as a time-dependent hazard, based on a previous modelling exercise (31). ART increased life expectancy and reduced the risk of progressing to TB.

A survey was undertaken in the ZAMSTAR communities to inform the demography, household structure and rate of moving household in the model (32). Birth rates depended on calendar time

according to estimates from the UN Economic & Social Affairs Population Division (33), and mortality from causes other than TB or HIV was modelled via UN one-parameter life-tables (34) with a time-varying life-expectancy at birth calibrated to match the growth predictions for each country. Household movement followed an algorithm that approximately preserved the distribution of household sizes as the population grew, over the 30 years of each model run (1980 to 2010). The correct magnitude of demographic stochasticity was captured by initializing model runs with a population of 25,000, resulting in a population size after 30 years comparable with those of the study communities.

TB transmission followed age-dependent mixing patterns, informed by a social contact study in these communities. Household transmission of TB was also included. The probability of detection and treatment outcomes were based on national level estimates. The timing of TB detection, conditional on detection followed a Weibull distribution.

The household intervention was modelled assuming perfect coverage of its components: all co-prevalent TB cases living in the same household as an index TB patient were detected and initiated on treatment; children under 5 and PLHIV were given IPT courses; all those eligible for ART were detected and started on therapy. The possibility of behavior change around care-seeking for subsequent TB among members of intervention households was modelled by multiplicative increases in the odds and rapidity of detection and treatment.

Diffusion of behavior change beyond intervention households was modelled as a susceptible-infected (SI) infection process. For the 6 month duration of the index cases' treatment course,

individuals in intervention households were assumed to transmit behavior change to behavior-change naive individuals in the population, with a constant transmission coefficient.

Calibration was via a pragmatic fit-weighted sampling scheme. 8 summary statistics were chosen as calibration targets base on data availability and anticipated relevance to key parameters: the HIV prevalence, ART prevalence among PLHIV, TB prevalence, TB treatment prevalence, ARI and the household HIV and TB clustering from the ZAMSTAR trial, and also the UN HIV prevalence time series scaled to meet the ZAMSTAR HIV prevalence, in order to shape the history of the HIV epidemic. So that each target contributed equally, the squared error from each target was rescaled by the median of its error distribution, before summing the 8 errors to produce an overall measure of fit. Each parameter sample was given a weight whose negative logarithm equaled the total error statistic divided by its 1st percentile. The priors were flat over intervals of +/-5% for natural history parameters that were not influential for the fit, and larger ranges for those that were influential. Parameter sampling for these 37 parameters followed a Latin hypercube design, and 2500 runs were performed for each intervention scenario.

To calculate the probability that the model impact exceeded the trial impact for a given hypothesis about the intervention mechanism, 10,000 bootstrap samples (comprising 12 intervention and 12 runs with no intervention) were drawn with replacement and weighted by fit from the 2500 runs for each intervention scenario. For each sample, the model impact was calculated from the 8 Zambian and 4 South African intervention runs and the 8 Zambian and 4 South African runs with no intervention. Measurement uncertainty around the true trial impact on ARI and prevalence was represented by a bivariate log-normal distribution. For each

bootstrap sample of runs, the model impact was calculated and the probability that this impact exceeded the true trial impact calculated. The mean over the bootstrap samples was then taken. The sensitivity of this result to parameter uncertainty was assessed with a one-way analysis, repeating this bootstrap procedure with each parameter in turn restricted to values in the highest and then the lowest 10% of its range.

RESULTS

The ensemble of model runs, generated by sampling across all parameter ranges and weighting by goodness-of-fit to 8 epidemiological indices, was generally consistent with observed data (see Figure 1). However, the annual risk of *M.tb.* infection was systematically overestimated and the observed extent to which HIV clustered in households was underestimated in the model (Figure 1, panels 3 and 4, respectively). The population growth over the time period 1980 to 2010 matched estimated country trends (see Additional file 1). The distribution of household sizes was maintained approximately constant through movement between households as communities grew (see Additional file 1).

Under assumptions of perfect implementation and acceptance, 6.6% of the general population was directly reached by the household intervention in the model (weighted-bootstrap 95% range: 5.7% - 7.5%). This compares with 6.1% reported in the trial. Modelled cumulative coverage of IPT and ART as a result of the household intervention reached 0.28% (95% range: 0.24% - 0.32%), and 1.3% (95% range: 1.1% - 1.4%), which were each larger than achieved during the trial.

