IJTLD state of the art review: The effect of general-population systematic tuberculosis screening on case notification rates

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ABSTRACT

Background: Understanding how TB case notification rates (TB-CNR) change with TB screening and their association with underlying TB incidence/prevalence could inform how they are best used to monitor screening impact.

Methods: We undertook a systematic review to identify articles published between 1/1/1980-13/4/2020 on TB-CNR trends associated with general-population TB screening. Using a simple compartmental TB transmission model, we modelled TB-CNRs, incidence and prevalence dynamics during 5 years of screening.

Results: From 27,282 articles, seven before/after studies were eligible. Two involved population-wide screening. Five used targeted screening. The data suggest screening is associated with initial increases in TB-CNRs. Increases were greatest with population-wide screening, where screening identified a large proportion of notified people with TB. Only one study reported on sustained screening; TB-CNR trends were compatible with model simulations. Model simulations always showed a peak in TB-CNRs with screening. Following the peak, TB-CNRs decline but are typically sustained above baseline during the intervention. Incidence and prevalence decrease during the intervention; the relative decline in incidence is smaller than the decline in prevalence.

Conclusions: There were few published data on TB-CNR trends with TB screening. These data are needed to identify generalisable patterns and enable method development for inferring underlying TB incidence/prevalence from TB-CNR trends.

Keywords: active case-finding; enhanced case-finding; community; mathematical modelling, incidence, prevalence

INTRODUCTION

An estimated three million people with tuberculosis (TB), ~30% of those with incident disease, are either not diagnosed or not reported through national TB programmes each year[1]. Systematic TB screening (henceforth called TB screening), where individuals at risk of TB are systematically identified using any test/procedure[2], can contribute to closing this case-detection gap. For TB screening to be effective, people with TB in the community who would otherwise remain undiagnosed or be diagnosed after a long delay, need to be identified and linked to care[2, 3]. This should decrease the prevalence of infectious TB in the community and therefore TB transmission and incidence[2, 3]. Recent World Health Organization guidelines recommend general-population TB screening where TB prevalence is ≥0.5% and in sub-populations with structural risk factors for TB[2]. However, there is currently no standardised way to measure and monitor the impact of TB screening to guide local decision-making. As countries renew their interest in TB screening to find, test and treat "the missing millions", this gap needs to be urgently addressed.

When measuring the effect of prevention interventions, incidence is the main outcome of interest. However, measuring TB incidence directly is not practicable; this would require long-term follow-up of very large cohorts, which is costly and logistically challenging. Prevalence surveys are often used by researchers but are also extremely resource-intensive and challenging to conduct routinely. TB case notifications collected under routine programmatic conditions are readily available data sources. In well-functioning healthcare systems, with complete, quality-assured surveillance data, TB case notification rates (TB-CNRs) can be a proxy for TB incidence[4]. But this is not the case in most TB endemic settings, where TB-CNRs may be substantially lower than incidence due to shortfalls in detection and reporting. Further, TB-CNRs can change when incidence does not; for example, changes to diagnostic tests and case definitions can alter TB-CNR trends.

With TB screening, we anticipate TB-CNRs should initially increase. As TB prevalence and incidence fall, TB-CNRs should subsequently fall. A recent systematic review evaluating if

TB screening increased TB-CNRs (measured as a single TB-CNR ratio), found mixed results[5]. But a single point estimate does not capture TB-CNRs dynamics over time. Understanding these dynamics, and the relationship between TB-CNRs and TB incidence/prevalence, could inform how TB-CNRs can be used to monitor the impact of screening on TB incidence. Therefore, we set out to: 1) systematically identify published trends in TB-CNRs under general-population TB screening; and 2) used mathematical modelling to simulate the TB-CNRs, incidence and prevalence dynamics we could expect with general-population screening, and determined the epidemiological factors influencing these dynamics.

METHODS

Definitions

In this paper we define these terms as follows: Passive case-finding (PCF) is the routine diagnosis of symptomatic individuals self-presenting to health services. Bacteriologically-confirmed TB is smear, GeneXpert MTB/RIF and/or culture positive TB. All TB is the sum of clinically-diagnosed and bacteriologically-confirmed TB. Baseline TB-CNR is the TB-CNR in the year before the start of screening. Screening coverage is the proportion of the target and/or whole population screened. Baseline case-detection rate (CDR) is the ratio of the number notified to the number of estimated people with incident TB, before screening was implemented.

Systematic review

Eligibility criteria – study designs, populations, interventions, comparators and outcomes

We included studies investigating the effect of general-population screening strategies on TB-CNR trends. Randomized trials and observational studies were eligible. Only studies conducted in general-populations, urban and/or rural, among adults (≥15 years) and children

or adults alone, were included. Screening could be population-wide or targeted to part of the population. Where screening was targeted but TB-CNRs reported for a wider population, the targeted population/s should have constituted ≥5% of the wider population, to distinguish from household contact management alone in high TB prevalence settings. Authors' judgement was used to determine if this was likely if data were not provided. General-population screening could be accompanied by screening in risk groups (e.g household contacts). The comparator was PCF, either in the same population before screening was introduced and/or in a control population, or another screening strategy.

The outcomes were bacteriologically-confirmed and all TB-CNRs. As we wanted to determine how screening affected TB-CNR trends, only studies reporting/allowing the calculation of ≥3 annualised TB-CNRs, before, during and/or after screening were included.

We excluded studies conducted before the DOTS strategy was introduced, as they do not represent contemporary TB epidemiology. Only articles published in English, French and Spanish were included.

Search strategy

A systematic review conducted by Kranzer 2013[6], synthesising data published between 1/1/1980-13/10/2010, investigated the population-level effects of TB screening. We updated this review using similar methods. Our search was nested within a systematic review conducted by Chaisson 2021[7], investigating the number needed to screen to detect a person with TB in any population. For the number needed to screen review, Pubmed, EMBASE, Scopus and the Cochrane Library were searched from 1/11/2010-13/4/2020. Subject headings and key words covered concepts of TB and screening (Appendix 1). Title, abstract and full-text screens were broad; original research studies reporting on screening for all TB were identified. These studies identified by the Chaisson 2021 review[7], and studies identified in the Kranzer 2013 review[6] were assessed for eligibility for our review.

Study selection was undertaken by a single reviewer. Initial shortlisting was based on titles and abstracts. Inclusion was based on full-text review of shortlisted studies.

Data extraction, synthesis and analysis

Data were extracted into case report forms. Variables extracted included study design, setting and population, PCF algorithm, screening strategy, co-interventions, proportion of the population targeted with screening, screening coverage, proportion of notifications identified by screening, number notified and TB-CNRs. Due to the heterogeneity of included studies (target populations, screening strategies), data synthesis was narrative.

Where screening coverage was not reported, and if screening was one-off/over short durations, coverage was calculated as the ratio of the number screened to the total population size assuming all individuals were only screened once. Where the proportion of notifications identified by screening was not provided, it was calculated as the ratio of the number of persons with TB identified by screening to the number notified during the intervention period assuming 70% of screened persons with TB were notified, as the literature suggests that ~30% of people with TB identified by screening are not treated[6].

Where only the numbers notified were reported, annualised TB-CNRs were calculated based on the reported population size without accounting for population growth, as growth rates of study areas was not known. If data were only graphically presented, data points were extracted directly from graphs using the Engauge Digitizer tool[8], with data re-plotted on the original scale (Appendix 2) to ensure extracted data accurately reflected original graphs. Data were recategorized where possible, so that annualised TB-CNRs (before, during and after screening) were calculated from the month and year that screening started; calendar years were used when this was not possible. TB-CNR ratios relative to baseline TB-CNR were calculated for the screened population. Where comparator groups were available, TB-CNR ratios (in screened versus control populations) were also calculated, and then ratios relative to the baseline TB-CNR ratio calculated. Confidence intervals around TB-CNR ratios

were not calculated, because summary notification data from multiple communities could not be adjusted for the clustered design. Only studies reporting notifications for >1 quarter following the end of screening were used to estimate post-screening TB-CNRs, so that annualised data did not only include the quarter during which spill-over events from screening were likely.

