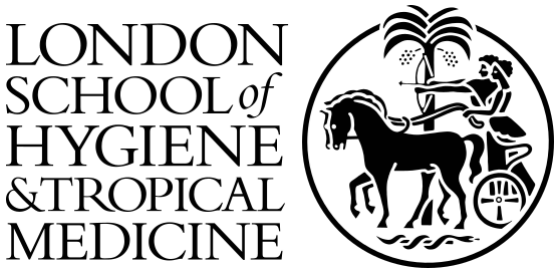

Can universal testing and treatment for HIV and community-wide active case finding for tuberculosis control the African tuberculosis epidemic?

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Abstract

Introduction: This thesis aims to address whether community-wide Universal Testing and Treatment for HIV (UTT) and systematic TB screening (TB screening), implemented by community health-workers, could control TB in high TB/HIV burden communities in sub-Saharan Africa and could improve the clinical outcomes of people with TB.

Methods and results: HPTN 071 (PopART) was a 3-arm cluster-randomised trial (CRT) conducted between 2013-2017 in 21 Zambian and South African communities. The intervention included UTT and TB screening in arm A. Arm B, received universal HIV testing with antiretroviral therapy (ART) according to national guidelines and TB screening. Arm C, the control, received the standard-of-care through routine services. A population cohort (PC) was established to measure the primary outcome of the trial (intervention impact on HIV incidence). This PhD, embedded within HPTN 071 (PopART) used the PC and routine TB notification data to address the study objectives.

A literature review found 18 observational studies which consistently showed increasing ART coverage was associated with decreased measures of population-level TB, and that TB notifications and diagnoses decreased coincident with increasing ART coverage. Decreases were greater among people living with HIV (PLHIV) than those who were HIV negative. In post-hoc analysis of a CRT of UTT, TB notification rates among PLHIV was 59% lower in the UTT arm compared to the control. While findings were consistent, study limitations prevent causal inferences. A systematic review identified seven general-population TB screening studies which suggested that TB screening was associated with initial increases in TB notifications. Among 38,474 PC-participants there was an ~45-50% decrease in self-reported TB incidence among PLHIV at the population-level in arm A compared to C, following the roll-out of the HPTN 071 (PopART) intervention. There was also some evidence that this translated to an ~50% decrease in incidence in the population overall.

Incidence in arm B and C was similar. No initial increases in self-reported TB in intervention arms were observed.

A systematic review found nine general-population studies (eight observational, one trial), which showed treatment success and case fatality were similar among individuals identified through screening and through routine care. In the Zambian arm A and B HPTN 071 (PopART) communities only 15% of people with TB starting treatment were identified through screening. Mode of diagnosis (community-wide TB screening versus through routine care) was not associated with treatment success or case-fatality. The odds of treatment success was 48% lower and case-fatality three times higher among PLHIV compared to those HIV-negative.

Conclusion: This thesis contributes to knowledge on the effect of UTT and TB screening on TB epidemiology. The data suggest that UTT could contribute to TB control. But, despite community-wide UTT, case-fatality among PLHIV with TB was high, highlighting their continued need for TB-prevention interventions.

Statement of own work

I Lilanganee Telisinghe, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

L Telisinghe (27th March 2024)

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Chapter 1: Introduction

An overview of the global TB epidemic

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* (MTB)[1-5]. TB is primarily spread through the airborne route, when an individual who has TB disease, generates aerosols with droplet nuclei containing MTB, through coughing, sneezing etc[1-6]. Infection with MTB can result in the clearance of infection, the control of infection by the immune system, or the progression from MTB infection to TB disease (Figure 1)[1, 2]. Of the quarter of the world's population estimated to be infected with MTB, only ~5-10% will ever progress to develop TB disease, over their lifetime[6, 7]. When a person develops TB disease, symptoms may be mild or go unrecognised, delaying healthcare seeking by months[1, 2, 8]. Indeed, there is growing evidence that a substantial proportion (median of ~50%) of prevalent undiagnosed TB is subclinical (i.e. has microbiological and/or radiological features of TB, but where individuals are asymptomatic or do not recognise they have symptoms), with subclinical TB also contributing to MTB transmission[8, 9].

There is effective curative treatment for TB disease[10]. Despite this, TB disease remains a major cause of morbidity and a leading cause of mortality from a single infectious agent worldwide[10]. Low- and middle-income countries are disproportionately affected by TB, with over 80% of all incident TB disease and deaths occurring in these settings[10]. Further, TB disease primarily affects adults, in the most productive years of their life[10]. Therefore, a United Nations Sustainable Development Goal target to ensure healthy lives and promote well-being for all at all ages, includes "ending the TB epidemic" by 2030 (Table 1)[11]. To END-TB the World Health Organization (WHO) has also set ambitious milestones and targets (Table 1): compared with 2015, a 20%, 50% and 90% reduction in TB disease incidence by 2020, 2025 and 2035 respectively, ultimately aiming to decrease TB incidence to <10 per 100,000 population by 2035[10, 12]. To this end, available tools need to be

optimised and used, in combination with universal health coverage, to accelerate the rate of decline in TB disease incidence to ~10% per year by 2025[10, 12].

But with current TB control efforts, the estimated global TB disease incidence rate was falling by only ~2% per year, with a reversal in trend between 2020 and 2022 due to the COVID-19 pandemic. The net reduction in TB disease incidence rate between 2015 and 2022 was ~9%; well below the 2020 and 2025 milestones[10]. The reduction in the number of TB deaths between 2015 and 2022, was only 19%[10].

Table 1: The World Health Organization End-TB Strategy milestones and targets for TB incidence and deaths

Measure	Milestones		Targets	
			SDG	END TB
	2020	2025	2030	2035
Reduction in TB incidence rate compared to 2015 (%)	20% (<85)[1]	50% (<55)[1]	80% (<20)[1]	90% (<10)[1]
Reduction in number of TB deaths compared to 2015 (%)	35%	75%	90%	95%

SDG = The United Nations Sustainable Development Goals include ending the TB epidemic by 2030;

[1]TB incidence per 100,000 population per year

The HIV associated TB epidemic in sub-Saharan Africa

The sub-Saharan African region has some of the highest TB disease incidence and mortality rates worldwide[10]. Of the 30 high TB burden countries globally (based on WHO estimated TB disease incidence), 17 (57%) are in sub-Saharan Africa[10]. Of these 17, six (~35%) have met the first END-TB strategy milestone of a 20% reduction in estimated TB disease incidence compared to 2015, but absolute incidence across the countries remains high (Figure 2)[10]. Nine (53%) have met the 2020 targets for decreased TB deaths[10]. Despite some gains in the region, countries still have a long way to go to meet the 2025 End-TB strategy targets. How current declines in TB disease incidence and TB mortality can be accelerated to achieve this using the current tools available, is unclear.

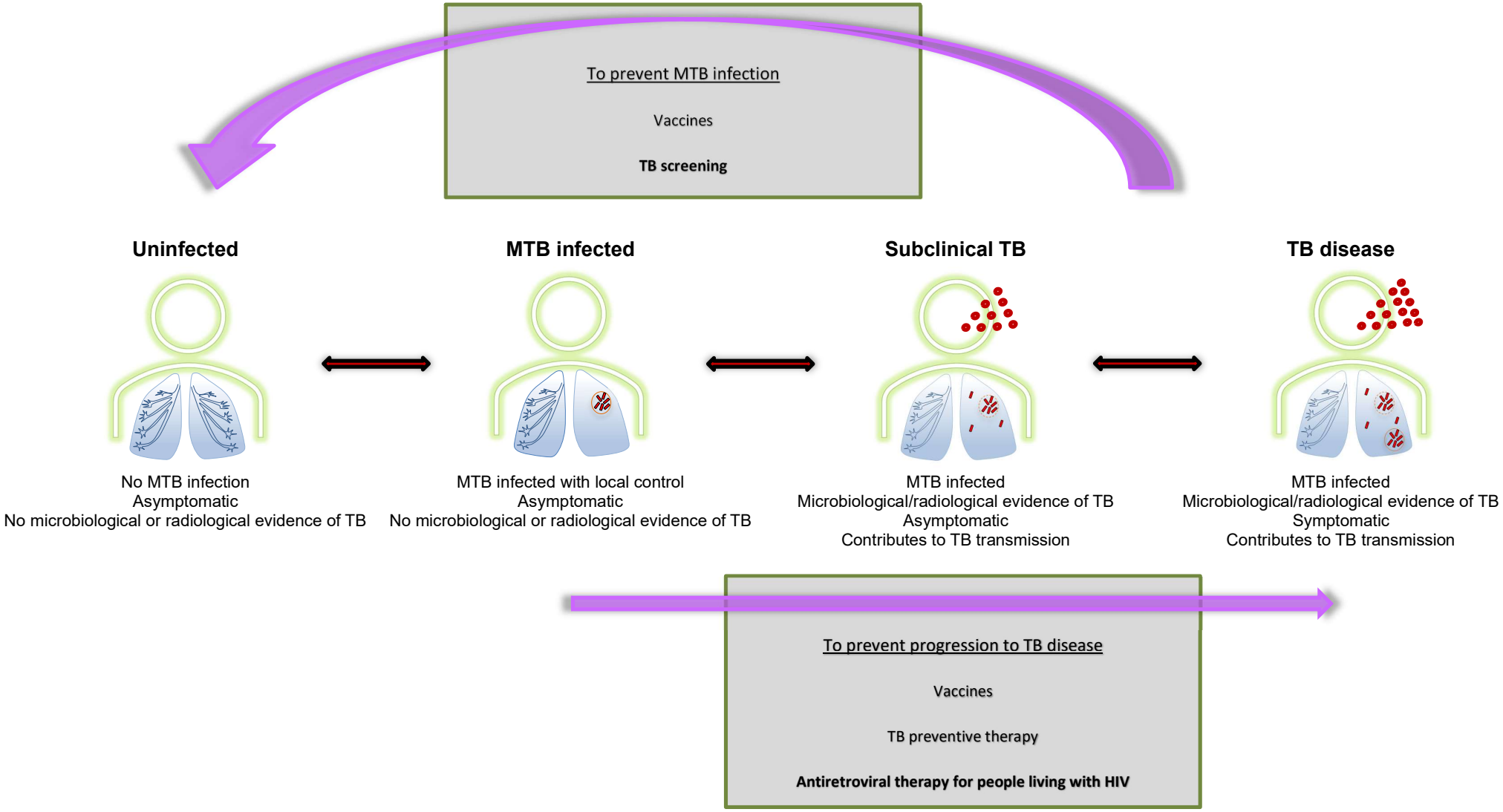


Figure 1: The spectrum of outcomes following infection with *Mycobacterium tuberculosis* (MTB) and the tools to prevent TB disease, which can be broadly categorised as tools to prevent progression to TB disease once infected with MTB, and tools to prevent infection with MTB

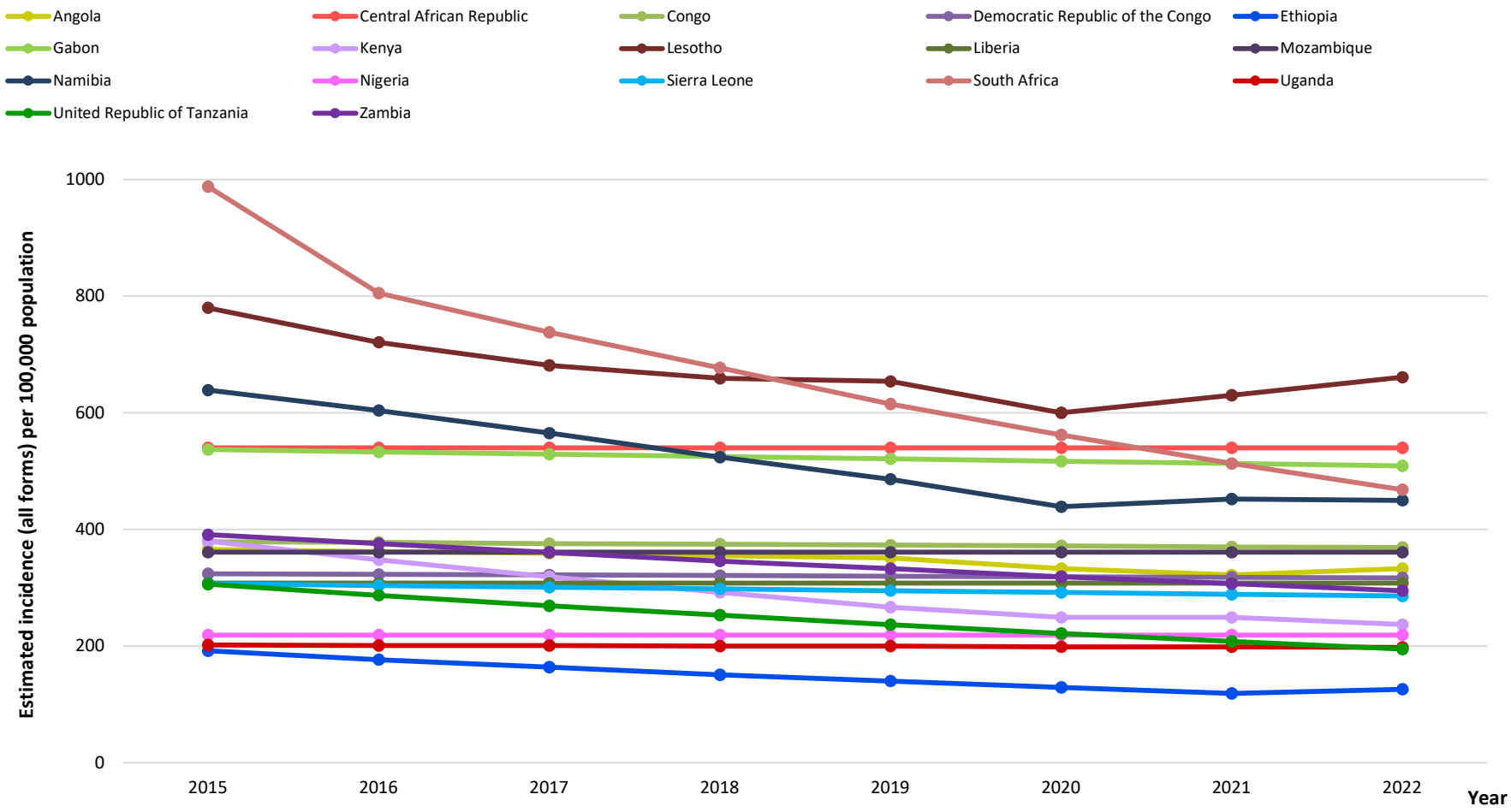


Figure 2: World Health Organization (WHO) estimated TB disease incidence (all forms) per 100,000 population between 2015 and 2022 for the 17 high TB burden countries (reproduced using data from the WHO Global TB Report 2023[10]).