However, even with these optimistic assumptions about the coverage of intervention components, the magnitude of effect observed in the trial could not be easily reproduced by direct effects alone. The results for bootstrap calculation of the probability that model results exceed those of the trial (analogous to a p-value), under different hypotheses around the nature and magnitude of behavior change, are shown in Table 1. This calculation accounted for the uncertainty in the measured trial effect due to sampling error, by comparing bootstrap samples from the posterior of trial impacts against fit-weighted samples of model impacts. The Monte Carlo errors for this probability were small (median 1%). Assuming the intervention had no impact on care-seeking behavior, but that implementation of the IPT, ART and case-finding elements of the household intervention had perfect coverage, the probability of the model generating equivalent or stronger impacts was only 0.023. Assuming that the intervention was able to halve the delay to TB detection and treatment for any subsequently incident TB among household members increased the probability slightly to 0.024. Assuming instead that the odds of detection doubled among household members directly reached by the intervention increased the probability to 0.026. Even when implausible assumptions about the direct effects on subsequent TB case finding were made (for instance, a tenfold increase in the odds of detection, and tenfold reduction in time to detection), the probability that the model impact was greater or equal to that of the trial was still only 0.040.

We therefore allowed for diffusion of behavior change beyond the households of newly diagnosed TB patients that were reached directly. This was modelled as a susceptible-infected process that, when driven by household members during the 6 months of the index cases'

treatment with an assumed effective contact rate of 2 people reached per year, reached 16.6% (95% range: 14.8% - 18.5%) of the population. With an assumed transmission coefficient of 5 per year 35.6% (95% range: 32.3% - 38.9%) of the population was reached. Assuming the diffusion, with behavior-change effective contact rates of 2 per year and 5 per year respectively, and relatively modest improvements in care-seeking behavior (1.5-fold speed-up in delay and increase in odds of detection) led to probabilities of 0.052 and 0.118 of the model impact being greater than the trial impact.

Our results were robust against one-way variation in the natural history parameters of the model. By repeating our bootstrap restricting to the upper 10% and lower 10% of values for each of the input parameters in turn resulted in the sensitivity ranges for the probabilities reported in Table 1. The results for each parameter are displayed in Additional file 1.

DISCUSSION

This mathematical modelling study shows that even perfect implementation of all components of a complex intervention aimed at promoting early HIV and TB diagnosis and linkage into care in households of TB patients was unlikely to reproduce the ZAMSTAR trial impact on undiagnosed TB and TB transmission rates at general community level, unless diffusion of behavior change beyond intervention households was assumed. Modelled impacts were consistent with those of the trial once transmission of behavior change during the index cases' treatment was assumed - whereby, for example, members of an intervention household were more likely to encourage

symptomatic friends or neighbors to seek TB investigations promptly.

This work is unique in having a variety of population measures of TB and HIV epidemiology, and demography, specific to the communities of interest, with which to parametrize and calibrate our model and the model itself was specifically designed for this intervention. Our approach to uncertainty in the natural history parameters for TB and its interactions with HIV means our conclusions are based on an average over runs and parameter values, weighted by their consistency with data from the trial. Our conclusions are therefore robust to variation in the underlying unobserved parameters.

The main limitation of this work is the lack of data relating to the type of behavioral change diffusion modeled here, as this was an unanticipated need. Detection characteristics are key to TB epidemiology and control, and are known to be difficult to measure. Our model had less difficulty generating the observed reduction in TB prevalence than the larger observed reduction in annual risk of *M.tb.* infection (ARI). This may be because our model does not include heterogeneity in TB cases' infectiousness other than smear status - an intervention that had a systematically larger impact in more infectious cases (for instance, those with more frequent cough and effective aerosolization), or in individuals with wider social contact networks, could reduce ARI more than prevalence. However, data do not exist to support this hypothesis, and the final prevalence survey found very similar levels of smear-positivity in the household and control arms (8). While the samples used in generating our conclusions generally agree well with measured quantities, we tended to underestimate the extent of intra-household HIV clustering. However, our conclusions were not sensitive to variation in this parameter.