Mathematical modelling

We undertook a simulation study to illustrate the typical dynamics of TB-CNRs, true TB disease incidence and prevalence during 5 years of TB screening. We developed a simple compartmental TB transmission model employing a standard structure to represent the processes of infection, progression to disease, and detection. The model structure and parameters are detailed in Appendix 3.

The TB model structure was stratified by HIV-status. A single incidence rate ratio applied to all pathways to TB disease captured the impact of HIV on TB incidence. A shorter duration was modelled for HIV-infected compared to HIV-uninfected TB disease. Population size and HIV prevalence were assumed to be constant.

Screening was modelled as a hazard ratio applied to the per capita rate of transition from infectious prevalent disease to treatment (the patient diagnostic rate[9]). This screening hazard ratio can be thought of as a smoothed representation of the improvement in case-detection with repeated rounds of screening, and was assumed to scale-up to its maximum value over a scale-up timescale before returning to its baseline value instantly at the end of the intervention. A higher number of screening rounds detecting a lower proportion of prevalent TB would have an approximately similar impact to a lower number of screening rounds detecting a higher proportion of prevalent TB.[10]

We ran the model ordinary differential equations on 1,000 input parameter sets, drawn using Latin hypercube sampling from priors capturing the uncertainty in evidence around these parameters, as well as the screening hazard ratio and scale-up timescale. The initial state

was a heuristic, parametrized by initial force-of-infection (Appendix 3). The model was run for 100 years to avoid initial transients, and for 20 years from the intervention start (after which most intervention effects fade) to compute cumulative incidence and notifications.

Because different parameters result in different baseline TB-CNRs, incidence and prevalence, we rescaled output metrics relative to baseline values and recorded the size and timing of peaks in TB-CNRs and troughs in incidence and prevalence. Changes to cumulative notifications and incidence compared to a matched-parameter counterfactual (PCF without screening) were also determined. Sensitivity of output metrics to parameters was evaluated using partial rank correlation coefficients. Time series were aggregated over quarters to reflect recording systems.

RESULTS

Systematic review

From 27,282 articles, seven before/after studies (n=4 with control populations) were eligible; n=3 were from South East Asia[11-13], n=2 from South Asia[14, 15] and n=2 from sub-Saharan Africa[16, 17] (Figure 1 and Table 1). Screening was population-wide in n=2 studies (Datiko 2017 in Ethiopia[16] and Codlin 2018 in Cambodia[11]; although the primary focus was those ≥55 years in Codlin 2018[11]). Datiko 2017 involved house-to-house screening[16]. Screening was targeted in n=5 studies. Target groups included those with structural risk factors (n=1; Shewade 2019[14]), neighbours and households of people with TB (n=3; Fatima 2016, Morishita 2016 and Aye 2018[12, 13, 15]) and nomadic populations (n=1; John 2015[17]). Screening was house-to-house in n=3 targeted screening studies (Fatima 2016, one intervention in Aye 2018 and Shewade 2019[12, 14, 15]). All studies involved symptom screening, which was combined with chest radiographs in n=2 (Morishita 2016 and Codlin 2018[11, 13]). Only Datiko 2017, reported on sustained (over 4.5 years) repeated rounds of screening[16]. Screening was one-off[11, 13-15] or over short time-periods (1-2 years)[12, 17] in the

rest. All studies except Shewade 2019[14], used more sensitive diagnostic algorithms in the screened population (e.g. Xpert MTB/RIF), compared to routine PCF/services (Table 1). Co-interventions included monetary support and training to healthcare workers, improved diagnostic capacity and other (e.g. public-private mix) case-finding activities.

Figure 2 summarises annualised TB-CNRs compared to baseline. While there were year-on-year fluctuations in TB-CNRs prior to screening, the overall trend was downward for both bacteriologically-confirmed and all TB. An approximately two-fold initial increase in TB-CNRs was observed with population-wide screening (Datiko 2017[16] and Codlin 2018[11]). In both studies, a large reported/calculated proportion of notifications was due to screening (range ~50-66%; Table 1). While Codlin 2018 did not report on all TB trends, aggregated data showed an 89% increase in people with all TB compared to expected notifications during the intervention period[11]. In Datiko 2017, while bacteriologically-confirmed and all TB-CNRs remained higher than baseline/control during the intervention (Figures 2-3), notifications peaked in years 1-2 and then decreased over time[16]. But data on screening coverage by year were not provided.

Targeted screening resulted in increases in bacteriologically-confirmed and all TB CNRs compared to baseline and/or control populations, but the magnitude of these increases were lower than with population-wide screening (Figures 2-3). In John 2015, Nigerian nomadic populations with risk factors for TB and poor healthcare access were screened. Estimated bacteriologically-confirmed and all TB-CNRs were higher than baseline (~1.3-1.6 fold) state-wide during the intervention[17]. Screening coverage is likely underestimated (~3% of the total population and ~21% of the target nomadic population screened, but case-finding and referral by community volunteers continued following screening days), and screening contributed ~23-26% of state-wide notified TB (Table 1). In other studies, screening coverage ranged from ~5-13% of the total population and contribution of screening to notifications from ~3-18% where these could be calculated (Table 1), with lower estimated increases in TB-CNR ratios (~1.1-1.3 fold; Figures 2-3)[12-15].

There were limited data on post-screening TB-CNRs (Figure 4). In Codlin 2018, bacteriologically-confirmed TB-CNRs returned to baseline values in the year following screening[11]. In Morishita 2016, bacteriologically-confirmed and all TB CNRs were below baseline values in the 1.5 years following screening[13].

Mathematical modelling

The simulated TB-CNRs, incidence and prevalence dynamics are shown in Figure 5. Figure 6 shows the direction and strength of the association between output metrics and parameters. The mean baseline TB incidence considered was 151 per 100,000 years (interquartile range 52–181 per 100,000 years).

An initial peak in TB-CNRs always follows the start of the intervention (Figure 5A). The height of the peak is largely determined by the screening hazard ratio (Figure 6, 1st-column), and its timing by the screening scale-up timescale. Because prevalence decreases as case-detection increases, the relative peak in TB-CNRs is almost always less than the screening hazard ratio quantifying the improvement in case-detection. For interventions that scale-up very rapidly or instantaneously, the TB-CNR peak occurs in the first time-period after the intervention starts. TB-CNRs decline after the peak but are typically sustained above baseline levels during the 5 year intervention period. Unlike TB-CNRs, incidence rates decline throughout the intervention period (Figure 5B). The relative incidence trough size is usually smaller than the TB-CNR peak, being on average 47% (interquartile range 32–61%) the size of the TB-CNR peak (Appendix 3), and depends most on (and increases with) the screening hazard ratio and the proportion of transmission that is recent (Figure 6, 2nd-column). Reductions in prevalence are relatively larger than reductions in incidence (Figure 5C). The trough is lower with higher screening hazard ratios, but shallower with higher baseline TB prevalence (Figure 6, 3rd-column).

At the end of the intervention, TB-CNRs fall sharply below baseline (notification trough), before rebounding to baseline levels. Prevalence rebounds with the same timescale as TB-

CNRs (they are proportional in the model). Unlike TB-CNRs and prevalence, incidence rates gradually rebound, as progression to disease following transmission takes time. Initial median rebound doubling times for relative TB-CNRs and incidence are ~6 months and ~9 years respectively.