In sub-Saharan Africa, the TB epidemic is mainly driven by the HIV epidemic[13-15]. Of the estimated 39.0 million people living with HIV (PLHIV) in 2022 globally, 66% and 53% were in sub-Saharan Africa and in southern and east Africa, respectively[16]. Similarly 51% and 38% of all estimated incident HIV infections occurred in sub-Saharan Africa and southern and east Africa, respectively[16]. HIV is a known potent risk factor for TB. Following infection with MTB, $CD4^+$ T-lymphocytes play an important role in the local control of MTB growth and its containment[17]. HIV primarily infects $CD4^+$ T-lymphocytes, resulting in a quantitative decline in their number and a qualitative decline in their function[18]. Consequently, HIV infection increases the risk of progressing to TB disease following recent and remote MTB infection[5, 19]. There is also some evidence to suggest that HIV infection may increase an individual's susceptibility to becoming infected with MTB, following exposure[5]. The risk of incident TB disease increases exponentially with decreasing $CD4^+$ T-lymphocyte count; an estimated 1.43 (95% credible interval: 1.16–1.88) fold increase in risk for each 100 cells/μL decrease in $CD4^+$ T-lymphocytes, from 1000 cells/μL[20]. Therefore, while the risk of TB disease among PLHIV is greatest with severe immune suppression, the risk is still high among PLHIV who have high $CD4^+$ T-lymphocyte counts, compared to those who are HIV negative.

During the 1990's, coincident with the rise in HIV prevalence, there was a steep rise in the estimated TB disease incidence in sub-Saharan African countries with a high prevalence of HIV (Figure 3)[14]. While the estimated TB disease incidence has decreased over time in southern and east Africa, where the HIV epidemic is concentrated, the proportion of people notified with TB disease who also live with HIV, continues to be high (Table 2)[10].

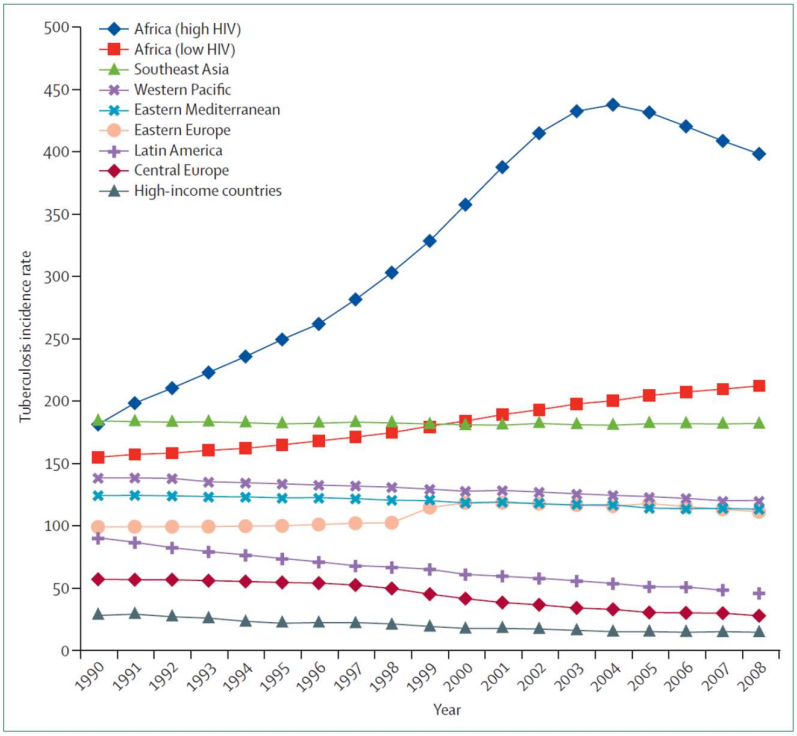


Figure 3: The estimated incidence of TB disease during the 1990's and early 2000's (using data from the World Health Organizations' 2009 Global Tuberculosis report) showing the marked increase in TB disease incidence in countries with a high prevalence of HIV (taken from *Lawn et al 2011*[14]).

Table 2: The estimated HIV prevalence and the proportion of people with new and relapsed TB disease who are also living with HIV among 10 high HIV burden east and southern African countries

Country	**Estimated HIV prevalence in 2022**[1,2]	**Proportion of people with TB who are also living with HIV in 2022**[3,4]
Botswana	16.4%	46.0%
Eswatini	25.9%	65.0%
Lesotho	19.3%	56.0%
Malawi	7.1%	48.0%
Mozambique	11.6%	25.0%
Namibia	11.0%	30.0%
South Africa	17.8%	54.0%
Uganda	5.1%	33.0%
Zambia	10.8%	32.0%
Zimbabwe	11.0%	51.0%

[1]among people aged 15-49 years; [2]taken from the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022 country factsheet[21]; [3]among all people with new and relapsed TB, the proportion with a known HIV status who were HIV positive; [4]taken from the World Health Organizations' 2022 country TB profile[22]

Strategies for TB control in sub-Saharan Africa

The most effective strategy to control TB, would be a vaccine that confers lasting protection from infection with MTB or from progression to TB disease, once infected (Figure 1)[23]. But to date, the only vaccine licensed for TB is the live attenuated *Mycobacterium bovis* bacilli Calmette-Guérin (BCG)[23]. While the BCG vaccine is one of the oldest and most widely used vaccines in the world, it does not confer lasting protection from TB disease into adulthood and has not controlled the TB epidemic in sub-Saharan Africa, despite its widespread use in the region[23-25].

TB preventive therapy is considered a critical component on the roadmap to achieve the goals of the WHO END-TB strategy[26]. Its use aims to prevent progression from MTB infection to TB disease[26-28]. Systematic reviews have shown that at the individual-level, TB preventive therapy can decrease the risk of TB disease by ~60% compared to no treatment[29, 30]. WHO recommends TB preventive therapy for risk groups (e.g. PLHIV, household contacts of people with TB disease) among whom, the risk of TB disease is higher than that of the background population[26]. But scale-up has been, especially in high TB burden countries, poor for several reasons including the lack of a test that can identify those at risk of progression[26-28]. A population-level impact with TB preventive therapy, is yet to be proven[26].

Combination antiretroviral therapy (ART) for HIV has been available since 1996[18, 31]. When taken appropriately it is very effective, decreasing viral replication and resulting in immune recovery[18, 32]. The $CD4^+$ T-lymphocyte recovery with ART is biphasic[33-37]. As shown in Figure 4, the initial rapid increase in $CD4^+$ T-lymphocyte counts with ART, is followed by a more gradual increase with the incremental gain in $CD4^+$ T-lymphocytes slowing down[33-37]. Higher $CD4^+$ T-lymphocyte counts at ART initiation are associated with higher $CD4^+$ T-lymphocyte recovery; a higher proportion of PLHIV achieve near normal $CD4^+$ T-lymphocyte counts when ART is initiated earlier[33-37]. Conversely, a higher proportion of individuals

initiating ART at very low baseline CD4$^+$ T-lymphocyte counts do not achieve immune reconstitution, with the absolute median CD4$^+$ T-lymphocyte count remaining below that of those initiating ART earlier[33-37]. A systematic review conducted in 2012, showed that at the individual-level, across all baseline CD4$^+$ T-lymphocyte counts, ART is associated with an ~65% reduction in the incidence of TB disease[38]. Since this review, several randomised trials have also shown a significant reduction (~45-60%) in incident TB disease and HIV-associated morbidity (including TB disease), when ART was initiated early[39-42]. In one trial, among individuals with CD4$^+$ T-lymphocyte counts of at least 500 cells/μL during most of their follow-up, initiating ART immediately was associated with a significant 44% lower incidence of HIV-associated morbidity (including TB disease) than deferring ART start[41]. When stratified by type of outcome, the incidence of TB disease was 55% lower with immediate ART initiation, but follow-up time and number of events in this subgroup were low, with the 95% confidence intervals just crossing one[41].

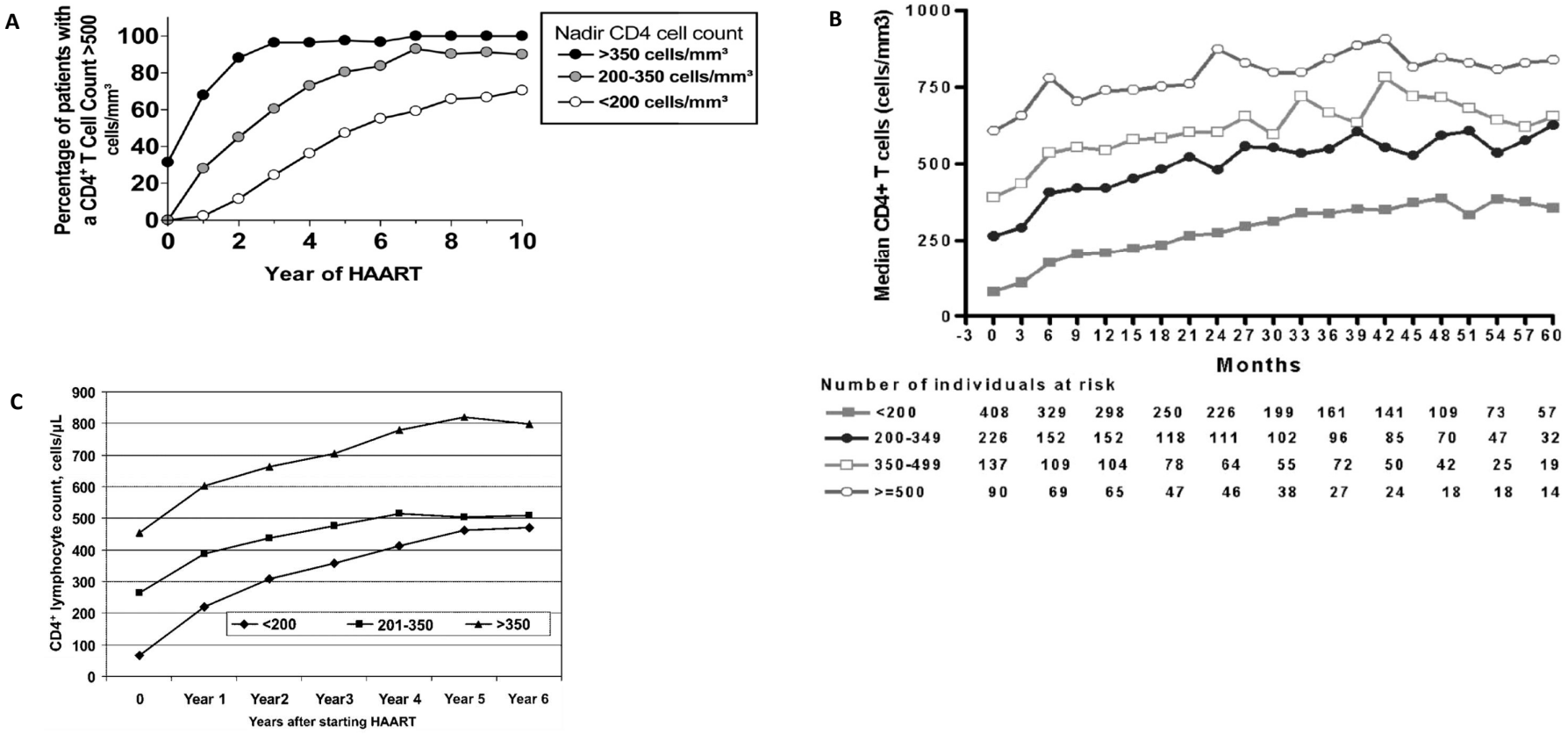


Figure 4: **A** - the percentage of people living with HIV taking antiretroviral therapy with a CD4+ T-lymphocyte count >500 cells/µL over time (in years), when stratified by baseline CD4+ T-lymphocyte count (*taken from Kelly et al. CID 2014*[34]). **B and C** – Median CD4+ T-lymphocyte count over time, stratified by baseline CD4+ cell count among people living with HIV taking antiretroviral therapy (*B taken from Garcia et al. JAIDS 2004*[33] *and C taken from Moore et al. CID 2007*[36]*])*

Therefore, at the individual-level, ART is potent at preventing TB disease, even at high $CD4^+$ T-lymphocyte counts. ART roll out in sub-Saharan Africa began in the early 2000's[43, 44]. Since this time, based on the evolving evidence, the $CD4^+$ T-lymphocyte threshold for ART initiation has increased from ≤200-250 cells/μL to ≤350 cells/μL, to ≤500 cells/μL[31]. Then in 2015, WHO recommended starting ART at the point of HIV diagnosis, irrespective of $CD4^+$ T-lymphocyte count (called "universal treatment for HIV")[45]. Given the ability of ART to prevent TB among PLHIV on ART and the scale-up of ART over time in sub-Saharan Africa, observational studies have tried to determine the potential of ART to control TB, both in the total population and among all PLHIV - those in and not in care and taking into account adherence to treatment and losses to follow up on treatment - where an individual-level effect may not necessarily translate to a group-level effect[39]. Several routine programmes have observed a coincident decrease in TB notification rates with increasing ART coverage over time[39]. While it is plausible that ART coverage in part explains these observations, a causal association based on these observations alone, cannot be inferred. Ultimately, to determine a casual association between increasing ART coverage and TB control at population-level, requires cluster randomised trials.

The HIV testing landscape is also changing in sub-Saharan Africa. The Joint United Nations Programme for HIV/AIDS (UNAIDS) 95-95-95 HIV targets call for 95% of PLHIV knowing their HIV status; 95% of those diagnosed with HIV receiving ART; and 95% of people receiving ART being virally suppressed[46]. To achieve these goals, routine programmes must go beyond providing ART only to those seeking HIV care. One possible approach is screening whole populations for HIV (whole communities where HIV epidemics are generalised and risk groups where it is focal). This "universal HIV testing" approach needs to be combined with linkage-to-care and support, to initiate "universal treatment for HIV", along with treatment adherence support as needed. The intervention, combining "universal HIV testing", linkage-to-care, and "universal treatment for HIV", along with support for PLHIV to navigate the care pathway to access and adhere to ART, is called universal testing and

treatment for HIV (or UTT)[47]. UTT aligns with the universal health coverage agenda, providing people-centred, community-based primary healthcare for HIV. There is now evidence from cluster randomised trials that different models of providing UTT are feasible, can help meet UNAIDS targets and can also help control the HIV epidemic[47, 48]. Mathematical modelling suggests UTT approaches could also substantially impact the TB epidemic in sub-Saharan Africa[49]. With annual testing and immediate ART start, the incidence of HIV-associated TB disease is predicted to decrease by ~50% when HIV testing coverage reaches 95%[49]. However, HIV-associated TB incidence is then predicted to fall more slowly, taking ~35 years for incidence to be reduced by ~95-98% with annual HIV testing and ART initiation within 2 years of seroconversion[49].

Therefore, UTT for HIV on its own may not be sufficient to END-TB by 2035. PLHIV on ART survive longer[39]. Their risk of incident TB disease, while lower, does not return to that of HIV negative individuals[39, 50-53]. Therefore, they have a high cumulative lifetime risk of TB disease. When TB disease occurs, it may be cavitatory and smear positive as immune function improves and therefore more infectious, resembling TB disease among HIV negative individuals[54, 55]. This would be coupled with the ongoing background risk of TB disease among those HIV negative, who account for >30% of all people with incident TB disease in sub-Saharan Africa[22]. Therefore, it is unclear if UTT alone can control TB in sub-Saharan Africa and achieve the impact needed to meet international targets.