The influence of social networks has been established for health-related behaviors and characteristics such as smoking (16), alcohol consumption (17), and obesity (18). This raises the possibility of indirect benefits for health interventions that seek to alter such behaviors, since there may be spillover of changes beyond individuals engaged directly by the intervention, mediated by social interactions. While such positive externalities or 'multiplier' effects are not well documented for public health interventions, they have been explored in detail for social interventions such as the Mexican *PROGRESA* program to improve school attendance (19–21). There has been speculation that similar indirect effects were involved in producing the impact of the DETECTB community active case-finding intervention for TB (22), however, and there is emerging evidence of spillover effects from an ongoing TB trial in Malawi (23). Interventions targeting behaviors relevant to infectious diseases stand to benefit twice from the indirect effects: once from transmission of behavior change, and again from infections averted. Designing effective behavioral interventions tailored to specific populations requires a sound understanding of the societies in question. Anticipating the potential for propagation of behavior change in interventions, and recording the data to quantify it where possible, is the first step towards being able to use mathematical models to generalize results from such trials to different settings.

While the management of household contacts of TB cases and the provision of IPT and ART in the households of newly detected TB cases are expected to generate individual- and household-level benefits, we conclude that an accompanying behavior change in the larger community outside the households reached is the most likely explanation for the observed population-level impact of the ZAMSTAR intervention.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

PJD, ELC and RGW contributed to the modelling approach. PJD designed and implemented the model, carried out the numerical experiments, analysed the results and wrote the first draft. NB, PGF and HA advised on the details of the trial, and its representation in the model. SF, AS and RH advised on the interpretation and analysis of trial data. SF analysed trial data specifically for use in this study. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

This work was supported by the Consortium to Respond Effectively to the AIDS TB Epidemic funded by the Bill and Melinda Gates Foundation [19790.01]; the Medical Research Council (UK) [G0802414 to R.G.W.]; and The Wellcome Trust [GR095878 to E.L.C.]. The funders had no involvement in the design, collection, analysis or interpretation of the data, in writing the report or in the decision to submit.

REFERENCES

1. WHO 2012. Global tuberculosis control 2012. Geneva: World Health Organization, 2012.

2. Ayles H, Schaap A, Nota A, Sismanidis C, Tembwe R, De Haas P, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. PLoS One. 2009;4(5):e5602.

3. Van't Hoog AH, Laserson KF, Githui WA, Meme HK, Agaya JA, Odeny LO, et al. High prevalence of pulmonary tuberculosis and inadequate case finding in rural western Kenya. Am J Respir Crit Care Med. 2011 May 1;183(9):1245–53.

4. Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. American Journal of Respiratory and Critical Care Medicine. 2007;175(1):87.

5. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro AE, Schaap A, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis. 2013;17(4):432–46.

6. World Health Organization. Systematic screening for active tuberculosis: principles and recommendations. 2013 [cited 2014 Apr 2]; Available from: http://apps.who.int/iris/handle/10665/84971

7. Ayles HM, Sismanidis C, Beyers N, Hayes RJ, Godfrey-Faussett P. ZAMSTAR, The Zambia South Africa TB and HIV Reduction study: Design of a 2x2 factorial community randomized trial. Trials. 2008;9(1):63.

8. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. The Lancet [Internet]. 2013 [cited 2013 Sep 12]; Available from: http://www.sciencedirect.com/science/article/pii/S0140673613611319

9. Bond V, Chilikwela L, Simwinga M, Reade Z, Ayles H, Godfrey-Faussett P, et al. Children's role in enhanced case finding in Zambia. Int J Tuberc Lung Dis. 2010 Oct;14(10):1280–7.

10. Chileshe M, Bond VA. Barriers and outcomes: TB patients co-infected with HIV accessing antiretroviral therapy in rural Zambia. AIDS Care. 2010;22 Suppl 1:51–9.

11. Murray EJ, Marais BJ, Mans G, Beyers N, Ayles H, Godfrey-Faussett P, et al. A multidisciplinary method to map potential tuberculosis transmission "hot spots" in high-burden communities. Int J Tuberc Lung Dis. 2009 Jun;13(6):767–74.

12. Murray EJ, Bond VA, Marais BJ, Godfrey-Faussett P, Ayles HM, Beyers N. High levels of vulnerability and anticipated stigma reduce the impetus for tuberculosis diagnosis in Cape Town, South Africa. Health Policy Plan. 2013 Jul;28(4):410–8.

13. Cassels S, Goodreau SM. Interaction of mathematical modeling and social and behavioral HIV/AIDS research. Curr Opin HIV AIDS. 2011 Mar;6(2):119–23.