Cumulative incidence is always lower with screening than without; larger relative reductions are more likely with higher screening hazard ratios and proportion of incidence from recent infection (Figure 6, 7th-column). Cumulative TB-CNRs can be either higher or lower with screening than without, and are more likely to be lower when the proportion of incidence from recent infection, baseline CDR, and HIV prevalence are higher (Figure 6, 8th-column).

DISCUSSION

We undertook a systematic review to identify literature on TB-CNR trends and used mathematical modelling to simulate TB-CNR, incidence and prevalence dynamics, associated with TB screening. Model simulations always showed a peak in TB-CNRs with screening. The timing of this peak is determined primarily by the screening scale-up timescale, and its height relative to baseline by the hazard ratio describing the impact of screening on case-detection (i.e. the relative increase in patient diagnostic rate). The relative drop in incidence is typically smaller and increases throughout the intervention. Synthesising data published between 1980-2020, we found very few studies describing trends in TB-CNRs with general-population TB screening. The available data suggests screening is associated with initial increases in TB-CNRs. Only one study allowed effects of sustained screening to be examined; it showed dynamic changes to TB-CNRs, compatible with model simulations.

A key finding of the systematic review was the limited data on TB-CNR trends with sustained general-population TB screening. Trials have been conducted to demonstrate the population effect of TB screening[5]; but these trials, containing a wealth of information on screening

effort and TB epidemiology (e.g. prevalence), do not report TB-CNR trends. Further, several TB-REACH projects have undertaken general-population TB screening[5]; but again data on TB-CNR trends have not been published. While notification data are 'noisy', difficult to interpret and do not directly reflect incidence, if generalisable data patterns are identified this can facilitate method development for inferring underlying TB incidence/prevalence from TB-CNR data. Therefore studies/programmes should publish longitudinal TB-CNR data (before, during and after screening), along with information on screening coverage, cascade (from number eligible for screening to number initiated on treatment) and appropriate control populations, where available.

There are several challenges to interpreting the systematic review data. No randomised trials were identified. As most data were extracted from graphs, TB-CNR ratios are subject to error. TB-CNR ratios are crude and confidence intervals were not calculated. Irrespective of setting, target population or screening strategy, TB-CNRs initially increased. The increase was greatest with population-wide screening, where screening identified a large proportion of notified people with TB. With targeted screening, increases were modest and compatible with year-on-year fluctuations. But given the limited scope of the screening strategies (including being one-off/short-term), this is in keeping with model findings, where the height of the TB-CNR peak is primarily determined by the screening hazard ratio. Both bacteriologically-confirmed and all TB-CNRs typically increased with screening, suggesting limited roles for increased false-positive clinical diagnoses or displacement of diagnoses from clinical to bacteriological categories due to more sensitive diagnostic tests. Co-interventions could also have contributed in part. But the TB-CNRs increased irrespective of the type of co-intervention and by magnitudes commensurate with screening strategy (i.e. population-wide versus targeted). Therefore, overall, the findings suggest screening is associated with true increases in TB-CNRs.

Screening should not be a one-off activity[18]. Previous modelling shows screening impacts, such as on the number of cases averted, are proportional to the number of screening

rounds[10]. But data on the optimal screening duration and frequency are needed to guide screening programmes. Even in most high TB prevalence settings, targeted screening is likely to be more feasible than population-wide screening. Studies did not report on sustained targeted screening, to allow longer-term trends in TB-CNRs to be determined. Only in Datiko 2017, was population-wide screening sustained[16]. In intervention communities, TB-CNR ratios compared to baseline initially increased and then fell, in keeping with model simulations. Changes in screening coverage could explain trends but were not reported. Data on the cost-effectiveness of different screening strategies at different TB prevalence thresholds are also needed to guide screening programmes. Where TB screening is implemented, monitoring and evaluation should follow World Health Organization recommendations[2], which focuses on the screening cascade and number needed to screen.

In the model, cumulative incidence is always lower with screening. Changes to incidence are slower and smaller than changes to TB-CNRs, and in part determined by the screening hazard ratio. The impact of screening on incidence and TB-CNRs is influenced by the proportion of incidence due to recent infection. When this is high, incidence is more responsive to decreases in prevalence due to screening, with larger reductions in incidence and cumulative notifications. Also, as shown previously[10], reductions in cumulative notifications are more likely with higher baseline CDRs; for poorly-performing PCF systems, more of the cases found by screening are ‘extra’ cases that would otherwise not have been found. Reductions in cumulative notifications are also more likely when HIV prevalence is higher. Decreases in cumulative notifications depend on decreased prevalence causing decreased transmission and therefore decreased incidence, outcompeting increases in case detection. Therefore higher HIV prevalence (with shorter timescales) shortens the feedback delay between reductions in prevalence and reductions in incidence, facilitating reductions in cumulative incidence, which in turn lowers cumulative notifications.

In the model, TB-CNRs decline rapidly from their peak due to rapid reductions in prevalence, even while enhanced case-detection is maintained, and dip below baseline at the end of the intervention. Two studies, both involving one-off screening, report conflicting data on post-screening TB-CNR changes. In Morishita 2016, where screening was targeted, post-screening TB-CNRs fell below baseline values[13], in keeping with model simulations. In Codlin 2018, with population-wide screening, post-screening TB-CNRs did not fall below baseline[11]. Increased awareness due to screening campaigns, especially those involving the whole population, may have durable effects on care-seeking and diagnostic practices, such that notifications do not sharply drop after the intervention ends. Other mechanisms such as care-seeking or transmission from outside the intervention populations may also contribute. More data on post-screening TB-CNR trends are needed, with research to understand observed trends.

For the systematic review, only four databases were searched with language restrictions. A single reviewer undertook study selection and data extraction. Therefore some relevant articles may have been missed. Publication bias and methodological quality of included studies were not assessed. Limitations of the modelling work include the neglect of any exogenous trends in transmission or routine detection, stochasticity, and considering prevalent TB as a single, uniformly infectious state. If people with TB found through screening are less infectious, impact on transmission may be lower.

In conclusion, based on mathematical modelling we expect TB screening to cause an initial peak and then decline in TB-CNRs. The peak size correlates with the intervention impact. Incidence declines during the intervention and is slower to rebound than TB-CNRs when the intervention ends. The very few studies we found in the literature suggest general-population TB screening is associated with initial increases in TB-CNRs. Only one study reported on sustained screening; TB-CNR trends were compatible with modelling expectations. The increasing adoption of resource intensive TB screening interventions makes publishing data

on TB-CNR trends, and understanding how to use routine notification data to measure screening impact, a priority.