In response to the resurgence of TB disease during the 1990's, WHO developed the Directly Observed Treatment, short course (or DOTs) strategy to control TB (Figure 5)[56]. This strategy focused on building political commitment for TB while strengthening health systems to detect and treat all symptomatic individuals with TB disease who self-present, aiming to decrease their duration of infectiousness[56]. It is however reliant on individuals with TB disease recognising they have symptoms, for the symptoms to be perceived as sufficiently serious to seek healthcare, and no barriers (individual or health system) to seeking healthcare, and a well-functioning health system[57]. It is now recognised that this approach

is wholly inadequate to control TB in sub-Saharan Africa[57-62]. National TB prevalence surveys from the region show a high prevalence of undiagnosed TB disease and a high TB disease prevalence to notification ratio (a proxy estimate for the duration of prevalent TB, with high values a crude indicator of delays in diagnoses and missed diagnoses)[8, 63, 64]. It is also estimated that ~30% of all people with incident TB disease are either never diagnosed or not notified; these "missing millions" represent the gap in detection of people with TB disease under current TB control efforts[10, 65]. To close this gap, decrease community-level MTB transmission and control TB in sub-Saharan Africa, provider-initiated prevention strategies must be coupled with the DOTs strategy[57].

Political commitment: for sustained TB control activities.

Finding people with TB disease: detection by sputum smear microscopy among symptomatic people with TB disease self-reporting to health services.

Standardized treatment regimen: of six to eight months for at least all confirmed sputum smear positive people with TB disease, with directly observed treatment (DOT) for at least the initial two months.

A regular, uninterrupted supply of all essential anti-TB drugs

A standardized recording and reporting system: that allows assessment of treatment results for each person with TB and of the TB control programme overall.

Figure 5: Components of the 1994 World Health Organization Directly Observed Treatment, short course strategy[56].

To control TB, WHO now recommends systematic TB screening in general populations (henceforth called TB screening) with a high prevalence of TB disease (>0.5%) or structural risk factors for TB[66]. TB screening, which is provider-initiated, aims to identify individuals with TB disease earlier on in their clinical course, when they may not have symptoms, may not be aware they have symptoms, only have minimal symptoms, or for whatever reason

have not sought healthcare or have not been diagnosed with TB disease[66]. Tools for screening include symptoms, chest radiographs (CXRs), and molecular WHO recommended rapid diagnostic tests[66]. While the most sensitive screening tool for undiagnosed prevalent TB disease is CXRs, symptoms are the easiest to implement[66]. Initiating treatment in individuals diagnosed with TB disease through TB screening should render them non-infectious (median time to smear and culture conversion ~20-27 and ~40-59 days respectively)[67], decreasing the transmission of MTB from these individuals (Figure 1)[66]. Randomised trials and non-randomised studies from mainly Asia, show TB screening is associated with lower TB disease prevalence in the population[68]. Earlier initiation of treatment, when disease is likely to be less severe, should also improve the clinical outcomes of people with TB disease who are identified through TB screening[66, 69].

Adding TB screening to a UTT model, would represent economies of scope. This combined approach would decrease the risk of incident TB disease among PLHIV and decrease MTB transmission in the population (to both PLHIV and HIV negative individuals) as a whole (Figure 6). This could result in large, sustained decreases in TB disease incidence in the population. Further the clinical outcomes of people with TB disease started on TB treatment (treatment success and case fatality), would also be expected to improve. But empirical data to support such an approach to TB control are lacking.

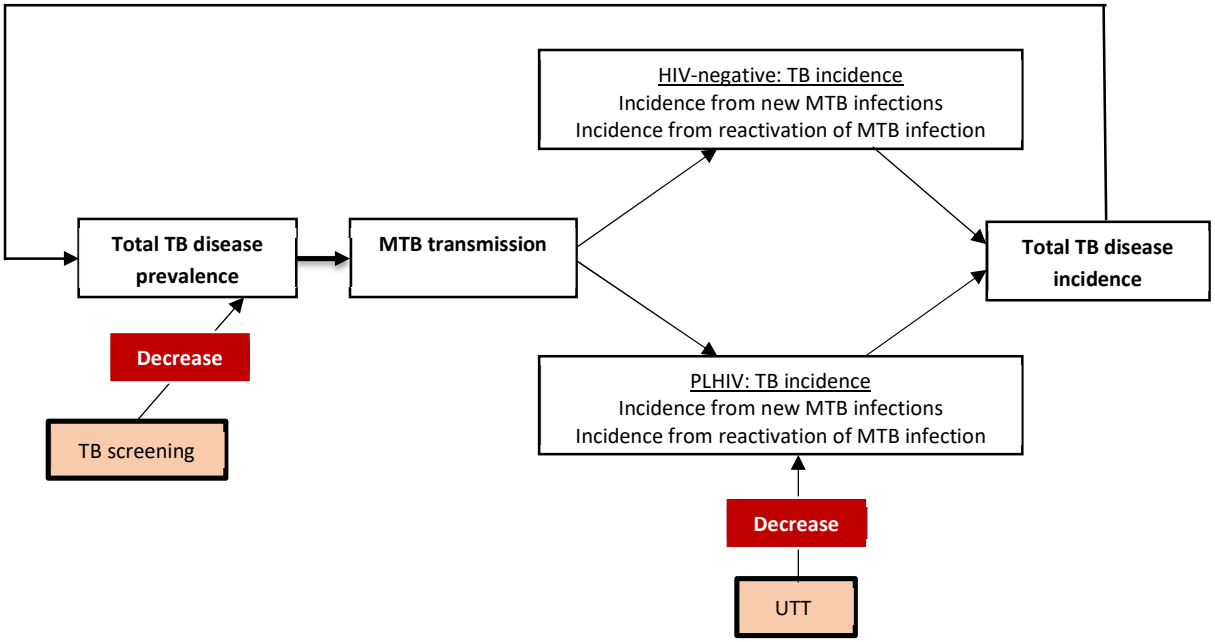


Figure 6: The potential mechanisms of action of universal testing and treatment for HIV and TB screening. TB=tuberculosis; MTB=mycobacterium tuberculosis; UTT=universal testing and treatment; PLHIV=people living with HIV; MTB=mycobacterium tuberculosis

Measuring the effect of TB control interventions

To measure the causal effect of any intervention in a study, incidence is the ideal outcome measure (Table 3). An intervention impact on TB disease incidence in cluster randomised trials is strong evidence for the hypothesis that an intervention can control TB. However, TB disease incidence is relatively rare, and therefore to measure it would require large cohorts that are followed-up over long periods of time, with repeated investigations to determine incident disease[70]. These are logistically challenging, costly and therefore not routinely feasible[70].

TB disease prevalence is an alternative research outcome (Table 3). Prevalence is influenced by both disease incidence and its duration[71]. Among PLHIV, TB disease, especially among those with severe immune suppression, has a short duration and high case fatality[64, 72-77]. Therefore, TB prevalence surveys in sub-Saharan African regions where

HIV is also prevalent, are likely to under-represent PLHIV with TB disease, due to length-biased sampling (where individuals need to have TB disease for long enough to be sampled by the prevalence survey). Interventions such as ART, would decrease TB disease incidence among PLHIV[38]. However, the increased survival of PLHIV on ART, combined with their continued increased risk of TB disease, and the potential for TB disease to resemble that of HIV negative individuals[54, 55] which typically is of longer duration, may increase the probability that incident TB disease among PLHIV is captured as part of a prevalence survey. The overall impact of an ART-based intervention on TB disease prevalence measured in trials would then depend on the relative contribution of the intervention to changes in incidence and duration. Therefore, while still informative, prevalence may not indicate the true TB control potential of an intervention. Further TB prevalence surveys, also require very large sample sizes, are resource intensive and costly, and extremely challenging to undertake.

TB notifications are routinely available programmatic data (Table 3)[70, 78]. They represent surveillance data which are collated nationally and reported to WHO[70, 78]. In well-functioning health systems, where nearly all individuals with TB disease are diagnosed, and the event captured through quality assured notification systems, TB notifications can be a proxy for TB disease incidence[70]. However, this is not the case in sub-Saharan Africa, where there are significant shortfalls at each step of the notification cascade and therefore TB notifications can be substantially less than TB disease incidence[70, 78]. Further, while notifications are meant to represent TB disease diagnoses, information reported from national registers often tend to be for those started on TB treatment[79, 80]. If shortfalls in TB notifications are similar across locations and comparisons are being made between them, in a cohort study this should not bias the ratio measure, with the ratio representing the intervention effect on underlying TB disease incidence.

In reality however, there are substantial differences in the availability and quality of TB notification data from different locations in sub-Saharan Africa, and there are several issues

which need to be considered when using notifications as a research outcome[70, 78, 80-82]. In many countries, TB notification data are mainly in paper form which can result in missing information. Notifications over time, do not represent fixed populations, and will be affected by migration into study sites, a particular problem in urban/peri-urban settings. Healthcare seeking behaviours will also affect TB notifications. If people with TB disease seek care outside study locations, which may be influenced by the availability of alternative services and convenience (especially among the young who work), notifications would be underestimated. Further, people with TB disease living outside study locations accessing care at the study sites, would need to be excluded from any analysis. This can be challenging if formal addresses are not available for dwellings (especially in informal settlements such as those seen in urban/peri-urban settings) or are poorly recorded. Further there is often no unique clinical identifier (e.g. like the NHS number in the UK) to track healthcare usage.

TB notifications can also change when underlying TB disease incidence does not; for example, changes to diagnostic tests and definitions can alter TB notification trends. TB screening (Figure 7) can also change TB notifications[68]. With TB screening, as individuals with undiagnosed prevalent TB disease are diagnosed and linked to care, TB notifications should initially increase[68]. The decrease in TB disease prevalence due to TB screening activities should decrease MTB transmission and TB disease incidence, resulting in a subsequent fall in TB notifications.

Further, measuring the effect of multiple TB control interventions, such as TB screening and UTT, on TB notifications could be challenging. Unlike the increase in TB notifications anticipated with TB screening, UTT for HIV should decrease TB disease incidence and therefore TB notifications among PLHIV (Figure 7). Overall TB notifications should also decrease if PLHIV contribute a substantial proportion of notifications as is the case in sub-Saharan Africa. PLHIV are more likely to have paucibacillary disease, and therefore do not contribute as much to MTB transmission as those who are HIV negative[83-90]. Nonetheless, if

population-level decreases in TB disease incidence among PLHIV are substantial and not outweighed by potential changes in infectiousness due to immune recovery with ART[54, 55], this should decrease MTB transmission (Figure 6), subsequently reducing TB notifications in the total population over time. The overall impact of combining UTT and TB screening on TB notifications is therefore likely to be complex and require careful analysis and interpretation. This, combined with the challenges of routine TB notification data, make using notifications as a study outcome, especially in mobile, densely populated, urban/peri-urban settings in sub-Saharan Africa, difficult.

Self-reported TB treatment (Table 3), a research outcome, is measured by asking people if they have started TB treatment[91]. If data collection is structured (especially if electronic with validity checks and rules, prompts, and inbuilt skip patterns), repeated in a cohort and conducted by trained research staff, trends in self-reported TB treatment should reflect trends in TB notifications. Indeed, it is plausible that self-reported TB is more likely to reflect true treatment starts in a population when there are significant quality issues with routinely collected notification data. Further, self-reported TB will reflect all treatment starts (both within study areas and outside study areas due to healthcare seeking behaviours) and data collected can represent a closed population over time. Under-reporting of treatment starts due to stigma or social desirability bias is possible[91]. If the underestimation is non-differential across study areas, in a cohort study this would not bias the ratio measure, with the ratio representing the intervention effect on underlying TB disease incidence. Therefore, self-report TB treatment offers significant advantages over using routine TB notifications to determine the impact of TB control interventions, if a research cohort is already in place. However, just like TB notifications, self-reported TB would also be expected to change with TB screening and therefore requires careful analysis.

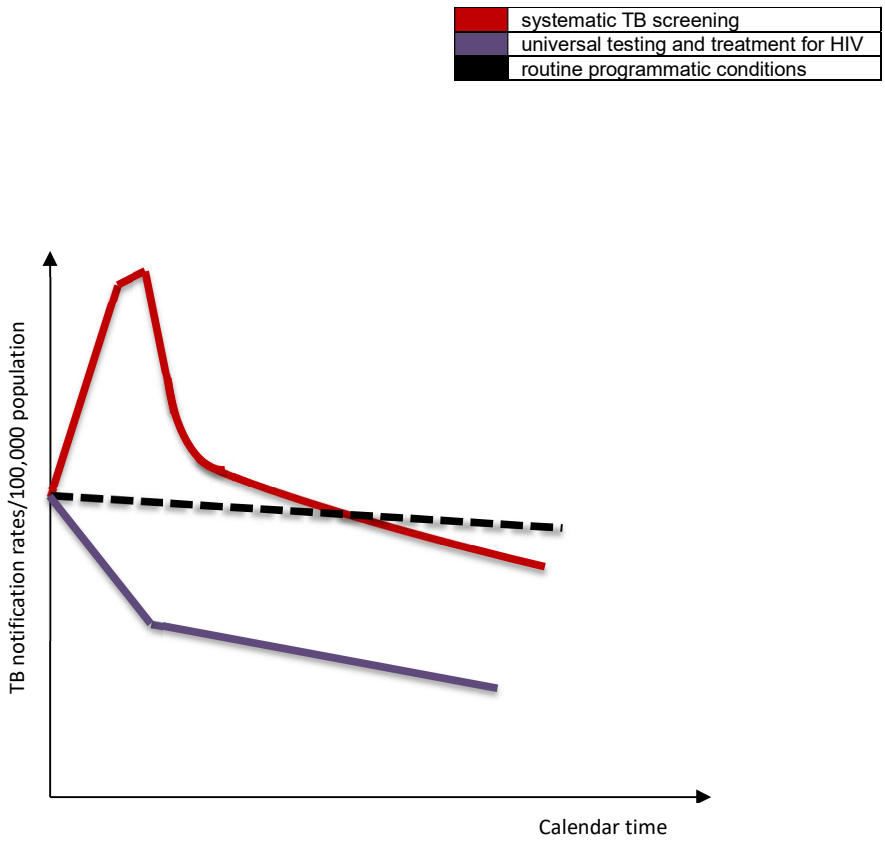


Figure 7: Anticipated changes to TB notifications with TB screening, universal testing and treatment for HIV and under routine programmatic conditions. The trends shown are purely illustrative and do not represent quantitative estimates of effect.