14. Pickles M, Boily M-C, Vickerman P, Lowndes CM, Moses S, Blanchard JF, et al. Assessment of the population-level effectiveness of the Avahan HIV-prevention programme in South India: a preplanned, causal-pathway-based modelling analysis. The Lancet Global Health. 2013;1(5):e289–e299.

15. White RG, Orroth KK, Korenromp EL, Bakker R, Wambura M, Sewankambo NK, et al. Can population differences explain the contrasting results of the Mwanza, Rakai, and Masaka HIV/sexually transmitted disease intervention trials?: A modeling study. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2004;37(4):1500–13.

16. Christakis NA, Fowler JH. The Collective Dynamics of Smoking in a Large Social Network. New England Journal of Medicine. 2008;358(21):2249–58.

17. Rosenquist JN, Murabito J, Fowler JH, Christakis NA. The Spread of Alcohol Consumption Behavior in a Large Social Network. Ann Intern Med. 2010 Apr 6;152(7):426–33.

18. Christakis NA, Fowler JH. The Spread of Obesity in a Large Social Network over 32 Years. New England Journal of Medicine. 2007;357(4):370–9.

19. Angelucci M, De Giorgi G, Rangel MA, Rasul I. Family networks and school enrolment: Evidence from a randomized social experiment. Journal of Public Economics. 2010;94(3):197–221.

20. Bobonis GJ, Finan F. Neighborhood peer effects in secondary school enrollment decisions. The Review of Economics and Statistics. 2009;91(4):695–716.

21. Lalive R, Cattaneo MA. Social interactions and schooling decisions. The Review of Economics and Statistics. 2009;91(3):457–77.

22. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of

symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet. 2010 Oct 9;376(9748):1244–53.

23. Choko A, Chavula K, Wiley B, Mdolo A, Webb E, Butterworth A, et al. Periodic active case finding for TB in Blantyre-Malawi: a follow-on experience from active case finding in Harare, Zimbabwe. 44th Union Conference on Lung Health (poster). Paris; 2013.

24. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect. 1997;119:183–201.

25. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. Clin Infect Dis. 2012 Mar;54(6):784–91.

26. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet. 1999 Feb 6;353(9151):444–9.

27. Tostmann A, Kik SV, Kalisvaart NA, Sebek MM, Verver S, Boeree MJ, et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clin Infect Dis. 2008 Nov 1;47(9):1135–42.

28. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Natl Acad Sci U S A. 2010 Nov 9;107:19485–9.

29. Murray CJ, Salomon JA. Modeling the impact of global tuberculosis control strategies. Proc Natl Acad Sci U S A. 1998 Nov 10;95:13881–6.

30. Stover J, Johnson P, Hallett T, Marston M, Becquet R, Timaeus IM. The Spectrum projection package: improvements in estimating incidence by age and sex, mother-to-child transmission, HIV progression in children and double orphans. Sex Transm Infect. 2010 Dec;86 Suppl 2:ii16–21.

31. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. The Lancet Global Health. 2014;2(1):e23–e34.