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REFERENCES

1. World Health Organization. Global tuberculosis report 2020 [Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf.
2. World Health Organization. WHO consolidated guidelines on tuberculosis - Module 2: systematic screening for tuberculosis disease 2021 [Available from: https://apps.who.int/iris/bitstream/handle/10665/340255/9789240022676-eng.pdf.
3. Lonnroth K, Corbett E, Golub J, Godfrey-Faussett P, Uplekar M, Weil D, et al. Systematic screening for active tuberculosis: rationale, definitions and key considerations. Int J Tuberc Lung Dis. 2013;17(3):289-98.
4. Glaziou P, Dodd PJ, Dean A, Floyd K. Methods used by WHO to estimate the global burden of TB disease 2020 [Available from: https://www.who.int/tb/publications/global_report/TB20_Technical_Appendix_20201014.pdf.
5. Burke RM, Nliwasa M, Feasey HRA, Chaisson LH, Golub JE, Naufal F, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. Lancet Public Health. 2021.
6. 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.
7. Chaisson LH, Naufal F, Delgado-Barroso P, Alvarez-Manzo HS, Robsky KO, Miller CR, et al. State of the Art Review: A systematic review of the number needed to screen for active TB among people living with HIV. Int J Tuberc Lung Dis. 2021;*In press*.
8. Engauge Digitizer [Available from: http://markummitchell.github.io/engauge-digitizer/.
9. Borgdorff MW. New measurable indicator for tuberculosis case detection. Emerg Infect Dis. 2004;10(9):1523-8.
10. Dodd PJ, White RG, Corbett EL. Periodic active case finding for TB: when to look? PLoS One. 2011;6(12):e29130.
11. Codlin AJ, Monyrath C, Ky M, Gerstel L, Creswell J, Eang MT. Results from a roving, active case finding initiative to improve tuberculosis detection among older people in rural cambodia using the Xpert MTB/RIF assay and chest X-ray. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2018;13:22-7.
12. Aye S, Majumdar SS, Oo MM, Tripathy JP, Satyanarayana S, Kyaw NTT, et al. Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016. Int J Infect Dis. 2018;70:93-100.
13. Morishita F, Eang MT, Nishikiori N, Yadav RP. Increased Case Notification through Active Case Finding of Tuberculosis among Household and Neighbourhood Contacts in Cambodia. PloS one. 2016;11(3):e0150405.
14. Shewade HD, Gupta V, Ghule VH, Nayak S, Satyanarayana S, Dayal R, et al. Impact of Advocacy, Communication, Social Mobilization and Active Case Finding on TB Notification in Jharkhand, India. J Epidemiol Glob Health. 2019;9(4):233-42.
15. Fatima R, Qadeer E, Yaqoob A, Haq MU, Majumdar SS, Shewade HD, et al. Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection? PLoS One. 2016;11(11):e0165813.
16. Datiko DG, Yassin MA, Theobald SJ, Blok L, Suvanand S, Creswell J, et al. Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. BMJ Glob Health. 2017;2(4):e000390.
17. John S, Gidado M, Dahiru T, Fanning A, Codlin AJ, Creswell J. Tuberculosis among nomads in Adamawa, Nigeria: outcomes from two years of active case finding. Int J Tuberc Lung Dis. 2015;19(4):463-8.
18. World Health Organization. Principles and practice of screening for disease 1968 [Available from: https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17&isAllowed=y.

TABLES

1. **Summary of included studies (n=7)**

FIGURES AND FIGURE LEGENDS

1. **PRISMA flow diagram of review process.** [1]study selection process for the number needed to screen review (*Chaisson et al* 2021); [2]starting point of the systematic review; [3]previous systematic review by *Kranzer et al* 2013
2. **Case notification rates relative to baseline for included studies.** All ratios (y-axis) represent annualised TB case notifications rates, relative to the baseline notification rate (i.e. case notification rate in the year prior to the start of screening). Top graph shows ratios for bacteriologically-confirmed TB and the bottom graph for all TB. Each line is defined by both colour and marker shape. Each study is shown in a different colour. Line marker shapes categorise study populations (marginalised and vulnerable populations, neighbourhood and household contacts, nomadic population and general population). Morishita 2016(a) represents the 15 communities screened first and Morishita 2016(b) the 15 communities which were screened second.
3. **Case notification rate ratios (intervention versus control) relative to the baseline rate ratio for included studies.** All ratios (y-axis) represent annualised TB case notifications rate ratios in intervention compared to control communities, relative to the baseline case notification rate ratio (i.e. in the year prior to the start of screening). Top graph shows ratios for bacteriologically-confirmed TB and the bottom graph for all TB. Each line is defined by both colour and marker shape. Each study is shown in a different colour. Line marker shapes categorise study populations (general population, marginalised and vulnerable populations, and neighbourhood and household contacts). Morishita 2016(a) represents the 15 communities screened first.
4. **Case notification rates relative to baseline following the end of screening.** All ratios (y-axis) represent annualised TB case notifications rates, relative to the

baseline notification rate (i.e. case notification rate in the year prior to the start of screening). Solid line denotes all TB and dashed lines bacteriologically-confirmed TB. Marker shapes categorise study population (general population and neighbourhood and household contacts). Morishita 2016(a) represents the 15 communities screened first.

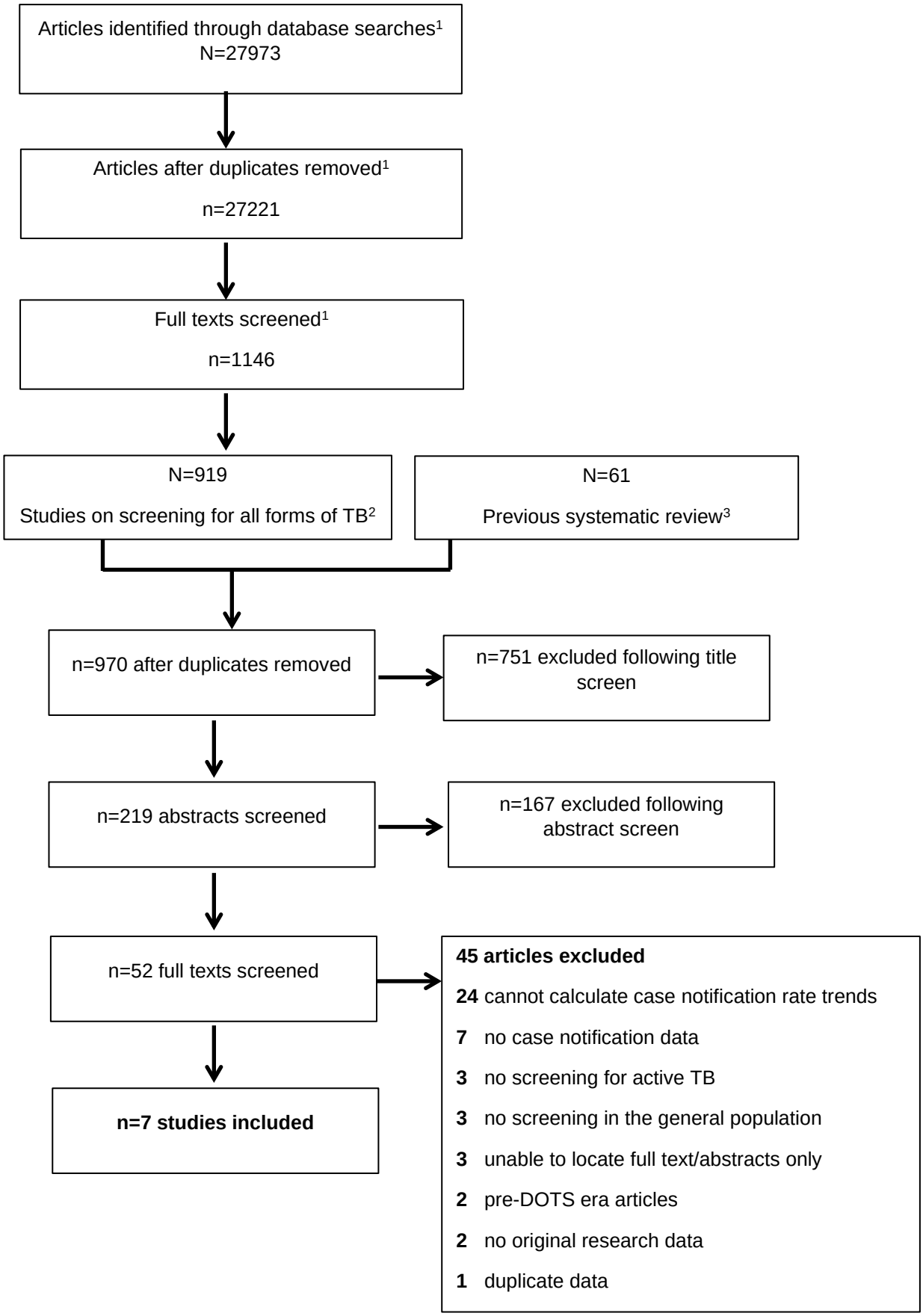
5. **Modelled dynamics of notifications (A), incidence (B) and prevalence (C) under TB screening.** All quantities are relative to the value at the start of the intervention (baseline); vertical dashed lines show the start and end of the intervention; red lines represent means and blue ribbons represent 95% quantiles.
6. **Factors most influencing modelled outcomes of TB screening.** The colour of tiles represents the sensitivity (measured by partial rank correlation coefficient) of a given metric (x-axis) to a given factor (y-axis). Red shades mean the metric increases with increases in the parameter; blue shades mean the metric decreases with increases in the parameter. Rows are ranked by the maximum absolute correlation coefficient for the associated factor. Screening HR = screening hazard ratio (intervention effect); CDR = baseline case-detection ratio; P:N ratio = baseline prevalence-to-notification ratio. TB prevalence and the proportion of TB incidence due to recent transmission are also at baseline. For troughs and peaks, the outcome is the height on the y-axis. Rebound timescales are quantified by initial doubling times during rebound.