Table 3: The anticipated effect of universal testing and treatment for HIV and TB screening on measures of TB disease frequency in a study

TB disease measure	**What is being measured?**	**Anticipated population-level impact between study groups receiving the intervention and the control group**		**Ease of measurement**
		UTT	**TB screening**	
Incidence Research data	New people with TB disease arising in the population	Decrease incidence	Decrease incidence	Very hard
Prevalence Research data	Incidence x Disease duration	Will be influenced by the effect of ART on the duration of TB disease (expected to increase this) among PLHIV in addition to the effect of ART on the incidence of TB disease among PLHIV (decrease).	Decrease prevalence	Hard
Notifications Routinely collected data	People with TB disease who are detected by the health system. Can be a proxy for incidence when notifications are complete, and quality assured. This is not the case in SSA where there can be substantial shortfalls in the notification process. The availability and quality of notifications can vary substantially between different locations. Can be affected by where people with TB disease choose to attend for diagnosis and care. If people with TB often seek care outside study locations, notifications for the study areas will under-estimate true notifications. In SSA people with TB often choose to attend alternative providers due to convenience, stigma etc and this can vary between study locations. Further notification data are mainly in paper form and there is no unique identifier that allows people with TB to be tracked across services.	Decrease in notifications among PLHIV and overall (where PLHIV contribute a large proportion of all notifications). In closed populations, if the underestimate in notifications is similar in the study groups, comparisons between groups will represent the effect of the intervention on underlying TB disease incidence (i.e. ratio measure will not be biased). Routine notifications in reality do not represent fixed populations, especially in urban/peri-urban SSA communities where there is migration into and within the community (can be as high as 30%). This can attenuate the effect of UTT on notifications (i.e. ratio measure biased towards the null).	Initial increase in notifications as people with TB disease are detected and linked to care. A subsequent fall in notifications is expected as underlying TB prevalence, MTB transmission and therefore TB disease incidence falls. In closed populations, how TB screening will influence notifications during screening and how this relates to underlying TB disease incidence is unclear. If the population is not fixed, the effect of screening will also depend on the prevalence of undiagnosed TB among those migrating into the community. If their prevalence is high, notification could continue to remain elevated with screening compared to the unscreened population.	Routinely available but can be hard to collect and use for research purposes if in paper form.

Self-reported TB treatment Research data	People with TB disease being diagnosed and treated in the health system who self-report this on questioning. Can be a proxy for incidence when data collection is quality assured, reporting is complete and TB disease diagnoses and treatments are also complete. Will be affected by shortfalls in TB diagnosis and treatment by the health system. Will be affected by under-reporting due to stigma and social desirability bias. May have over-reporting due to other treatments being erroneously reported as treatment for TB. But over-reporting is unlikely if data collection is structured, a cohort is followed-up regularly and in populations where TB disease is common and knowledge about TB and its treatment including duration is high (especially those involved in trials). Recall bias will be minimised by asking about recent treatment starts. Should not be affected by where people with TB disease seek TB diagnosis and treatment services.	Decrease in self-reported TB among PLHIV and overall (where PLHIV contribute a large proportion of all notifications) In a closed cohort, if the underestimate in self-reported TB is similar in the different study groups, comparisons between groups can represent the effect of the intervention on underlying TB disease incidence (i.e. ratio measure will not be biased). In a closed cohort, if any overestimate in self-reported TB is similar in the different study groups, comparisons between groups will result in the ratio measure being biased towards the null (i.e. impact will be underestimated)	Initial increase in self-reported TB as people with TB disease are detected and linked to care. Subsequent fall as underlying TB prevalence, MTB transmission and therefore TB disease incidence falls. In closed populations, how TB screening will influence self-reported TB during screening and how these relate to underlying TB disease incidence is unclear.	If a cohort is already established, easy to collect this information. If a cohort is not established, very hard to collect this information.

UTT=universal testing and treatment; ART=antiretroviral therapy; PLHIV=people living with HIV; SSA=sub-Sharan Africa

The HPTN 071 (PopART) cluster randomised trial

The HPTN 071 (PopART) trial was a three-arm matched cluster randomised controlled HIV prevention trial conducted in 21 Zambian and South African communities between November 2013 and July 2018[92]. There were 12 communities in Zambia and nine in the Western Cape Province of South Africa (Figure 8). All communities were urban or peri-urban and the catchment population of a health centre, through which study interventions were co-ordinated and delivered. All communities were geographically distinct and purposively selected based on high HIV prevalence (10-25%), high TB case notification rates (≥400/100,000 population), and a population ≥20,000. The average size of each community was ~44,000 (range 16,000-100,000), with a total population of ~1 million (~600,000 adults). A trial called ZAMSTAR, was undertaken by the same study team in Zambia and the Western Cape Province of South Africa, covering similar geographic areas as HPTN 071 (PopART), between 2005-2010[93]. In ZAMSTAR in 2010, the geometric mean prevalence of culture-confirmed TB among adults ≥18 years was 832 (501 in Zambia and 2288 in South Africa) per 100,000 population and the geometric mean incidence of infection among school children was 1.22 (0.66 in Zambia and 4.15 in South Africa) per 100 person years.

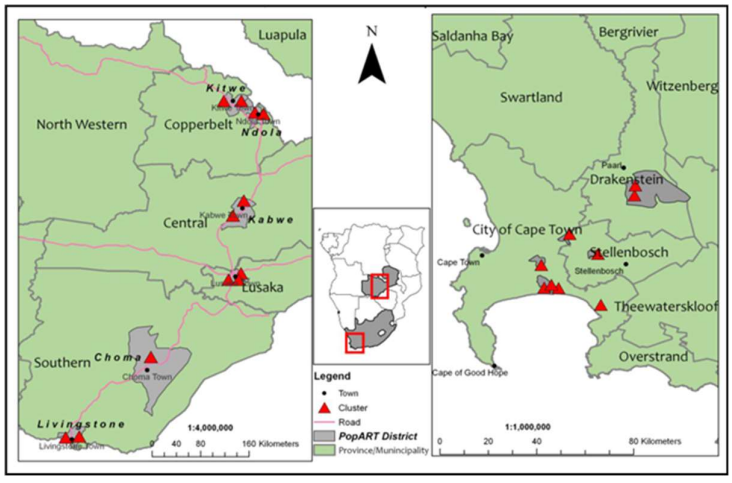


Figure 8: Location of the study communities taking part in the HPTN 071 (PopART) trial. There were 12 communities in Zambia, from the Copperbelt, Central, Lusaka and Southern Provinces. There were 9 communities in South Africa, all from the Western Cape Province.

In HPTN 071 (PopART), study communities were matched into groups of three or triplets, based on geography and estimated HIV prevalence, giving four matched triplets in Zambia and three matched triplets in South Africa. The communities in each triplet were then randomised to one of three study arms (two intervention arms [A and B] and a control arm [C]), using restricted randomisation to ensure balance across arms by population size, baseline ART coverage, and HIV prevalence (Figure 9). There were seven communities in each study arm.

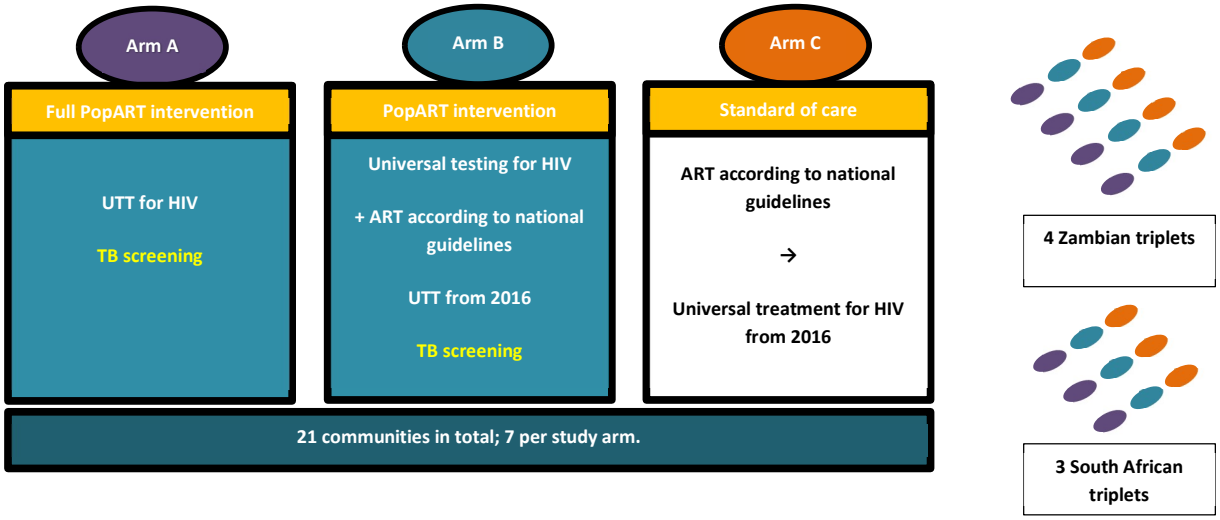


Figure 9: The three study arms. There were 2 intervention arms – arm A (7 communities) and B (7 communities). UTT=universal testing and treatment for HIV; ART=antiretroviral therapy.

The intervention and control arms

In the two intervention arms, A and B, comprising 14 communities, between 11/2013-12/2017, a door-to-door, community-wide, HIV/TB prevention intervention was delivered to all community members (adults and children) over three intervention rounds by a trained cadre of community workers called community HIV-care providers (or CHiPs; Figure 10). The first intervention round, during which the intervention was delivered for the first time and

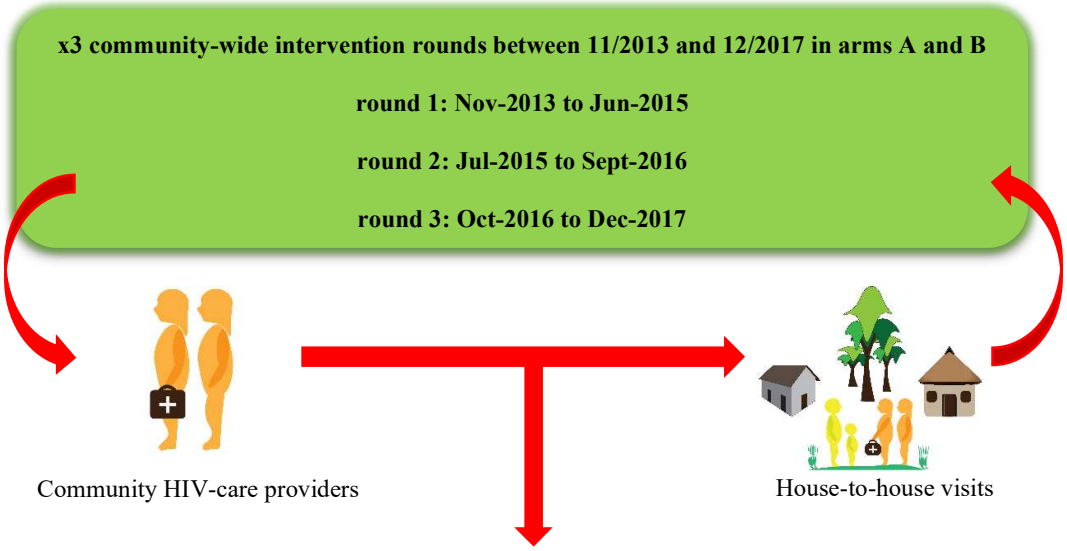
therefore scaled-up throughout the intervention communities, was between 11/2013 and 06/2015. Following this, two further intervention rounds at roughly annual intervals were delivered between 07/2015-12/2017. Within a community, CHiPs worked in pairs and were responsible for a zone of ~500 households. Each CHiP pair was responsible for delivering the intervention and all linkage-to-care and follow-up activities to all households in their zone. They enumerated all households in their zone and went door-to-door, visiting each household at least once during an intervention round. All CHiP activities were captured on electronic data capture devices, allowing the delivery of the CHiPs intervention to be monitored.

At each intervention round, CHiPs collected baseline demographic information on all household members, provided HIV/TB prevention messages, offered HIV testing using rapid tests to all household members including children with consent from parents/guardians (i.e. universal testing for HIV), promoted medical male circumcision and prevention of mother-to-child transmission of HIV services, and distributed condoms. All individuals who were newly diagnosed with HIV were referred for care and treatment services, at the community health centre. ART was commenced irrespective of $CD4^+$ T-lymphocyte count in arm A (i.e. universal ART) from 2013. In arm B, ART initiation followed national guidelines, with a $CD4^+$ T-lymphocyte threshold for ART initiation of ≤350 cells/μL at the start of the study. This changed to ≤500 cells/μL in Q3 of 2014 in Zambia and Q1 of 2015 in South Africa. This subsequently changed to universal ART in 2016; transition to universal ART started in Q2 2016 in Zambia and in Q4 2016 in South Africa. CHiPs followed up on all individuals referred for HIV care, to ensure linkage-to-care and to provide any ongoing care and adherence support as needed. The number of follow-up visits was dependent on individual circumstances, with no upper limit. Therefore, in arm A, there was UTT from the start of the study (2013). In arm B, there was universal HIV testing to support the scale up of ART coverage according to national guidelines. But all arm B communities also transitioned to

UTT by the end of 2016, giving a full calendar year during the intervention period – 2017 – when there was UTT in both arm A and B intervention communities.

In both intervention arms, a questionnaire (which included symptoms [cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month] and/or a known person with TB disease living in the household) was also used to screen all household members, including children, for TB at each intervention round. If screened positive, CHiPs collected and transported sputum for testing, according to national testing protocols at the community health centres. In Zambia, sputum was tested using GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA) if HIV positive or HIV status was unknown and smear if HIV negative. The testing protocol was the same during all three intervention rounds in Zambia. In South Africa, in the first intervention round, sputum was tested using GeneXpert MTB/RIF if HIV positive or HIV status was unknown and smear if HIV negative (i.e. the same as in Zambia). In the second and third intervention rounds, sputum was tested using GeneXpert MTB/RIF irrespective of HIV status. This screening and diagnostic process has a reported sensitivity of ~50-70%[94]. Sputum results were returned to the CHiPs. If sputum positive, CHiPs returned the result to the community member and linked them to TB treatment at the community health centres. All TB treatment followed national guidelines and was provided through routine TB services. CHiPs followed-up on all people with TB disease during treatment and provided them with any additional care and support as needed. The number of follow-up visits was dependent on individual circumstances, with no upper limit. All individuals who remained symptomatic but had negative sputum results were referred by CHiPs to the health centre for a clinical review. There was no difference in the TB screening intervention delivered in the two intervention arms.

Therefore, in intervention arm A, UTT was combined with TB screening from the start of the study. In arm B, there was universal HIV testing and ART initiation according to national guidelines, combined with TB screening. But for a full calendar year during the intervention period (in 2017) in all 21 communities, UTT was also combined with TB screening in arm B.



HIV	TB
HIV-testing at each intervention round using rapid tests (universal testing) Referred to community health facility if HIV-positive • Arm A – immediate ART start (universal treatment) • Arm B – ART start according to national guidelines. Became immediate ART (universal treatment) from 2016.	TB symptom screening at each intervention round using a questionnaire • Cough ≥2 weeks *or* • Night sweats *or* • Unintentional weight loss ≥1.5Kg in <1 month If symptomatic sputum collected: ***Zambia intervention round 1-3*** • Smear if HIV negative • Xpert MTB/RIF if HIV positive/status unknown ***South Africa intervention round 1*** • Smear if HIV negative • Xpert MTB/RIF if HIV positive/status unknown ***South Africa intervention round 2-3*** • Xpert MTB/RIF irrespective of HIV-status Referred to community health facility for TB treatment if sputum positive for TB

Figure 10: The HPTN 071 (PopART) HIV/TB intervention delivered at each intervention round in study arms A and B.

Trained community health workers called HIV-Care Providers or (CHiPs) visited each household in the community at least 3 times over the intervention period. In addition to screening and referral activities, CHiPs also followed-up on all referrals and provided treatment adherence support.