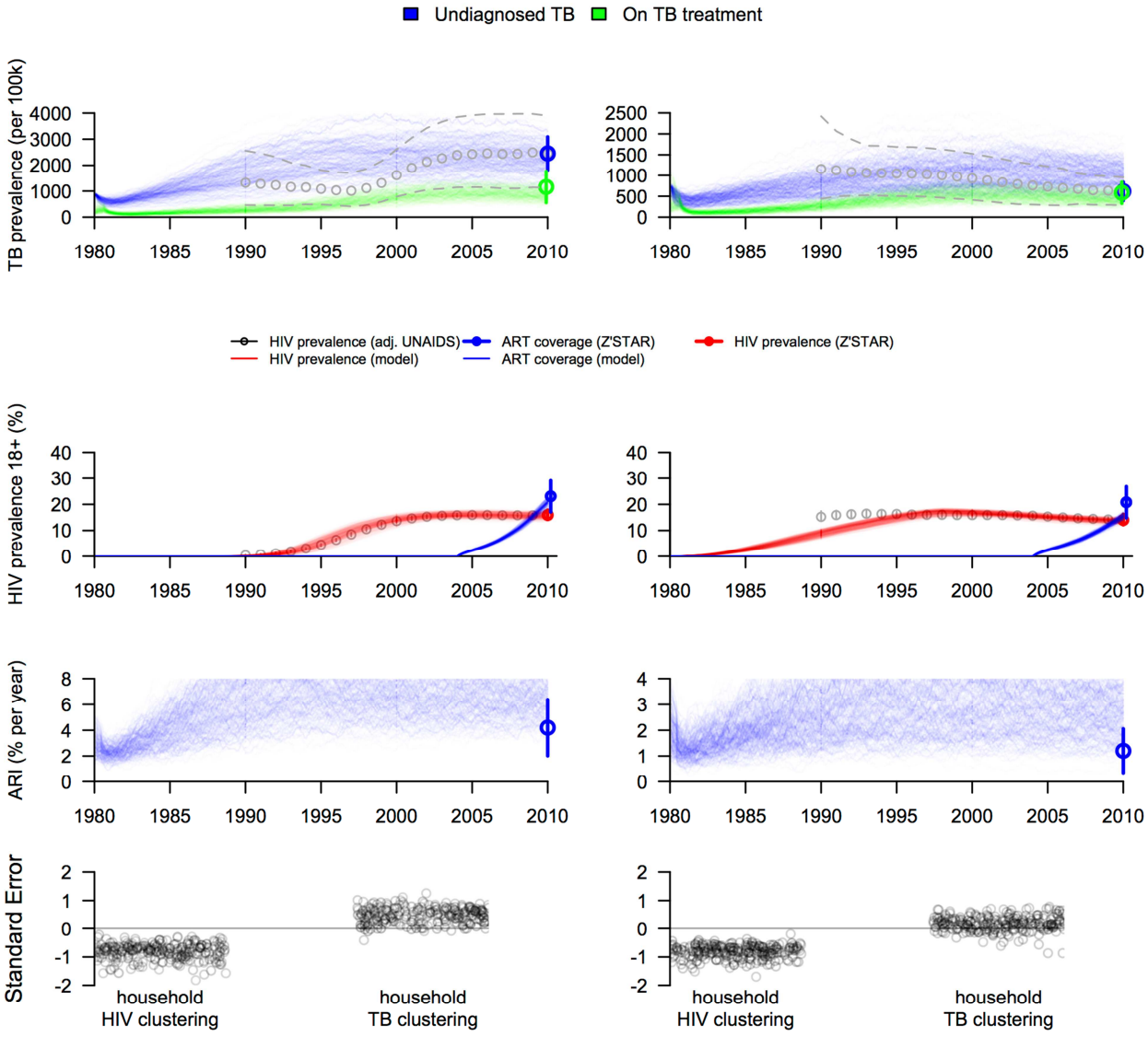
32. Dodd PJ, Looker, C, Plumb, I, Bond, V, Schaap, A, Shanaube K, et al. Mycobacterium tuberculosis infection incidence and social contact patterns in Zambia and South Africa. 2014. in submission.

33. World Population Prospects, the 2012 Revision [Internet]. UN Department of Economic and Social Affairs, Population Division. [cited 2013 Sep 13]. Available from: http://esa.un.org/wpp/Excel-Data/population.htm

34. Economic UND of I. Model life tables for developing countries. United Nations; 1982.

400

401 FIGURE LEGENDS



402

403

404

405

406

Figure 1: Visualisation of the ensemble of model runs and calibration targets. Left-hand panels are South Africa, right-hand panels are Zambia. Circles with confidence intervals represent data from the trial. The top panel shows the prevalence of undiagnosed TB (blue), and the prevalence of those on TB treatment (green). For reference, the WHO TB prevalence estimates for each country are shown in grey (circles are central estimates, dotted lines uncertainty ranges), with the prevalence rescaled to match the ZAMSTAR prevalence point estimate. The WHO data were not used in calibration. The second panel shows the model HIV prevalence (red) and ART prevalence among PLHIV (blue), and the UNAIDS country prevalence estimates in grey, scaled to match the ZAMSTAR point estimate. The third panel shows the annual risk of TB infection in children aged 5-12 (blue). The fourth panel shows the distribution of the difference between the modelled and the trial household HIV and TB clustering statistics, showing good agreement for TB clustering but some model undershoot for HIV clustering. Model data are displayed with opacity determined by goodness of fit.