Author; year; design	Country, setting and target group (where applicable)	PCF algorithm and screening strategy	Intervention period	Co-interventions	TB case definitions; outcome period	Screening target[1]; coverage[2]	Contribution of screening to outcome[3]	Additional information
Population-wide screening								
Codlin 2018 Before-after study	Cambodia - 4 rural districts with large catchment areas and limited health facility infrastructure. Population just over 1 million	PCF: smear microscopy for diagnosis of individuals self-presenting. Access to CXR is limited. Screening: 1 time, 1 day event in 75/78 district health facilities. 1-2 weeks before, TB IEC by village health support groups to catchment population. Intervention focused on those ≥55 years, but all symptomatics encouraged to attend screening with follow-up and transport enablers. Screening day - Symptom and CXR screening. Symptomatic + abnormal CXR - spot specimen for Xpert. Clinical review of CXR if Xpert negative	07/2013 to 03/2014	Monetary support to health facility staff for starting TB treatment and HH contact tracing	New bact+ TB Before, during and after screening	Target - all, but primary focus ≥55 years age group[4] Coverage – unable to calculate.	Calculated: Bact+ 56% All TB 51%	89% and 119% additional all and new bact+ notifications across all ages compared with trend-expected notifications during intervention period. In the 4 quarters after screening, bact+ notifications were 25% higher than trend expected.
Datiko 2017 Controlled before-after study	Ethiopia – rural and urban villages with limited health care access Intervention - Sidama zone. Population 3.5 million Control - Hadiya zone with similar characteristics. Population 1.2 million	Routine services include fortnightly HH visits by community workers, TB IEC and referring symptomatics to health centres, where smear microscopy is used for diagnosis. Screening: As above *AND* training community workers to symptom screen, collect sputum and prepare smears with transport to health facilities. Xpert testing for children, PLHIV and those symptomatic with 2 negative smears. HH contact screening.	10/2010 to 03/2015	Asymptomatic child (<5 years) HH contacts offered IPT. LED microscopes to high volume centres and Xpert machines to 2 centres	All TB Bact+ TB Before and during screening	100% targeted. Coverage – unable to calculate	66% of smear+ TB identified through screening	Intervention – smear+ CNR peaked at 129/100,000 in Q2 of Year 1. CNR fell by ~9%/year to 80/100,000 at intervention end ($p<0.01$). 37% decrease in all TB at intervention end ($p<0.01$). Control - CNR during intervention period similar to baseline ($p>0.1$)
Targeted screening								
Shewade 2019 Controlled before-after study	India - Jharkhand state which is mainly rural and one of the least developed states. 15/24 districts chosen Intervention – 36/43 TB units in the 15 districts Control – 7/43 TB units Target group – marginalised/vulnerable populations[5]	PCF: Smear microscopy for diagnosis of individuals self-presenting Screening: Intervention start staggered across the TB units. Community volunteers training. Vulnerable/marginalised populations[5] mapped. Media activities and one-off house-to-house visits with symptom screening. If symptomatic referred for sputum microscopy. Sputum collection if individuals had difficulty reaching the diagnostic centres.	2013-2015	Technical support to the NTP, engaging rural health care provider and NGO, strengthening district TB forums	All TB Bact (smear+) TB. Before and during screening	Target - no information. Coverage – unable to calculate	Unable to calculate	There was a significant change in smear+ and all TB CNR before and after screening was implemented in the intervention group (after adjusting for secular and seasonal trends and clustering).
Aye 2018 Controlled before-after study	Myanmar Intervention - 6 townships. Population 1.7 million Control - 7 townships. Chosen based on similar geographical area and population mix to intervention sites Target groups – neighbours (and HH contacts) of people with TB and all community members at identified sites	PCF: no information Screening: sites identified (using TB case spot maps) for community volunteer led activities[6]. Intervention 1: Bact+ TB diagnosed between 2012-2013 – neighbours (in the 10-30 surrounding HH) and HH contacts screened. Intervention 2: community IEC +/- mobile clinic. Both interventions: symptom screening. If symptomatic sputum collected and transported for microscopy. If positive escorted for treatment. Escorted for CXR if smear- but symptomatic, child <8 years or no sputum. 2 sites - Xpert if PLHIV, MDR contact or previous TB.	Intervention 1: 07/2014 to 12/2016. Intervention 2: started 07/2014; 2301 IEC sessions and 389 mobile clinics	Public-private mix case finding, NTP (mobile CXR units, contact tracing) and NGOs (community-based TB care)	All TB Before and during screening	Target – no information. Coverage (calculated) - ~13% of total population screened	by year for all TB: 2014: 5% 2015: 18% 2016: 18%	The average difference in CNRs between intervention and control townships decreased during the intervention period, from what it was before the intervention period. But this decrease was not statistically significant.