Arm C was the standard of care arm. Communities in arm C received the standard of care through routine health services. This included routine HIV counselling and testing through health centres or non-governmental organizations where such services were available. Linkage to HIV care depended on individuals seeking care without additional support. Similarly, people with symptoms of TB, would need to self-present to health centres for diagnosis and care. All diagnosis and treatment followed national guidelines. There were no HPTN 071 (PopART) related community-wide HIV testing or TB screening activities in arm C communities. However, as is the case across many urban/peri-urban communities in sub-Saharan Africa, there were HIV testing and TB screening initiatives, through non-governmental organizations and Department/Ministries of Health, especially on World AIDS Day and World TB Day. During these initiatives, communities were offered HIV testing and TB screening. However, unlike the HPTN 071 (PopART) intervention in the arm A and B communities, these activities were limited in time and scope.

Across both the intervention and control communities, activities to strengthen the health centre services were conducted from the start of the study. This ensured that appropriate HIV and TB diagnostic and treatment services were provided to all those who seek care, irrespective of study arm.

CHiPs intervention results

Data on CHiPs HIV and TB activities in the HPTN 071 (PopART) intervention communities have already been published (Table 4)[95-97]. Data over all three intervention rounds were only available for Zambian communities. In South Africa, quality assured data were only available for the third intervention round. Detailed information on migration and population turnover was only captured in the last intervention round (round 3), based on observations of high population turnover in intervention round 2. But broadly, the migration patterns were

likely to be generalisable to intervention round 2. Among all those aged ≥15 years who were enumerated and eligible to participate in intervention round 3 in arm A, ~45% were previously resident in the community and had not participated or were newly resident in the community area (including those moving into and within the community). In Zambia, at each intervention round, ~20-30% of those aged ≥15 years who were eligible for the intervention in arms A and B, did not take part. ART coverage increased across communities after each intervention round and was higher in arm A than in arm B. However, population turnover attenuated the gains in ART coverage. Among those previously resident in the community and who had not participated, or who were newly resident in the community area, ART coverage prior to the third intervention round was much lower (~50-75%) than among those that had taken part in at least one previous intervention round (~80%). Further, their ART coverage following the third round of the intervention remained lower (~65-80%) than among those who had participated in one previous intervention round (~85-90%). The intervention was less good at reaching young men, a population with a higher risk of TB disease.

In Zambian arm A and B communities, the proportion of people who were identified as TB screen positive increased over time (from 1.2% in intervention round 1 to 2.7% in intervention round 3). All Zambian intervention communities were visited in January 2017 to strengthen TB screening activities, coincident with the increase in proportion identified as screen positive through CHiPs TB screening in intervention round 3. The yield of TB disease from screening activities also increased over the intervention rounds, from 81/100,000 population in intervention round 1 to 110/100,000 in intervention round 3.

Table 4: CHiPs enumeration and HIV and TB intervention data for arm A and B communities, by country

CHiP activity		Arm A		Arm B		A and B
		Male	Female	Male	Female	
Among the population ≥15 years who were enumerated in intervention round 3 in Zambia	Proportion previously resident but did not participate in intervention round 1 or 2	14%	6%	-	-	
	Proportion newly resident in the community area in round 3 (moved in from outside the community or within the community)	37%	36%	-	-	
Proportion of the enumerated population ≥15 years who consented to participate in Zambia	In intervention round 1	-	-	-	-	83%
	In intervention round 2	64%	86%	-	-	71%
	In intervention round 3	67%	86%	-	-	75%
ART coverage in Zambia	Before intervention round 1	42%	46%	42%	46%	-
	After intervention round 1	57%	64%	52%	58%	-
	After intervention round 2	65%	75%	67%	73%	-
	After intervention round 3	76%	84%	71%	81%	-
Proportion of PLHIV who knew their HIV status before intervention round 3 in Zambia	Among PLHIV who participated in intervention round 1 and/or 2	91%	91%	-	-	-
	Among PLHIV who resided in the community area but did not participate in intervention round 1 and/or 2	66%	77%	-	-	-
	Among PLHIV who were newly resident in community area	57%	65%	-	-	-
Proportion of PLHIV who knew their HIV status after intervention round 3 in Zambia	Among PLHIV who participated in intervention round 1 and/or 2	96%	97%	-	-	-
	Among PLHIV who resided in the community area but did not participate in intervention round 1 and/or 2	76%	86%	-	-	-
	Among PLHIV who were newly resident in community area	78%	90%	-	-	-
ART coverage in Zambia before intervention round 3	Among PLHIV who participated in intervention round 1 and/or 2	81%	82%	-	-	-
	Among PLHIV who resided in the community area but did not participate in intervention round 1 and/or 2	62%	74%	-	-	-
	Among PLHIV who were newly resident in community area	54%	62%	-	-	-
ART coverage in Zambia after intervention round 3	Among PLHIV who participated in intervention round 1 and/or 2	86%	88%	-	-	-
	Among PLHIV who resided in the community area but did not participate in intervention round 1 and/or 2	66%	80%	-	-	-
	Among PLHIV who were newly resident in community area	66%	78%	-	-	-
ART coverage in South Africa	After intervention round 3	72%	87%	73%	85%	-
Zambia TB screening: screen positive	Intervention round 1	-	-	-	-	1.2%
	Intervention round 2	-	-	-	-	1.2%

	Intervention round 3	-	-	-	-	2.7%
Zambia TB screening: yield of TB disease/100,000 population*	Intervention round 1	-	-	-	-	81
	Intervention round 2	-	-	-	-	93
	Intervention round 3	-	-	-	-	110
South Africa TB screening: screen positive	Intervention round 3	-	-	-	-	5.8%
South Africa TB screening: yield of TB disease/100,000 population*	Intervention round 3	-	-	-	-	380

ART coverage = estimated proportion of PLHIV on ART among the total population of PLHIV (extrapolated using study intervention data); *yield=the number newly diagnosed with TB disease/all participants screened for TB (per 100,000 population).

Primary objective of HPTN 071(PopART) and the Population Cohort

The primary objective of HPTN 071 was to investigate the effect of the combination HIV prevention package, on HIV incidence, measured through a randomly selected cohort of adults aged 18-44 years, followed-up over 36 months irrespective of enrolment HIV-status. This cohort was called the Population Cohort or PC. The 18-44 year age group was chosen to recruit adults among whom a measurable change in HIV incidence due to the study interventions was likely to occur. A census of all households in the 21 communities was conducted prior to the start of the study. Using this as the sampling frame, a simple random sample of households was generated. In each household, all eligible adults were listed, and using a computer programme, a single eligible adult was chosen at random. If the individual consented to take part, detailed survey information and blood for HIV testing was collected. If the individual refused consent or there were no eligible adults in the household, the next household on the list was visited. The cohort was enrolled between 11/2013 and 03/2015; this was called the PC0 visit. Irrespective of their HIV-status, the entire cohort was followed up at 12-, 24- and 36-months post-enrolment (called PC12, PC24, and PC36 respectively). At each PC visit, the detailed survey questionnaire was repeated, and blood collected for HIV testing. Due to the target for enrolment at PC0 not being met (Table 5), additional participants were recruited at PC12 and PC24.

Results of HPTN 071 (PopART) have been published (Table 5)[98]. HIV viral load suppression was higher in arm A than in arm B among PLHIV. HIV viral load suppression was higher in both intervention arms than in the control arm. HIV incidence, between PC12 to PC36 (i.e. after the intervention had been established) was 10% lower in arm A and 30% lower in arm B compared to the control arm; only the latter was statistically significant. This was an unexpected finding, especially given ART coverage and HIV viral load suppression was higher in arm A than in arm B. In both interventions arms combined (arms A+B), HIV incidence was 20% lower, compared to the control arm.

Table 5: Enrolment to the Population Cohort and viral load suppression and HIV incidence, by study arm

	Arm A	Arm B	Arm C	Arm A vs C	Arm B vs C
Total enrolled at PC0	12,671	13,404	12,399	-	-
Among those eligible for follow-up at PC12					
PC12 – proportion who discontinued trial	16%	12%	12%	-	-
PC12 – proportion who missed visit	19%	24%	19%	-	-
PC12 – new enrolees at PC12	1714	1967	1333	-	-
Among those eligible for follow-up at PC24					
PC24 – proportion who discontinued trial	13%	12%	15%	-	-
PC24 – proportion who missed visit	21%	21%	21%	-	-
PC24 – new enrolees at PC24	2413	0	2400	-	-
Among those eligible for follow-up at PC36					
PC36 – proportion who discontinued trial	27%	27%	29%	-	-
Geometric mean of proportion with HIV viral load suppression at PC24	72%	68%	60%	aPR 1.16 (95%CI 0.99-1.36); p=0.07	aPR 1.08 (95%CI 0.92-1.27); p=0.30
Geometric mean of rate of incident HIV from PC12 to PC36 per 100 person years	1.45	1.06	1.55	aRR 0.93 (95%CI 0.74-1.18); p=0.51	aRR 0.70 (95%CI 0.55-0.88); p=0.006

PC=population cohort; 95%CI =95% confidence interval; aPR=adjusted prevalence ratio; aRR=adjusted rate ratio

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Chapter 2: The aims and objectives of this thesis and the study designs and methods employed to address these.

Rationale for the research undertaken

Tuberculosis (TB) is a significant cause of morbidity and mortality in parts of southern Africa, where the TB epidemic is mainly driven by the HIV epidemic[1, 2]. While many countries in the region have made gains in TB control, most are far short of the decreases in population-level TB disease incidence needed to meet the World Health Organization (WHO) END-TB strategy targets and milestones; compared to 2015, a 50% and 90% reduction in TB disease incidence by 2025 and 2035 respectively[1].

Combining community-wide universal testing and treatment for HIV (UTT) and systematic TB screening (TB screening), could be one approach to drive down population-level TB disease incidence in high TB/HIV burden settings. UTT should decrease TB disease incidence among people living with HIV (PLHIV) at the population-level[3]. Mathematical modelling predicts a substantial ~50% decrease in the incidence of population-level HIV-associated TB disease once full UTT coverage is reached[3]. TB screening, now recommended by the WHO in populations with a high TB burden or structural risk factors for TB, has been shown to decrease the prevalence of TB disease in populations[4, 5]. This should decrease *Mycobacterium tuberculosis* (MTB) transmission in the population, thereby decreasing TB disease incidence among PLHIV and those HIV negative[5]. However, evidence to support this combined approach is lacking. If TB screening identifies people with TB disease earlier on in their clinical course, this could also improve their clinical outcomes on treatment[6]. Further early antiretroviral therapy (ART) initiation among PLHIV through UTT, should also contribute to improving the clinical outcomes of PLHIV who have TB disease. But again, evidence for this is lacking.

HPTN 071 (PopART) was a cluster randomised HIV prevention trial conducted in 21 high TB/HIV burden urban and per-urban communities in Zambia and the Western Cape of South

Africa between November 2013 to July 2018[7, 8]. There were 3 study arms; two intervention arms (A and B) and a control arm (C). In the two intervention arms, a community-wide HIV/TB prevention intervention was delivered over three intervention rounds between 2013-2017. The intervention included UTT and TB screening. A population cohort (PC) was established to measure the primary outcome of the trial (impact of the intervention on HIV incidence). Embedded within the established infrastructure of HPTN 071 (PopART), I conducted this original research, using self-reported TB treatment data within PC and routine TB notification data collected from the study communities to address the identified knowledge gaps, and generate evidence to inform policy and practice in sub-Saharan Africa. Self-reported TB (which should reflect TB notifications) and routine TB notification data can change with TB screening, and therefore may not fully represent changes to underlying TB disease incidence. Therefore, understanding how to analyse these data when TB screening is implemented formed a further part of this research, to enable researchers and programme implementers to better use routinely available TB data.

The Medical Research Council, UK, awarded me a Clinical Research Training Fellowship (MR/N020618/1) to undertake this work. I conceived the overall project presented in this thesis, developed the research questions, worked up the methods to be employed to address the research questions, was involved in collecting the routine TB notification data in Zambia (where it was in paper form) and overseeing data extraction in South Africa (where it was electronic), undertook all systematic reviews and literature reviews, worked with mathematical modellers to understand how to analyse the PC and TB notification data, worked up the methods to prepare the PC data for analysis, and undertook all the analyses presented in this thesis. I wrote the amendments to the HPTN 071 (PopART) protocol for this work. In addition, I wrote the sections pertaining to this work which were incorporated in the Tuberculosis Reduction through Expanded Anti-retroviral Treatment and Screening (TREATS) project protocol. The TREATS project was led by the London School of Hygiene and Tropical Medicine (LSHTM) in the same study communities as HPTN 071 (PopART) to

determine the impact of the HPTN 071 (PopART) interventions on TB outcomes. Applications for ethical approval were submitted to and obtained from the biomedical research ethics committees in the UK (LSHTM), Zambia (University of Zambia), and South Africa (Stellenbosch University and Pharma-Ethics Research Committee).

Aims and objectives

The overarching aim of the research was to investigate whether UTT and TB screening could control TB in high TB/HIV burden communities in sub-Saharan Africa and could improve the clinical outcomes of people with TB started on TB treatment.

Objectives

1) To investigate the effect of increasing ART coverage on measures of population-level TB to understand the potential role that UTT could play in controlling TB based on empirical data.
2) To investigate changes to routine TB notifications with TB screening based on empirical data and determine whether changes were compatible with mathematical model simulations of changes to TB notifications with TB screening and what this tells us about changes to underlying TB disease incidence.
3) To investigate the effect of the HPTN 071 (PopART) interventions of UTT and TB screening on the incidence of self-reported TB treatment in PC in the 21 study communities (arm A versus C and arm B versus C).
    - Incidence of self-reported TB as collected within PC
    - Incidence of self-reported TB linked to routine TB notification data
4) To investigate whether TB screening can identify people with TB disease earlier in their clinical course and improve their clinical outcomes.
5) To investigate the association between how TB disease was diagnosed (TB screening versus self-presentation to health services) and the clinical outcomes (treatment success and case fatality) of people with TB disease on TB treatment in the eight Zambian HPTN 071 (PopART) arm A and B intervention communities.

Hypotheses, study designs, and methods to address the research objectives

Objective 1 - To investigate the effect of increasing ART coverage on measures of population-level TB to understand the potential role that UTT could play in controlling TB based on empirical data.

Hypothesis: increasing ART coverage in sub-Saharan Africa, as part of routine ART scale-up, is associated with decreased population-level TB (e.g. TB notification rates, TB disease prevalence).

Rationale: ART is known to decrease the risk of incident TB disease among PLHIV who take ART[9]. The individual-level effect of ART is necessary if ART is to have a population-level impact on TB disease incidence. But this individual-level effect may not necessarily translate to a population-level impact among all PLHIV in a population (which includes those in and not in HIV care, taking into consideration adherence to ART, losses to follow-up etc) or to the population as a whole. Therefore, this literature review was undertaken to synthesise the evidence on the impact of ART scale-up in sub-Saharan Africa on measures of TB at the population-level. This provides the foundation from which to understand whether UTT (where ART coverage is high), can control TB.