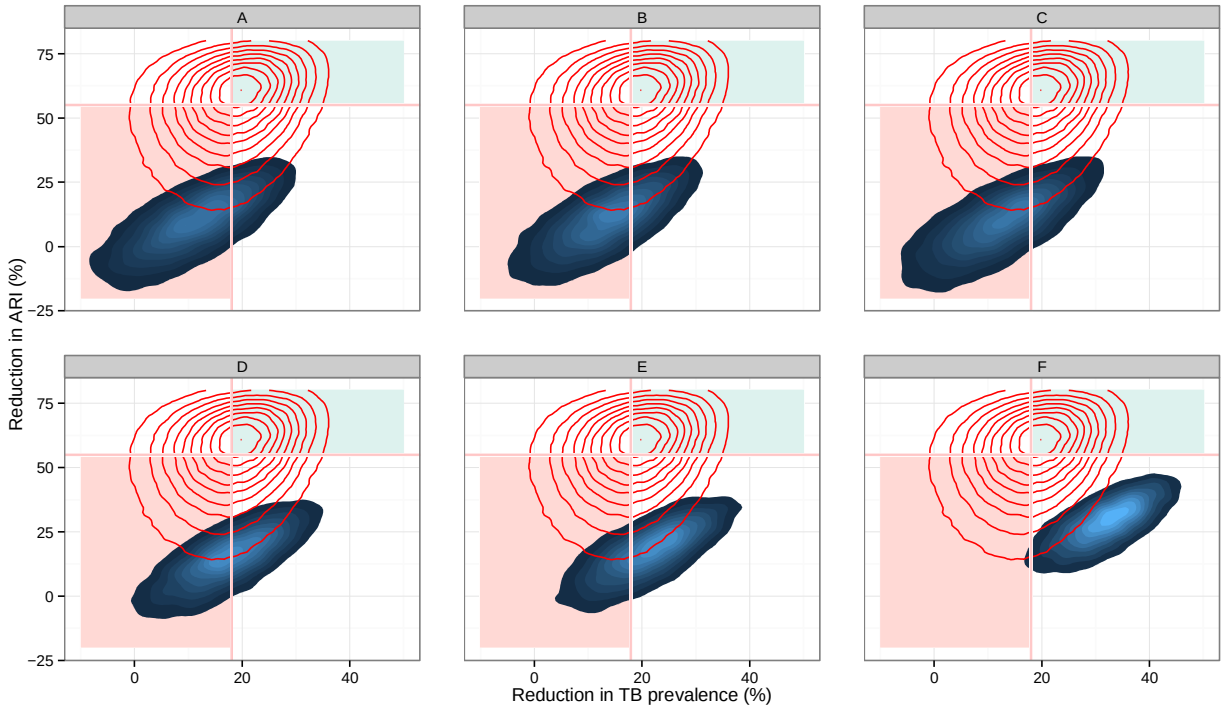


Figure 2: Model and trial impacts compared under different hypotheses for the intervention mechanism. The density of modelled impacts on TB prevalence and annual risk of infection (ARI) in blue, with the posterior density for the true ZAMSTAR trial impacts displayed with red contours. Cluster-level correlation between measured ARI and prevalence impacts are included (see Additional file 1). The red vertical and horizontal lines correspond to the trial impact point estimates. The region shaded pale red has smaller impacts than the trial point estimates; the region shaded pale green has both impacts larger than the trial point estimates. . All interventions included perfect coverage of the case-finding, IPT and ART components of the household intervention. Hypothesis A included no further elements. Hypotheses B-F allowed members of households reached by the intervention to permanently change their care-seeking behavior, so as to be detected and started on treatment with higher probability and shorter delay (B: 2x shorter detection delay; C: 2x odds of detection; D: 10x odds of detection and 10x shorter

detection delay). Hypotheses E and F also allowed members of households still receiving the intervention to transmit care-seeking behavior changes to others in the population (E: 1.5x odds of detection and 1.5 shorter detection delay, diffusion coefficient 2/yr; F: 1.5x odds of detection and 1.5 shorter detection delay, diffusion coefficient 5/yr.)

TABLES

Intervention assumption	Probability model impact exceeds true impact	Sensitivity range
A: No behaviour change	0.023	[0.015 - 0.036]
B: 2x shorter detection delay	0.026	[0.016 - 0.043]
C: 2x odds of detection	0.024	[0.016 - 0.039]
D: 10x odds of detection and 10x shorter detection delay	0.040	[0.029 - 0.067]
E: 1.5x odds of detection and 1.5 shorter detection delay, diffusion coefficient 2/yr	0.052	[0.042 - 0.089]
F: 1.5x odds of detection and 1.5 shorter detection delay, diffusion coefficient 5/yr	0.118	[0.098 - 0.163]

Table 1: The probability that the modelled trial impacts on TB prevalence and transmission were both larger than the trial results, under various assumptions about unobserved changes care-seeking behavior. All interventions included perfect coverage of the case-finding, IPT and ART components of the household intervention. Assumptions B-F allowed members of households reached by the intervention to permanently change their care-seeking behavior, so as to be detected and started on treatment with higher probability and shorter delay. Assumptions E and F allowed members of households still receiving the intervention to transmit care-seeking behavior changes to others in the population. The Monte Carlo relative standard error in these probabilities had a median of 1%, and the sensitivity range obtained by repeating the bootstrap twice for each model parameter: restricting samples the top and then the bottom decline for each parameter.