Fatima 2016 Before-after study	Pakistan - Punjab Province 4 districts with half the population living in slums. Population 18 million Target group - people living within a 50meter radius from a TB patient's HH (and HH contacts).	PCF: smear microscopy for those self-presenting. Xpert for MDR-TB contacts and patients with treatment failure. Screening: Index smear+ TB between 07/2013-06/2015 - field officers and lady health workers (primary and maternal health workers) conducted one-off symptom screening of people living within a 50meter radius from the index patient's HH and of HH contacts. If symptomatic sputum for microscopy. 2nd sample for Xpert if microscopy negative. CXR if unable to produce sputum. Contacted by project staff with results. Specialist paediatric care referral for child (<15 years) with presumptive TB.	07/2013 to 06/2015	-	New bact+ TB Before and during screening	Target – no information. Coverage (calculated) - ~5% of total population screened	Calculated: Bact+ 10% All TB 3%	8% and 7% increase in all and bact+ notified TB during the intervention period.
Morishita 2016 Before-after study with year of screening (1 or 2) determined by random allocation	Cambodia - 30 operational districts (OD) with high TB CNR (>125/100,000), poverty and health care access barriers. Intervention[7] – Year 1 15 ODs; Year 2 15 ODs Population ~2.9 million in 15 ODs Target group – neighbours (and HH contacts)	PCF: sputum microscopy for those self-presenting. Referral for CXR after antibiotic trial if TB still suspected. Screening: Smear+ TB treated in the preceding 2 years - Community volunteers/health worker visits HH and 10 neighbouring HHs. Symptom screen at neighbouring HH, with next-nearest HH included if few symptomatics (not defined). All HH and symptomatic neighbourhood contacts invited for one-off screening at health facilities. Screening with CXR and symptoms. Abnormal CXR - sputum for Xpert. Clinical assessment if Xpert-.	Year1 02/2012 to 12/2012 Year 2 05/2013 to 03/2014	-	All TB Bact+ TB Before and during screening for all 30 ODs. There are post-screening data over 18 months for the 15 ODs that received the intervention in Year1	Target – no information. Coverage – unable to calculate	Unable to calculate.	In all 30 ODs: 65% and 68% increase in all and bact+ TB compared to baseline. 46% and 53% increase in all and bact+TB compared to trend adjusted expected number. In the 15 ODs which received the intervention in Year1: 218% and 199% cumulative reduction in all and bact+ notifications in the 18 months after screening compared to trend adjusted expected number.
John 2015 Before-after study	Nigeria - Adamawa state. Total population 3.7 million, of which 12% (450,000) are nomadic with poor health care access, living in poorly ventilated, overcrowded tents with high levels of malnutrition Target group – nomadic population	PCF – smear microscopy for those self-presenting. Xpert for retreatment TB. Screening - series of community screening camps targeting nomadic communities. Health messages via radio and TV. Community volunteers from nomadic communities trained on TB detection and treatment support. 378 nomadic communities/settlements visited once throughout the implementation period. Screening days - IEC, systematic symptom screening of all present. Sputum for microscopy if symptomatic. Following screening day, community volunteers continued to identify symptomatics and refer them for microscopy. Xpert if x2 negative smears.	Jan 2012-Dec2013	Training on TB detection and treatment support provided to health care workers	All TB Bact+ (smear+) TB Before and during screening	Target 12%. Coverage (calculated) - ~21% of nomadic population screened; (~3% of total population)	Calculated[8]: Bact+ 23% All TB: 26%	Bact+ and all TB notifications increased by 50% and 24% compared to expected number. NB: NTP classified Xpert+ TB as smear- TB. Therefore "bact+" only refers to smear+ TB.

PCF=passive case finding; TB=tuberculosis; CXR=chest radiograph; IEC=information, education and communication, Xpert=GeneXpert MTB/RIF; HH=household; bact+=bacteriologically-confirmed; PLHIV=people living with HIV; IPT=isoniazid preventive therapy; LED=light emitting diode; smear+=smear positive; CNR=case notification rate; NTP=national TB programme; NGO=non-governmental organization; smear-=smear negative; MDR=multidrug resistant; Xpert-=GeneXpert MTB/RIF negative; TV=television; Xpert+= GeneXpert MTB/RIF positive

[1]proportion of the population targeted by screening; [2]proportion of the target population (or whole population) screened. Where these data were not available in the manuscript, this was calculated as the number screened/total population size, when screening was one-off or over a limited time period; [3]Proportion of notified TB that were identified by screening (unless otherwise indicated). Where these data were not available in the manuscript, it was calculated as the number of people with TB identified through screening/total number of notifications, assuming 70% of screen identified people with TB were notified;; [4]~10% Cambodian population ≥55 years in 2013 (https://www.populationpyramid.net/cambodia/2013/). [5]included slums, tribal areas, scheduled caste communities, areas where occupational lung diseases is high, areas where individuals with high risk of acquiring TB reside including stone crushing/mining/weaving industry/unorganized labour (construction workers etc)/homeless, high HIV/AIDS burden areas, areas or communities with high TB incidence (including prisons) and among household contacts of sputum smear positive TB patients; [6]Unclear if Intervention 1 and 2 were conducted in the same areas. [7]For the 15 Operational Districts that received the intervention in Year1, the 15 Operational Districts that received the intervention in Year2 provided comparator data for the period before and during screening. For the 15 Operational Districts that received the intervention in Year 2, there were no comparator data. [8]number of all TB notified provided in the manuscript. 94% of smear and Xpert positive TB were notified, but the proportion notified among smear positives, which was defined as bacteriologically-confirmed, was not provided.



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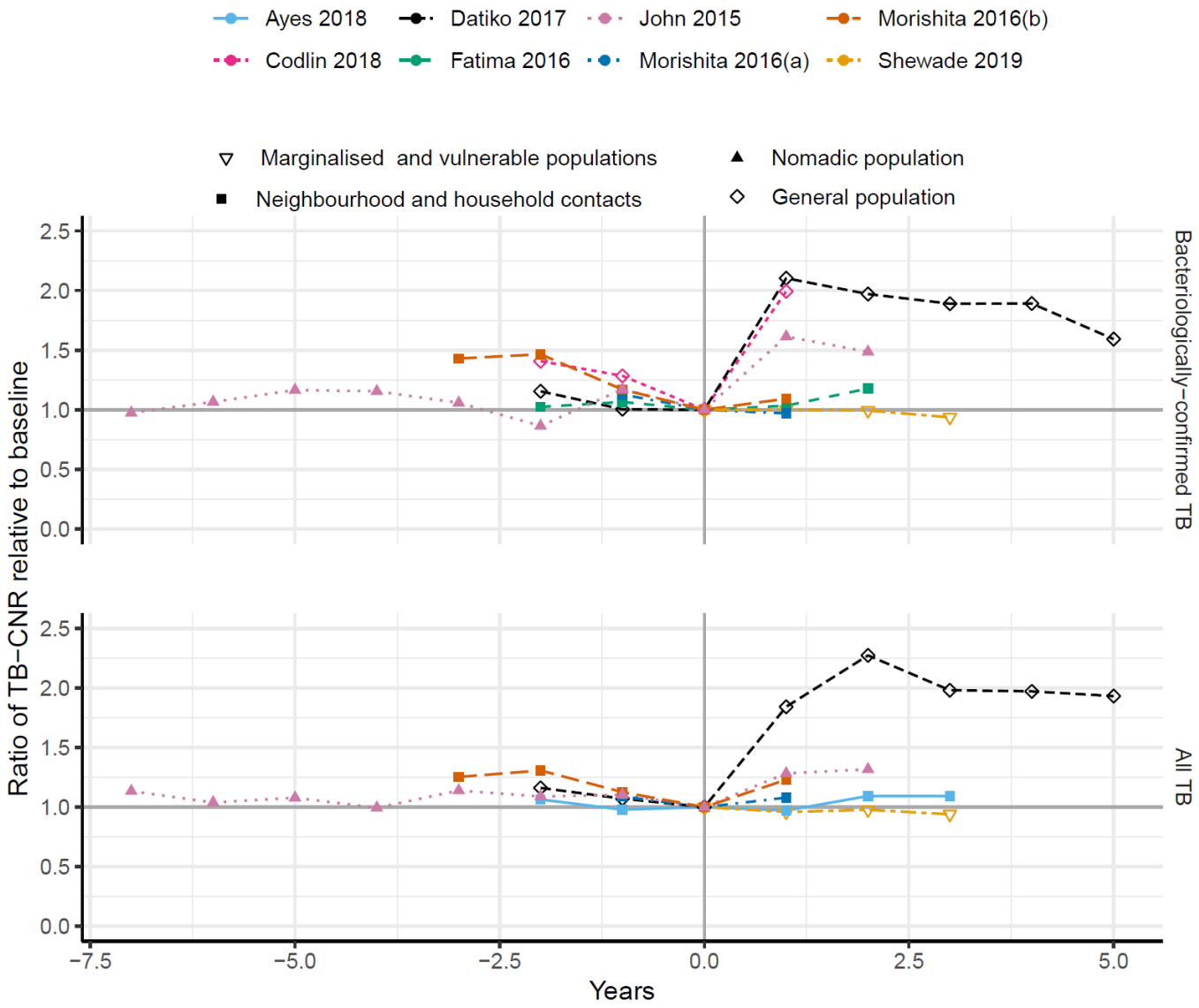