Study design: Literature review using systematic methods

Methods: Studies investigating the effect of increasing ART coverage on population-level measures of TB in general populations in sub-Saharan Africa were included.

Eligibility criteria, population, intervention, comparator, and outcomes: Randomized trials and observational studies were eligible. Only studies conducted in sub-Saharan African general populations, urban and/or rural, among adults and children or adults alone, were included. Special populations, such as mine workers and prisoners were excluded, as were mathematical modelling studies which did not include any new empirical data. The intervention was increasing ART coverage due to scaling up ART and changes to CD4+ T-

lymphocyte thresholds at which ART was initiated. The comparator was lower ART coverage (in the same population at a different point in time or in a different population) or the pre-ART era. The outcomes were TB disease prevalence, TB disease incidence, TB notifications, MTB infection incidence or MTB infection prevalence. Only articles published in English were included.

Search strategy: EMBASE and MEDLINE were searched from inception to the 5th of September 2022. Subject headings and key words covered concepts of TB and ART coverage (Table 1 and 2).

Table 1: Search terms in EMBASE

1	exp highly active antiretroviral therapy/ or exp antiretrovirus agent/
2	(HAART or ART or cART or antiretrovir* or anti-retrovir* or retrovir*).ti,ab.
3	hiv treat*.ti,ab.
4	hiv therap*.ti,ab.
5	hiv drug*.ti,ab.
6	hiv agent*.ti,ab.
7	(hiv adj2 (treat* or therap* or drug* or agent*)).ti,ab.
8	anti-hiv treat*.ti,ab.
9	anti-hiv therap*.ti,ab.
10	anti-hiv drug*.ti,ab
11	anti-hiv agent*.ti,ab.
12	(anti-hiv adj2 (treat* or therap* or drug* or agent*)).ti,ab.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp lung tuberculosis/ or exp latent tuberculosis/ or exp Mycobacterium tuberculosis/ or exp tuberculosis/
15	exp tuberculosis control/
16	(TB or tuber*).ti,ab.
17	14 or 15 or 16
18	exp epidemiology/
19	exp prevalence/
20	exp incidence/
21	exp disease notification/
22	exp bacterial transmission/ or exp disease transmission/
23	exp infection rate/ or exp infection risk/ or exp infection/
24	(epidem* or trend* or prevalen* or inciden* or transmi* or notification* or burden or infect*).ti,ab.
25	18 or 19 or 20 or 21 or 22 or 23 or 24
26	17 and 25
27	13 and 26
28	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
29	Animal experiment/ not (human experiment/ or human/)
30	28 or 29
31	27 not 30
32	limit 31 to english

Table 2: Search terms in MEDLINE

1	exp Anti-Retroviral Agents/ or exp Antiretroviral Therapy, Highly Active/ or exp Anti-HIV Agents/
2	(HAART or ART or cART or antiretrovir* or anti-retrovir* or retrovir*).ti,ab.
3	hiv treat*.ti,ab.
4	hiv therap*.ti,ab.
5	hiv drug*.ti,ab.
6	hiv agent*.ti,ab.
7	(hiv adj2 (treat* or therap* or drug* or agent*)).ti,ab.
8	anti-hiv treat*.ti,ab.
9	anti-hiv therap*.ti,ab.
10	anti-hiv drug*.ti,ab
11	anti-hiv agent*.ti,ab.
12	(anti-hiv adj2 (treat* or therap* or drug* or agent*)).ti,ab.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp lung tuberculosis/ or exp latent tuberculosis/ or exp Mycobacterium tuberculosis/ or exp tuberculosis/
15	(TB or tuber*).ti,ab.
16	14 or 15
17	exp epidemiology/
18	exp prevalence/
19	exp incidence/
20	exp Disease Transmission, Infectious/
21	exp Infection/
22	exp Disease Notification/
23	(epidem* or trend* or prevalen* or inciden* or transmi* or notification* or burden or infect*).ti,ab.
24	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
25	16 and 24
26	13 and 25
27	exp animals/ not humans.sh.
28	26 not 27
29	limit 28 to english

Study selection, data extraction and synthesis: 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 were extracted into a case report form. Variables extracted included study design and setting, ART programme information including changes to ART initiation criteria and calendar years for these changes, changes to ART coverage, TB outcome measure, data sources or methods to determine the outcome, and the impact of changing ART coverage on TB outcomes, where investigated. Due to the heterogeneity of included studies (populations, outcomes), data synthesis was narrative.

My role: I developed the PICO question, worked up the eligibility, inclusion and exclusion criteria, and search strategy including the search terms. I ran the searches. I undertook all title, abstract and full text screens. I extracted the data and summarised the findings.

Objective 2 - To investigate changes to routine TB notifications with TB screening based on empirical data and determine if changes were compatible with mathematical model simulations of changes to TB notifications with TB screening and what this tells us about changes to underlying TB disease incidence.

Hypothesis: With TB screening, TB notifications should initially increase following which they should decrease. The changes and the timing of these changes are reproducible and therefore enable the use of routine TB notifications to determine the impact of TB screening interventions and determine how underlying TB disease incidence has changed.

Rationale: In 2021, WHO recommended TB screening in populations with a high prevalence of TB disease or structural risk factors for TB disease[5]. As countries move to implement TB screening, how to measure and monitor the impact of screening is unclear. Monitoring TB disease incidence and prevalence is not practicable. TB notifications are routinely available programmatic data on the number of new TB disease diagnoses and/or treatment starts. But they can change with TB screening; we anticipate TB screening to cause an initial increase in TB notifications, as people with undiagnosed prevalent TB disease are linked to care. Decreases to TB disease prevalence in the population should decrease MTB transmission and therefore TB disease incidence. These changes should subsequently decrease TB notifications. But whether these anticipated changes to TB notifications occur and the timing of these changes, has not been systematically evaluated. Understanding these changes and how they relate to underlying TB disease incidence will guide on how to analyse TB notification data (when to look for changes and what these changes tell us).

Study design: Systematic review and mathematical modelling

Systematic review methods: Studies investigating the effect of TB screening strategies in the general population on trends in TB notifications were included.

Population, intervention, comparator, outcomes, and eligibility criteria: Randomized trials and observational studies were eligible. Only studies conducted in general populations, urban

and/or rural, among adults and children or adults alone, were included. The intervention was TB screening, using any screening strategy (i.e. any combination of screening tools and diagnostic tests) that was population-wide or targeted to part of the population. Where TB screening was targeted but TB notifications were reported for a wider population, the targeted population/s needed to constitute ≥5% of the wider population, to distinguish from household contact management alone in high TB prevalence settings. Judgement was used to determine if this was likely if data were not provided. General population TB screening could be accompanied by co-interventions such as screening in risk groups (e.g household contacts). The comparators were routine care (where people with TB disease self-present to healthcare services for diagnosis and treatment), either in the same population before screening was introduced and/or in a control population, or with another screening strategy. The outcomes were bacteriologically-confirmed and all TB notifications. To determine how TB screening affected TB notification trends, only studies reporting/allowing the calculation of ≥3 annualised TB notification rates, before, during and/or after screening were included. Studies conducted before the Directly Observed Treatment, short course strategy was introduced, were excluded as they did not represent contemporary TB epidemiology. Only articles published in English, French and Spanish were included.

Search strategy: The search for studies meeting the eligibility criteria was nested within a systematic review conducted by Chaisson et al 2021[10]. The review by Chaisson et al 2021[10] was undertaken to inform the 2021 WHO TB screening guidelines[5]. Therefore, it used similar methods and updated the systematic review conducted by Kranzer et al 2013[6], which informed the 2013 WHO TB screening guidelines[11]. For the review by Chaisson et al 2021[10], 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 (Table 3). Title, abstract, and full-text screens were broad; original research studies reporting on TB screening for all forms of TB in any population (e.g. general populations, people attending healthcare, miners etc) were identified. All studies identified by

the Chaisson et al 2021 review[10] were assessed for eligibility. In addition the studies identified in the Kranzer et al 2013[6] review reporting on TB notifications in any population group undergoing TB screening, covering the period 1/1/1980-13/10/2010 were also assessed for eligibility.

Table 3: Search terms used by Chaisson et al 2021[10] in Pubmed are shown below. These were adapted for EMBASE, Scopus and the Cochrane Library.

#1	"tuberculosis"[MeSH Terms]
#2	"tuberculosis"[tw] OR “Pulmonary Consumption”[tw] OR “Consumption, Pulmonary”[tw] OR Phthisis[tw] OR “Tuberculoses”[tw] OR “MDR-TB”[tw] OR “XDR-TB”[tw] OR “MDR TB”[tw] OR “XDR TB”[tw]
#3	#1 OR #2
#4	“Mass Screening”[MeSH Terms] OR “Mass Chest X-Ray”[MeSH Terms] OR "contact tracing"[MeSH Terms] OR “health surveys”[MeSH Terms] OR “Cross-Sectional Studies”[MeSH Terms] OR “Epidemiologic Studies”[MeSH Terms]
#5	“Mass Chest X Ray”[tw] OR “Mass Chest X-Rays”[tw] OR “screenings”[tw] OR “screening”[tw] OR “cross-sectional”[tw] OR “case-detection”[tw] OR “case finding”[tw] OR “contact tracing”[tw] OR “health survey”[tw] OR "prevalence survey"[tw] OR “prevalence studies”[tw] OR "mass radiography"[tw] OR "contact examination"[tw]
#6	#4 OR #5
#7	#3 AND #6
#8	("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))
#9	#7 NOT #8
#10	("2010/11/01"[EDAT] : "3000/12/31"[EDAT] OR "2010/11/01"[CRDT] : "3000/12/31"[CRDT]) OR ("2010/11/01"[PDAT] : "3000/11/31"[PDAT])
#11	#9 AND #10

Study selection, data extraction, and synthesis: 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 were extracted into case report forms. Variables extracted included study design, setting and population, the algorithm used to diagnose people with TB disease self-presenting to routine services, TB screening strategy, co-interventions, proportion of the population targeted with screening, TB screening coverage, the proportion of notifications identified by TB screening, the total number notified and TB notification rates over the reporting period.

Where TB screening coverage was not reported, if screening was one-off or 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 TB screening was not provided, it was calculated as the ratio of the number of persons with TB disease identified by screening to the total number notified during the screening period, but assuming that only 70% of screened persons with TB disease were notified. This was because the literature suggests that ~30% of people with TB disease identified by TB screening are not linked to care and treated[6].

Where only the numbers notified were reported, annualised TB notification rates were calculated based on the reported population size without accounting for population growth, as population growth rates in study areas were not known. If data were only graphically presented, data points were extracted directly from graphs using the Engauge Digitizer tool[12], with data re-plotted on the original scale to ensure extracted data accurately reflected original graphs. Data were recategorized where possible, so that annualised TB notification rates (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 notification rate ratios relative to the baseline TB notification rates were calculated for the screened population. Where comparator groups were available, TB notification rate ratios (in screened versus control populations) were also calculated, and then ratios relative to the baseline TB notification ratio calculated. Confidence intervals around TB notification rate ratios were not calculated, because a person can experience more than one TB event, which requires allowance for clustering. Only studies reporting notifications for >1 quarter following the end of screening were used to estimate post-screening TB notification rates, so that annualised data did not only include the quarter during which spill-over events from screening were likely. Due to the heterogeneity of included studies (target populations, screening strategies), data synthesis was narrative.

My role: I developed the PICO question, worked up the eligibility, inclusion, and exclusion criteria, and the approach to embed this work within the broader systematic reviews conducted by Chaisson et al 2021[10] and Kranzer et al 2013[6]. I undertook all title, abstract,

and full text screens. I extracted the data. I worked up the methods to analyse the extracted data, so that they could be compared across studies, and summarised the findings.

Mathematical modelling methods: The aim was to predict changes to TB notification rates with repeated rounds of TB screening in a general population and address four themes.

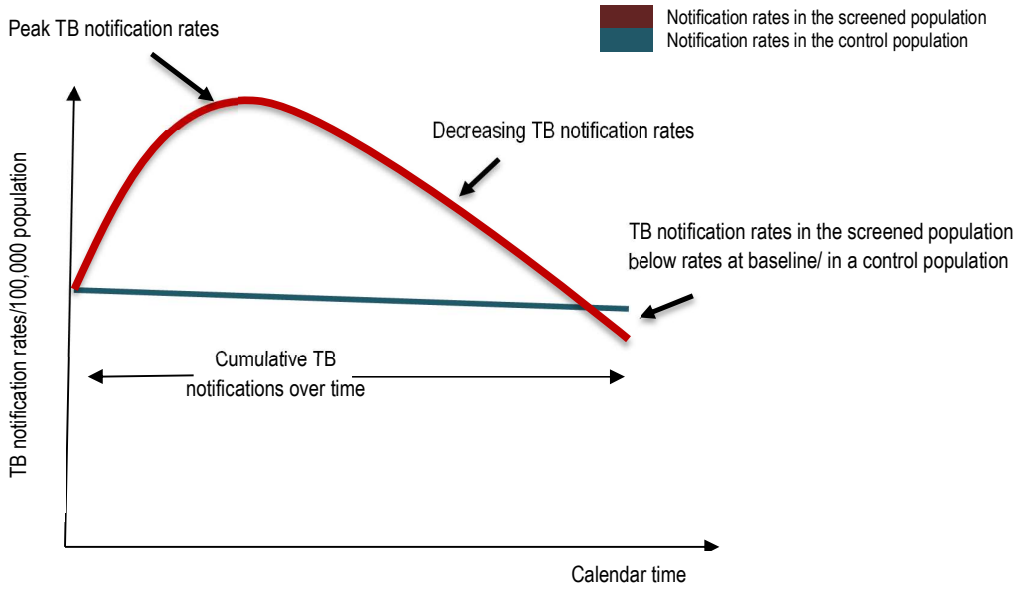

Figure 1: Hypothesised changes to TB notification rates with TB screening

Theme 1: Peak in TB notification rates (Figure 1)

- Is there a peak in TB notification rates with TB screening?
- When does the peak occur?
- What parameters determine the size and timing of the peak?
- What does the peak tell us about changes to underlying TB disease incidence?

Theme 2: Fall in TB notification rates following the peak with repeated rounds of TB screening (Figure 1)

- When does the fall in TB notification rates occur?
- What does this tell us about underlying TB disease incidence?

Theme 3: TB notification rates in the screened population compared to baseline/a control population (Figure 1)

- Will TB notification rates in the screened population fall below baseline/a control population?
- When does this fall occur?
- What does a lower TB notification rate in the screened population compared to baseline/a control population tell us about underlying TB disease incidence?

Theme 4: Cumulative TB notifications in a screened population would be expected to be lower over time reflecting decreases to MTB transmission due to TB screening

- What parameters determine whether this happens?
- What does this tell us about underlying TB disease incidence and the total number of cases averted?

To address these questions, a simulation study of the typical dynamics of TB notifications, true TB disease incidence and TB disease prevalence during 5 years of TB screening was conducted. A simple compartmental TB transmission model employing a standard structure to represent the process of MTB infection, progression to TB disease, and detection through routine services (i.e. notifications under routine programme conditions) was developed. The TB model structure was stratified by HIV status. Population size and HIV prevalence were assumed to be constant.