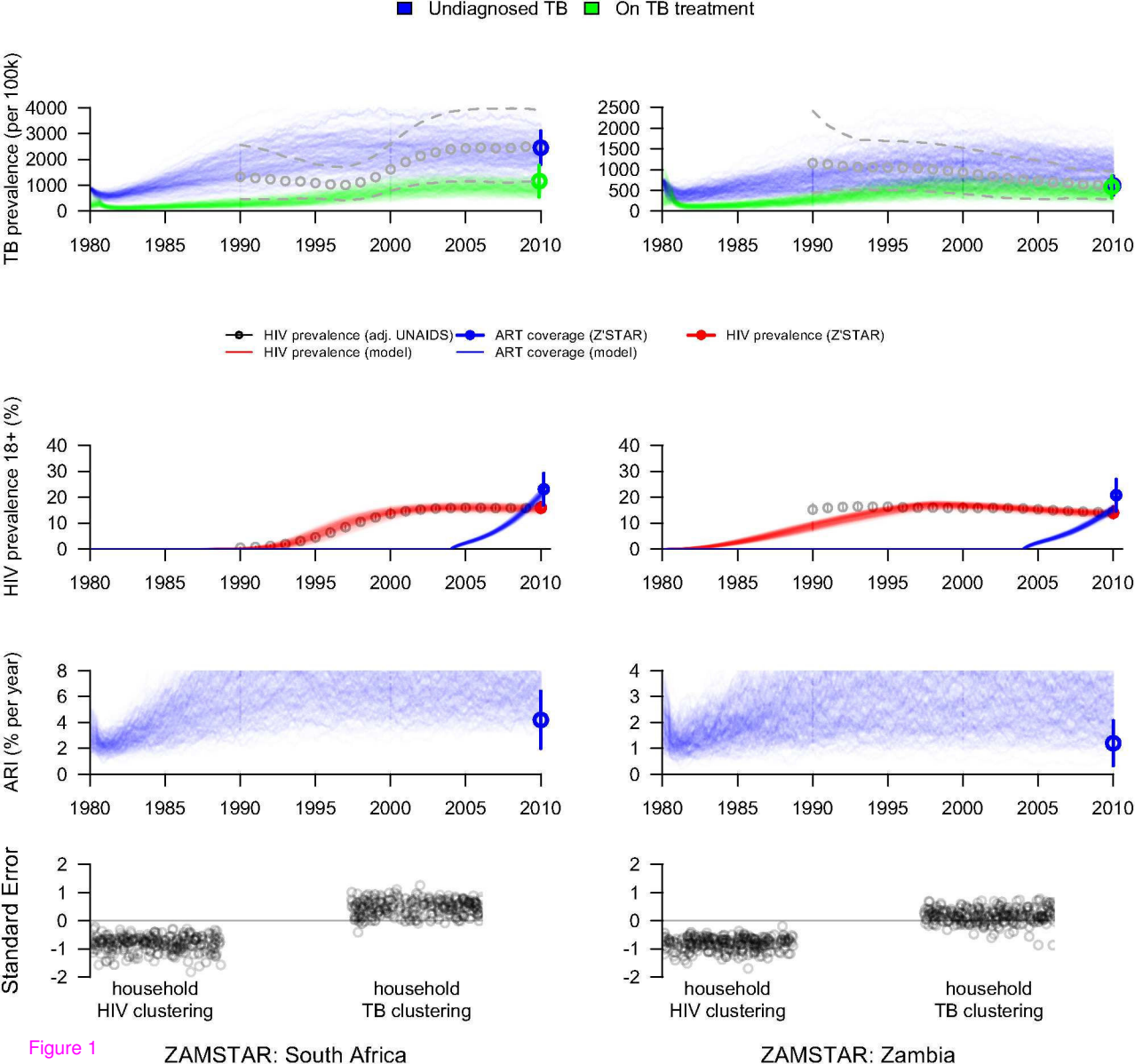


Figure 1

ZAMSTAR: South Africa

ZAMSTAR: Zambia

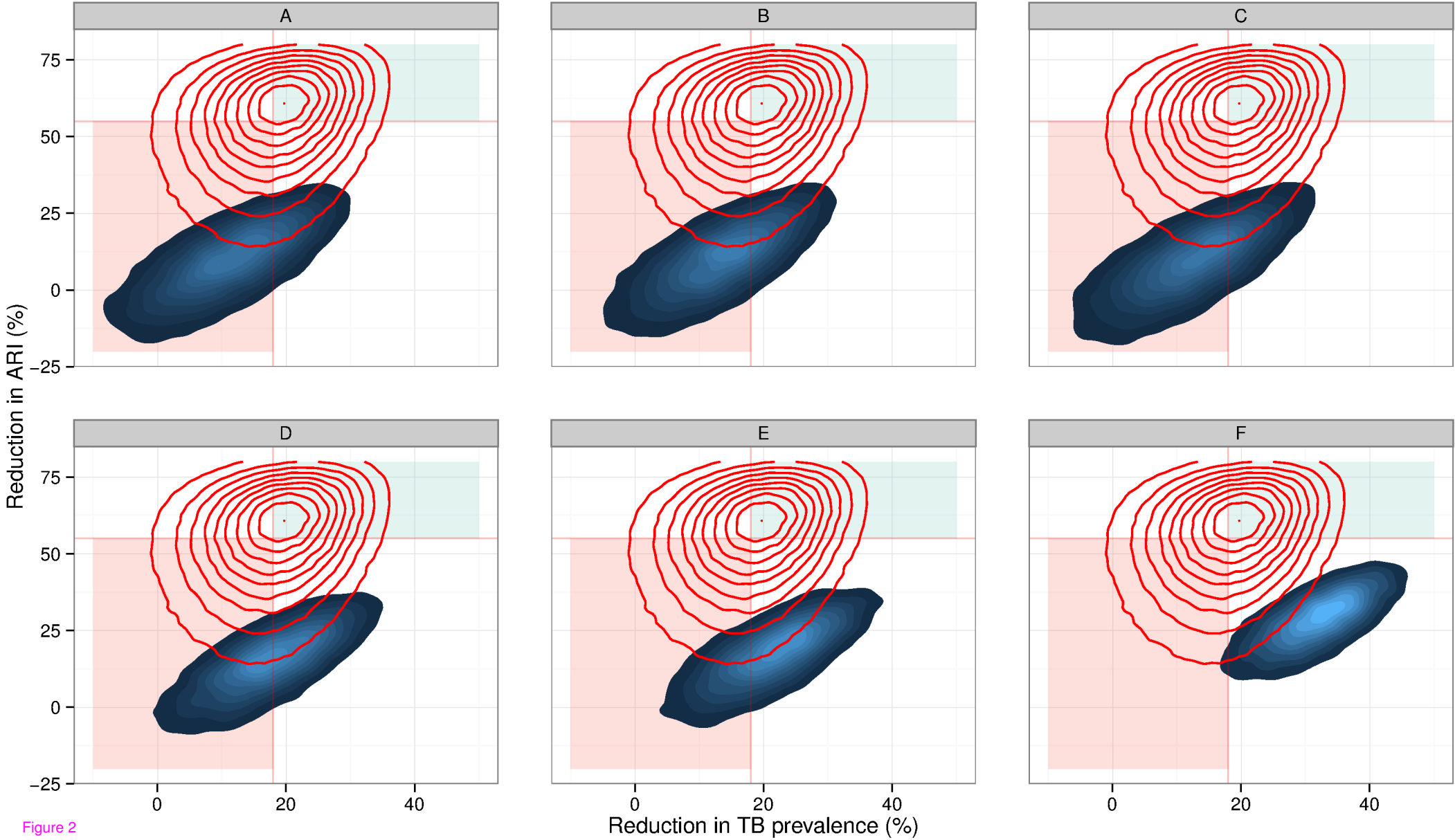

A
B
C
D
E
F
75
50
25
0
−25
0
20
40
Reduction in ARI (%)
Reduction in TB prevalence (%)

Figure 2

Additional files provided with this submission:

Additional file 1: ZAMSTAR_si_submit.pdf, 2648K
http://www.biomedcentral.com/imedia/5700415511472446/supp1.pdf