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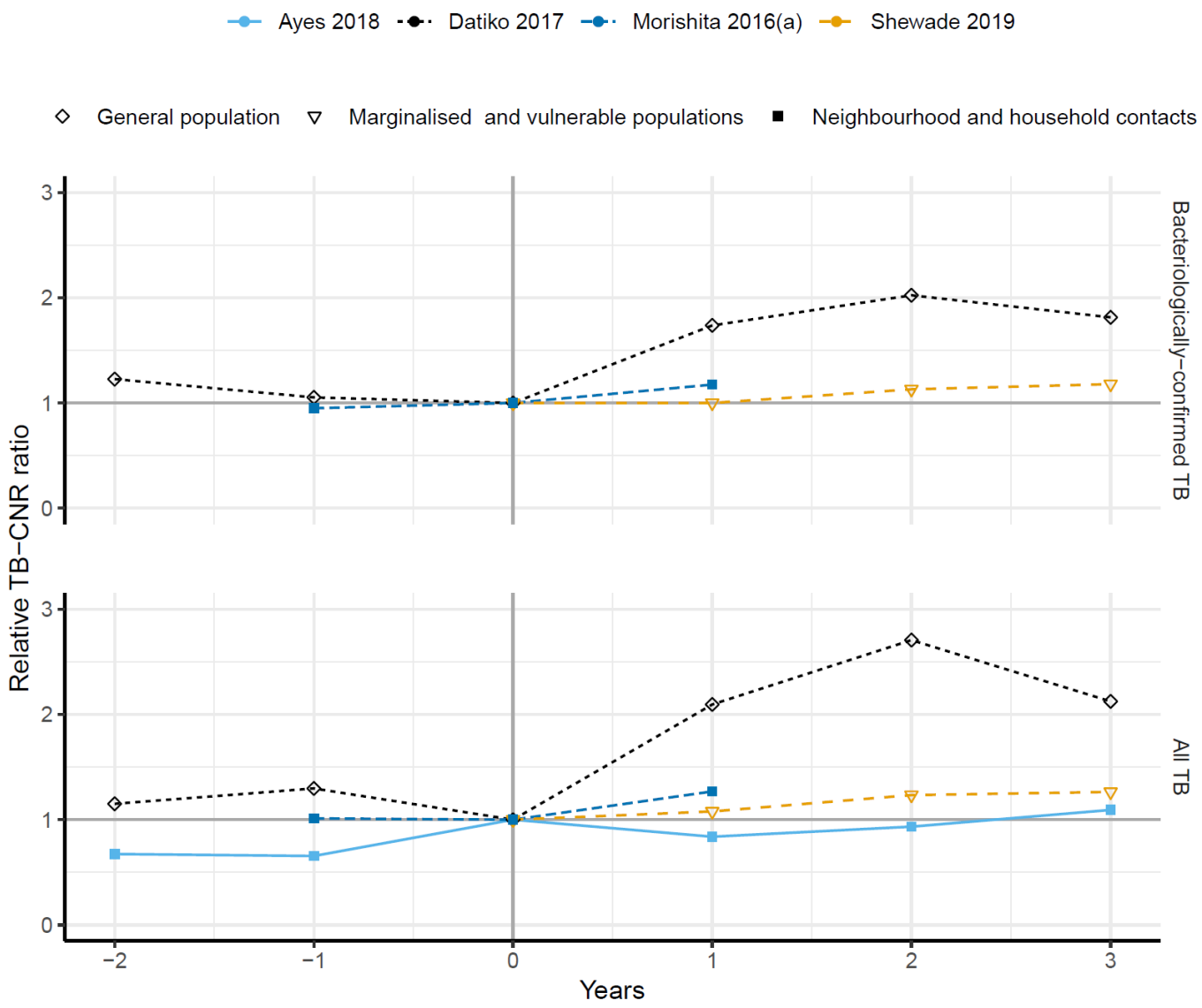

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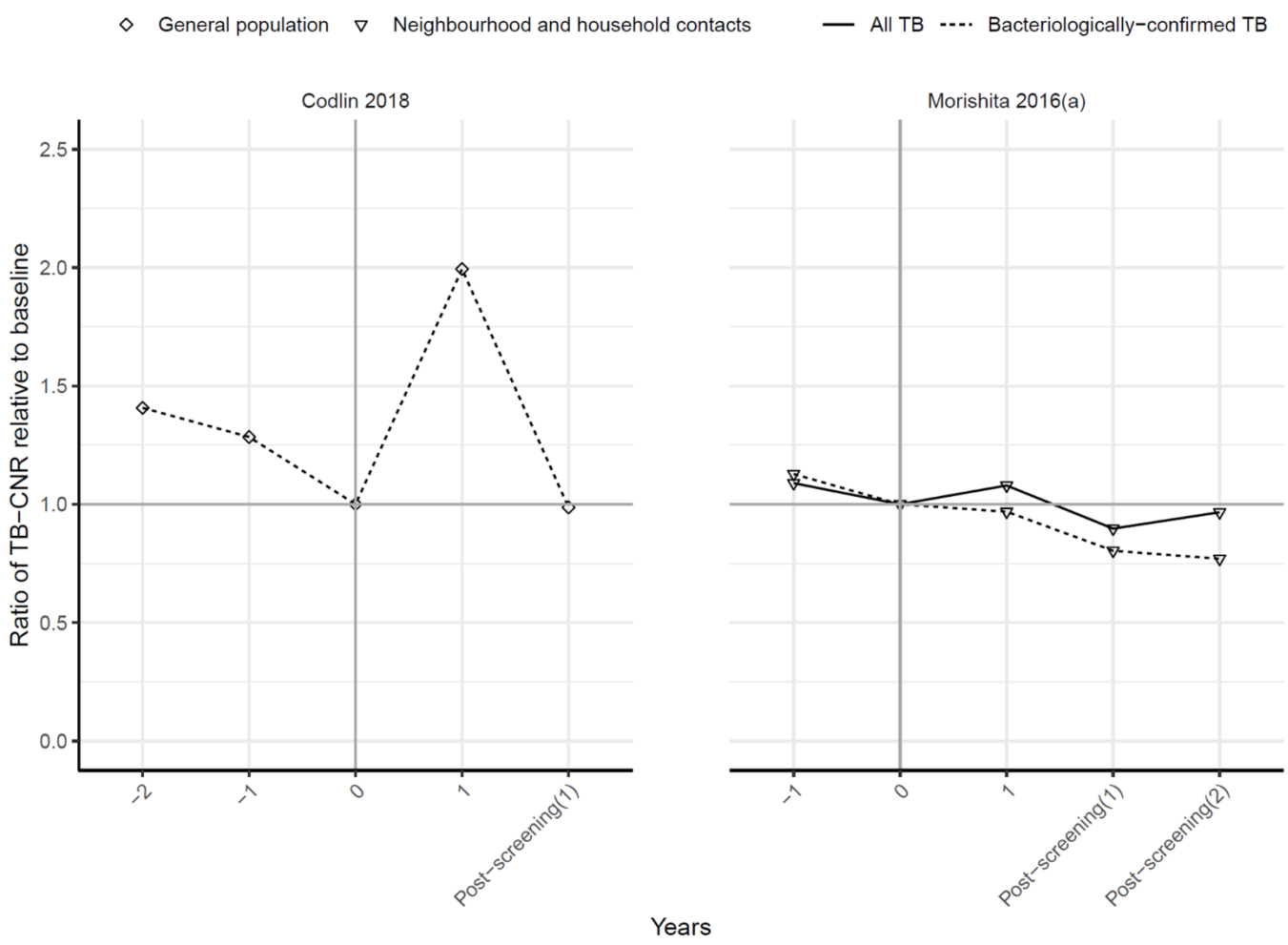