TB screening was modelled, as a hazard ratio applied to the per capita rate of transition from infectious prevalent TB disease to TB treatment, scaling up to its maximum value over a scale-up timescale before returning to its baseline value instantly at the end of the intervention. The model was run for 20 years from the intervention start (after which most intervention effects fade) to compute cumulative TB disease incidence and TB notifications. All outputs were rescaled relative to baseline values and the size and timing of peaks in TB notification rates and troughs in TB disease incidence and prevalence were recorded.

Changes to cumulative TB notifications and TB disease incidence compared to a matched-parameter counterfactual (routine care with no screening) were also determined. Time series were aggregated over quarters to reflect recording systems.

My role: I developed the questions to be addressed and approached Pete Dodd, an expert in the field of TB mathematical modelling at Sheffield University to collaborate on this work. Pete Dodd and Debebe Shaweno undertook the mathematical modelling. We reviewed the outputs together to interpret the findings from mathematical modelling and put the empirical findings from the systematic review in context with the model findings.

Objective 3 - To investigate the effect of the HPTN 071 (PopART) interventions of UTT and TB screening on the incidence of self-reported TB treatment in PC in the 21 study communities (arm A versus C and arm B versus C)

Hypothesis: UTT and TB screening will decrease self-reported TB treatment incidence in arm A compared to arm C. In arm B, decreases in self-reported TB treatment incidence, compared to arm C will be lower than that observed between arm A and C, as ART initiation between 2014-2016 followed national guidelines (which was CD4+ T-lymphocyte threshold <350 cells/μL to Quarter-2 2014 in Zambia and Quarter-4 2014 in South Africa, and <500 cells/μl to Quarter-2 2016 in Zambia and Q4-2016 in South Africa; Figure 2). In the intervention arms there will be an initial increase in self-reported TB treatment incidence compared to the control arm due to TB screening. This will be followed by decreases in self-reported TB treatment incidence in the intervention arms, compared to the control arm. These decreases will result from a combination of decreased HIV-associated TB disease incidence among PLHIV (due to UTT in arm A and universal HIV testing with ART initiation according to national guidelines in arm B) and decreased MTB transmission (due to TB screening and decreases in HIV-associated TB incidence).

Rationale: self-reported TB treatment in PC should reflect notifications. Therefore, comparing self-reported TB treatment in intervention arms compared to the control, should reflect the effect of the HPTN 071 (PopART) intervention on TB notifications. TB notification data could be distorted if people with TB disease from outside study communities sought healthcare from study community health centres, people with TB disease from study communities sought healthcare outside the study community health centres, and these healthcare-seeking behaviours varied by community. Restricting to PC (where all individuals were from study communities) and the use of self-report (which was more likely to capture treatment started outside study community health centres) may provide estimates that are closer to true treatment starts for the study community population alone. Further there were detailed data on individuals in the cohort, allowing differences in characteristics of PC

participants in the study arms to be explored and adjustment for potential confounders. While incidence in this cohort will depend on healthcare-seeking and diagnosis, with potential under-reporting due to stigma and social desirability bias, it nonetheless provides a more affordable incidence measure, that allows the impact of the interventions on underlying TB disease incidence to be explored. This work addresses the question of whether UTT combined with TB screening can control TB.

Deviation from original research plans: The objective as originally stipulated, aimed to determine the incidence of self-reported TB treatment among PC participants, and compare the incidence by study arm. Following this, the aim was to link individuals who self-reported TB treatment to TB notification data at the community health centres. This would have allowed the incidence of treatment for bacteriologically confirmed TB to be summarised and compared between study arms. However, there were challenges with the data linkage in both countries. In South Africa, there were shortfalls in TB notifications captured through the Electronic TB Registers, across multiple communities and multiple calendar years, during the study period. Therefore, we did not have TB notification data for South Africa that could be used. In Zambia all TB notification data were in paper form and needed to be captured electronically, which formed part of the research work presented (see Objective 5). However, there were missing registers (for parts of a calendar year and occasionally for whole calendar years) for multiple communities in Zambia. Therefore, we would not have been able to link PC data to TB notification data, for large periods of PC follow-up in Zambia. Due to these challenges the linkage work proposed could not be undertaken.

Alongside the work among PC participants, we wanted to summarise overall TB notification rates for the study communities over the trial period, and compare TB notification rates in arm A versus arm C and in arm B versus arm C. However, due to the quality of the available data this work could not be undertaken.

Study design: Cluster randomised trial

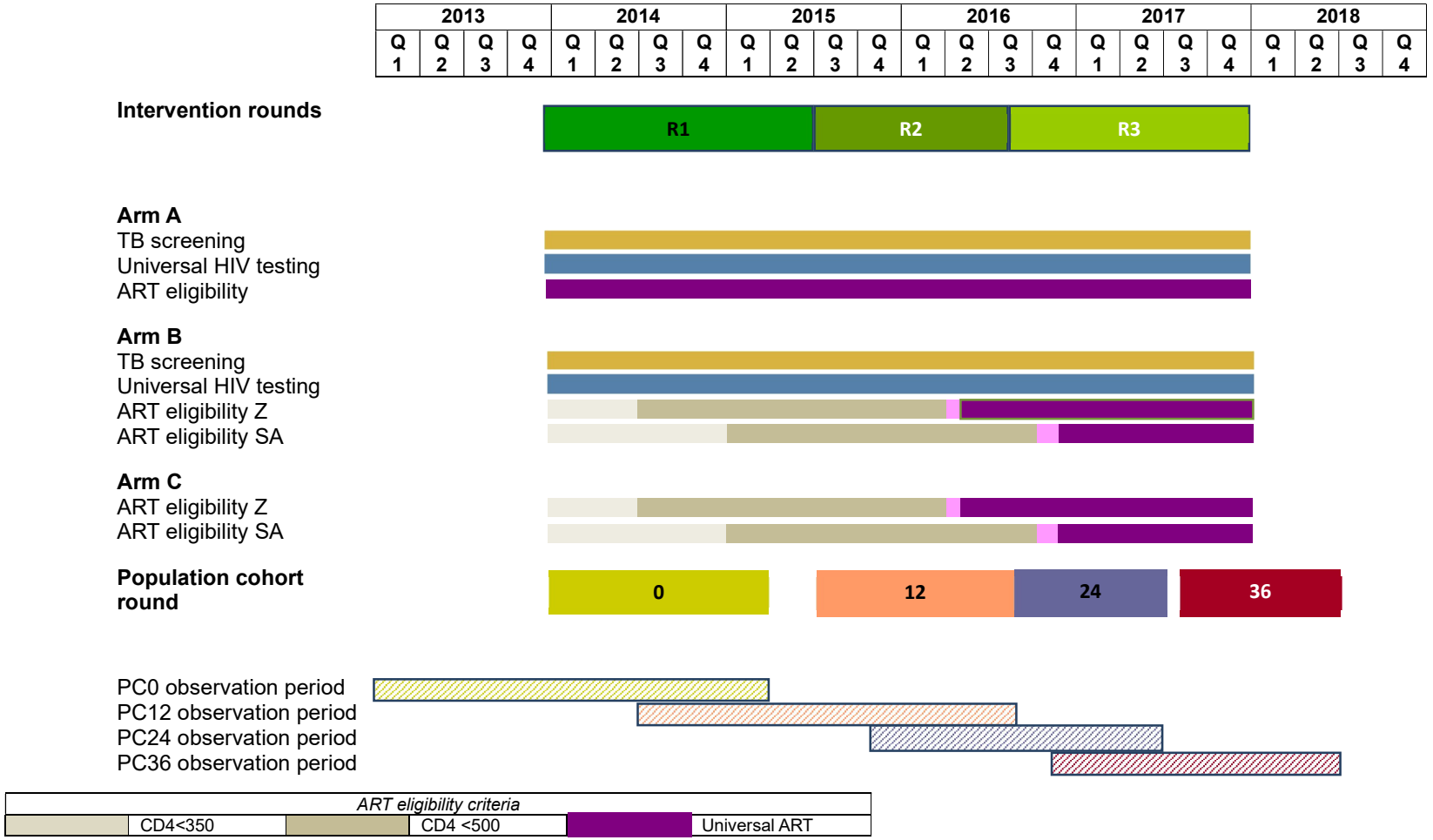

Figure 2: The intervention rounds, intervention components, ART eligibility criteria, Population Cohort rounds (PC0 to PC36) and the observation period for the TB analysis (generated as 14 months before the date of the PC visit). Q=Quarter; Z=Zambia; SA=South Africa; ART=Antiretroviral therapy; PC=Population Cohort. Transition to universal ART (shown in light pink) in Zambia: 19th April to 9th May 2016 and in South Africa: 10th October – 21st November 2016

Methods: The PC was established between 11/2013-03/2015 to measure HIV incidence, the primary outcome of the HPTN 071 (PopART) trial. One adult aged 18-44 years was randomly selected from a random sample of households in all 21 communities. This baseline enrolment visit was called PC0. A total of 38,474 PC participants were enrolled at PC0 from both Zambia and South Africa. The entire cohort enrolled at PC0 was followed-up at 12, 24 and 36 months (called PC12, PC24 and PC36 respectively; Figure 2). PC36 ended in 07/2018. Because PC0 enrolment targets were not met, additional participants were also enrolled at PC12 and PC24; these participants were called PC12N and PC24N. There were 5014 and 4813 PC participants enrolled at PC12N and PC24N respectively.

At each PC visit, trained research staff administered a structured questionnaire using electronic data capture devices. The electronic questionnaire had skip patterns and inbuilt prompts and validity checks, which allowed research staff to move easily within questionnaire sections, limiting errors in asking questions and documenting responses. It also facilitated information sharing, about what the questions pertained to and their purpose, to ensure that participants understood what was being asked. The same questionnaire (with some minor modifications over time) was administered to the entire cohort at each PC visit. Research staff were trained/re-trained on the questionnaire before each PC visit. At each PC visit (PC0 through to PC36), each PC participant seen was asked a series of questions to determine if they had started TB treatment in the preceding 12 months (Figures 3 and 4).

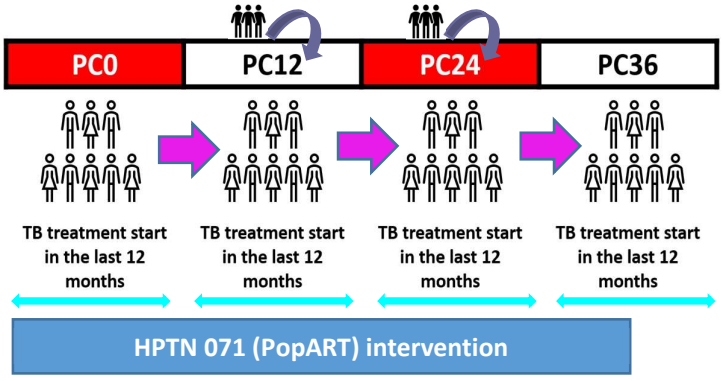

Figure 3: The HPTN 071 (PopART) PC enrolment and follow up

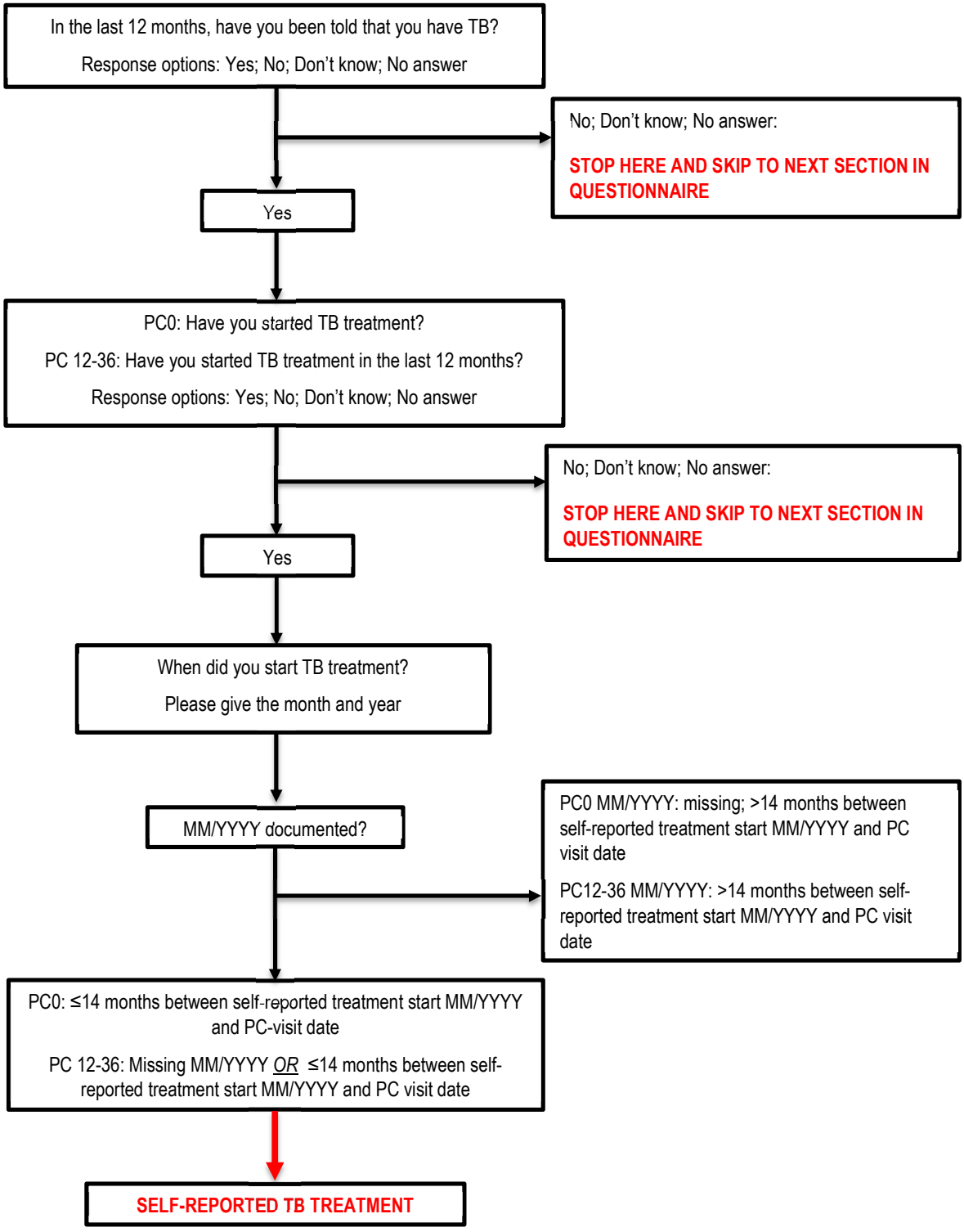

Figure 4: Flow of questions asked at each PC visit from each PC participant to determine if they had started TB treatment in the preceding 12 months AND the criteria used to determine self-reported TB treatment. MM/YYYY=Month/Year

At each PC visit, blood was also collected from all PC participants, irrespective of their HIV status, for laboratory HIV testing. A single fourth generation HIV test was performed on all blood samples at study laboratories in Zambia and South Africa. To quality control HIV results, additional HIV testing was performed at the HPTN Laboratory Center in Baltimore, USA, following a pre-specified algorithm, to determine the final HIV status at each PC visit.