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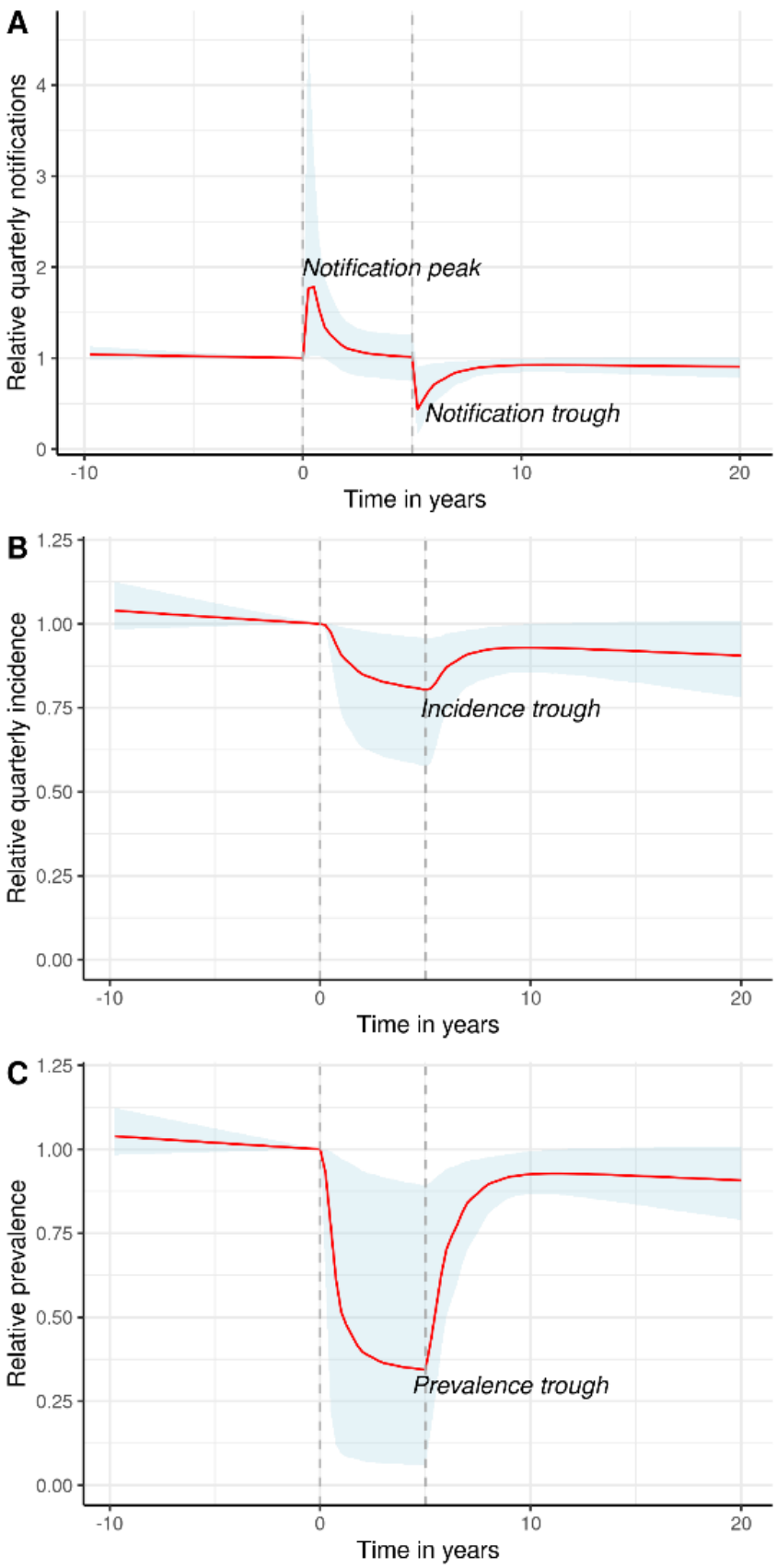

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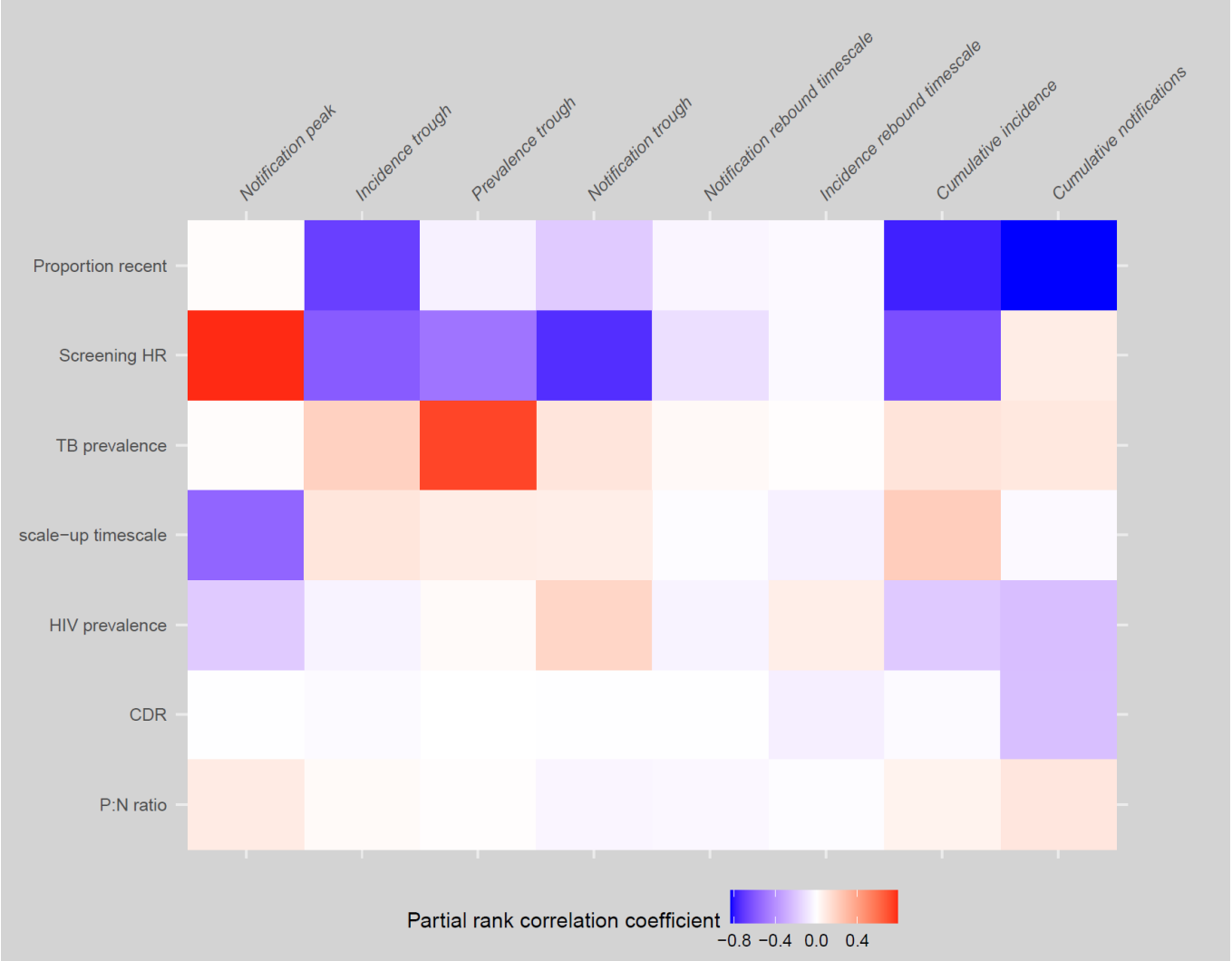

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