Case definition: The intention of the questionnaire was to determine treatment starts in the 12 months preceding each PC visit. Using data collected in the questionnaire, at PC0, self-reported TB was defined as starting TB treatment in the 14 months before the PC visit (Figure 4). Duration was calculated as the difference between the self-reported TB treatment start and PC0 visit month and year. A 14-month eligibility period was used for analysis, to allow for possible errors in recalling month of TB treatment start. PC participants who self-reported starting TB treatment >14 months before the PC visit (4% of all those self-reporting TB treatment at PC0), were excluded from the case definition. In addition, PC participants who could not recall the month and year of TB treatment start (~20% of all those self-reporting TB treatment at PC0) were excluded, as the question that asked about starting TB treatment did not specify if treatment was started in the last 12 months.

For each of PC12, PC24, and PC36 separately, a similar method was used to determine PC participants fulfilling the TB case definition (Figure 4). PC participants who started TB treatment in the 14 months before the PC visit were included in the case definition. PC participants who reported starting TB treatment >14 months before the PC visit were excluded from the case definition (13%, 10% and 4% in PC12, PC24 and PC36 respectively). But individuals who could not recall the month and year of TB treatment start (13%, 10% and 10% at PC12, PC24 and PC36 respectively) were included in the case definition for PC12 through to PC36. This is because the question about starting TB treatment specifically asked, “if treatment was started in the last 12 months”.

The analysis was restricted to PC participants enrolled at PC0 only (i.e. a closed cohort). This was because self-reported TB treatment incidence in PC participants enrolled at later visits (PC12 and PC24) may not have been representative of study community incidence as 1) there was significant migration into communities and movement within community areas (which in intervention communities could have represented movement from areas not receiving the intervention to intervention areas)[13]; 2) how long a PC participant had resided within the community was not an eligibility criterion for enrolment and data on migration was not captured in the PC questionnaire; 3) the question asked about TB treatment in the 12 months before a PC visit. As TB disease takes months/years to develop following infection, reported TB treatment starts could be more likely to represent transmission events that occurred outside study communities.

Analysis: two methods were used - a cohort analysis and a cross-sectional analysis.

The cohort analysis was the primary analysis. Figures 5 to 12 detail the steps used to explore and prepare the cohort for analysis. The steps were:

- Step 1 – generating observation times for each PC visit that took place for each PC participant.
- Step 2 – exploring multiple episodes of self-reported TB treatment.
- Step 3 – defining the date of self-reported TB treatment start.
- Step 4 – defining the date of entry and exit from the cohort.
- Step 5 - generating gaps in observation time by calendar year.
- Step 6 – splitting follow-up time into calendar years and removing the calculated gaps in observation time.
- Step 7 – assigning HIV status for each calendar year and running sensitivity analysis on HIV status.

In the cohort analysis the reported year of TB treatment for PC participants meeting the case definition was used to allocate all TB episodes to calendar years and the data then analysed

by calendar year. This allowed patterns in the data to be investigated to determine if and how self-report TB treatment incidence changed with UTT and TB screening. Self-reported TB treatment incidence was expected to decrease with UTT scale-up; while, with TB screening, incidence was initially expected to increase (due to individuals being diagnosed and linked to care) and then decrease (due to decreased MTB transmission). Therefore, understanding patterns in the data were critical to interpreting findings.

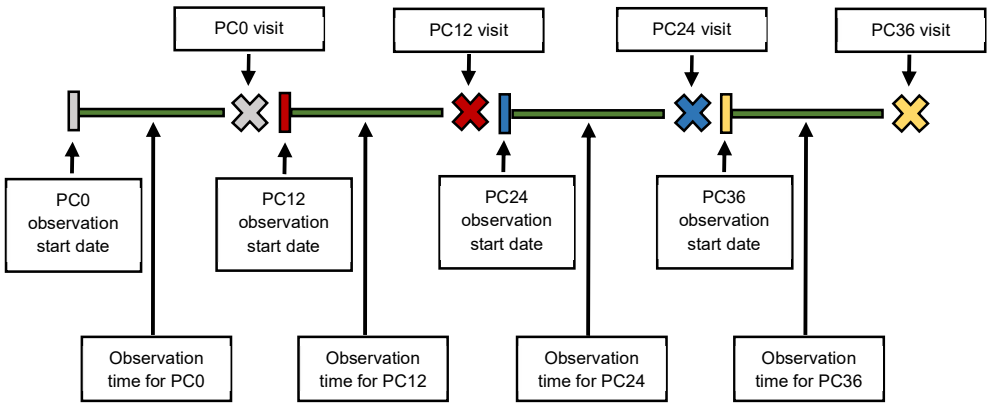

Figure 5: Step 1 – Generating observation time for each PC visit. Because self-reported TB was determined over the 14 months before each PC visit, for each PC participant, an observation start date, 14 months before each PC visit was generated. The time between the observation start date for a PC visit, and the date of that PC visit was the observation time for that PC visit, during which the outcome (self-reported TB treatment) was determined.

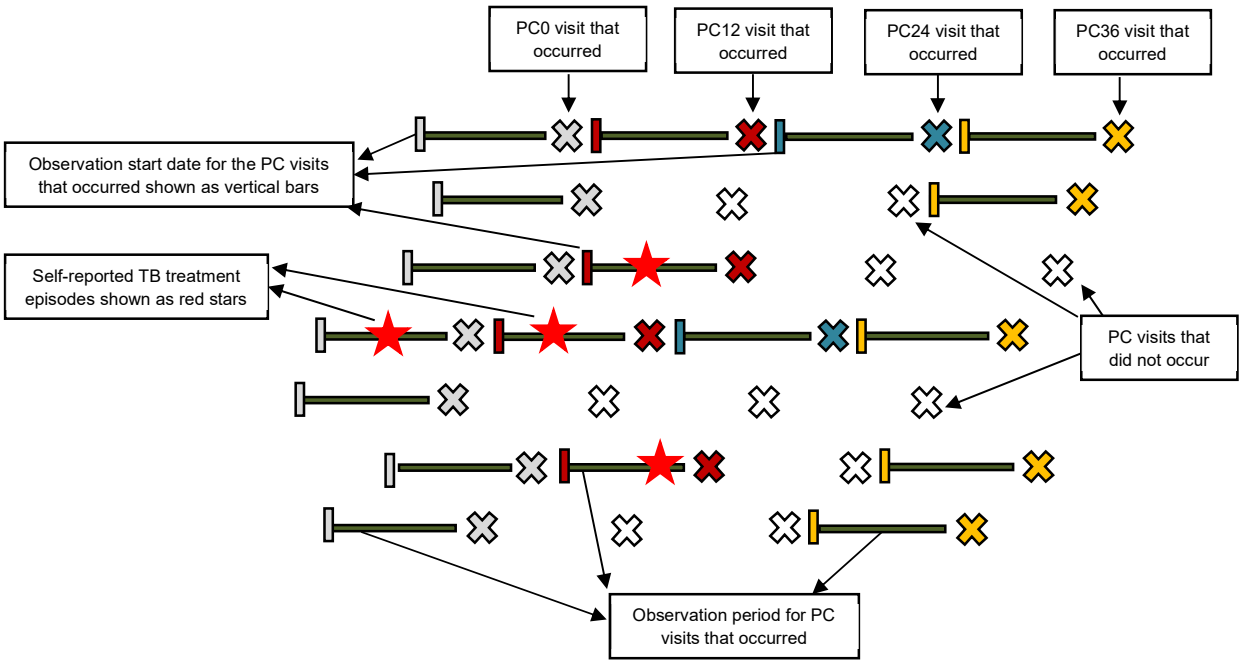

Figure 6: Step 1 - Example of the distribution of PC visits that occurred, the observation start date and observation time for PC visits that occurred, missed PC visits that did not occur, and self-reported TB treatment meeting the case definition. The total enrolled at PC0 was 38474. TB treatment was self-reported by 628 of whom 55/628 (9%) self-reported TB treatment at >1 PC visit.

Characteristics of 55 PC participants with >1 self-reported TB treatment episode

Characteristic		>1 self-reported TB episode	
		n/N	%
Study arm	A	7/55	13%
	B	26/55	47%
	C	22/55	40%
Country	Zambia	15/55	27%
	South Africa	40/55	73%

Among these 55 PC participants with >1 self-reported TB treatment episode, 45 (82%) had month and year of TB treatment starts.

If interval between the two self-reported TB treatment start months/years was ≤14 months, these were considered as starting TB treatment for the same TB episode. This is because TB treatment takes 6-8 months. New TB events following MTB infection take months/years to develop. Therefore 2 self-reported TB treatment starts within 12 months are unlikely to represent TB disease due to new transmission events. They are more likely to represent treatment after lost to follow-up, re-treatment after failure etc. As month of TB treatment start may have been recalled incorrectly a 14-month period between two self-reported TB treatment starts was allowed.

Characteristic		n/N	%
Number of months between TB treatment starts among 34/45 (76%) where interval between self-reported TB treatment start months/years was ≤14 months. 33/34 (97%) reported starting TB treatment at consecutive PC visits.	same month/year	11/34	32%
	>0 to ≤2 months	9/34	26%
	>2 to ≤6 months	2/34	6%
	>6 to ≤9 months	5/34	15%
	>9 to ≤12 months	6/34	18%
	>12 to ≤14 months	1/34	3%
Number of months between TB treatment starts among 11/45 (24%) where interval between self-reported TB treatment start months/years was >14 months. 7/11 (64%) did **not** report starting TB treatment at consecutive PC visits	>14 to ≤18 months	2/11	18%
	>18 to ≤24 months	4/11	36%
	>24 months	5/11	45%
Arm of n=11 where interval between self-reported TB treatment start months/years was >14 months	A	1/11	9%
	B	4/11	36%
	C	6/11	55%
Country of n=11 where interval between self-reported TB treatment start months/years was >14 months	Zambia	4/11	36%
	South Africa	7/11	64%

Among 10/55 (18%) month and year for at least 1 self-reported TB episode was missing. Therefore interval between treatment starts could not be ascertained. All self-reported TB treatment episodes occurred at consecutive PC visits. For these 10 individuals, the median time between the PC visits at which they self-reported TB treatment was 11.8 months (range 9.5-13.6 months).

The frequency measure of interest was incidence. There were very few repeat TB treatment starts that were likely to represent treatment starts for unique TB episodes. The most plausible estimate of repeat treatment starts for unique TB episodes was 1.8% (11/628 who all had a duration between self-reported TB treatment start months/years of >14 months). The maximum value was likely to be 3.3% (21/628, which included the 10 PC participants for whom interval between TB treatment starts could not be calculated, but who all reported TB treatment start at consecutive PC visits). Therefore, only the first self-reported TB treatment episode was kept for all PC participants to determine self-reported TB treatment incidence.

Figure 7: Step 2 – Exploring multiple episodes of self-reported TB treatment and logic for restricting the analysis to the first self-reported TB treatment episode

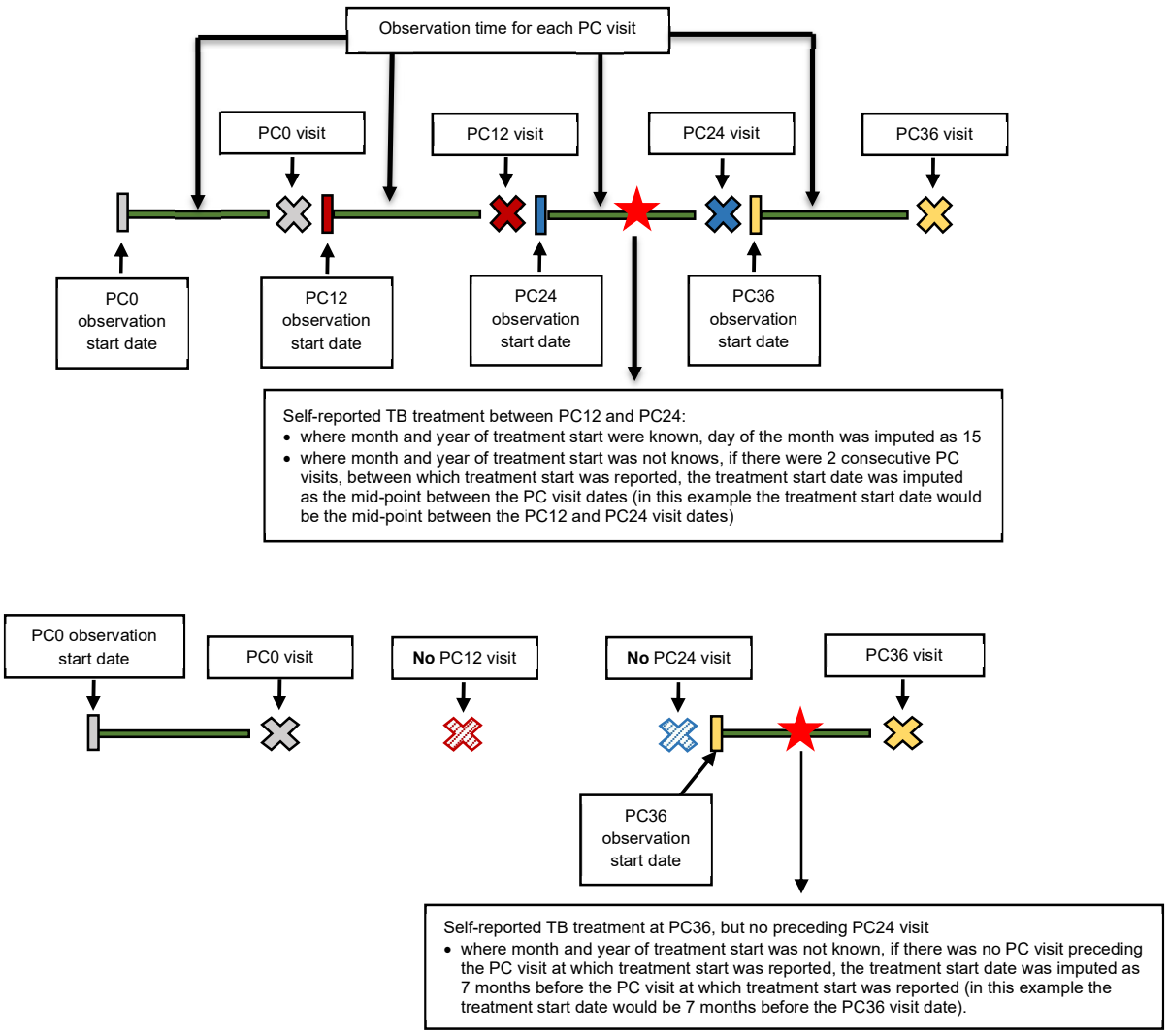

Figure 8: Step 3 – Defining the date of self-reported TB treatment for n=628 individuals who self-reported TB treatment start. 587/628 (93%) provided a month and year of treatment start. The day of the month was imputed as 15 for these individuals. 41/628 (7%) did not provide a month and year of TB treatment start. For these individuals, the date of TB treatment start was imputed as the mid-point between two consecutive PC visits, or 7 months before the PC visit where treatment was reported if PC visits were not consecutive.

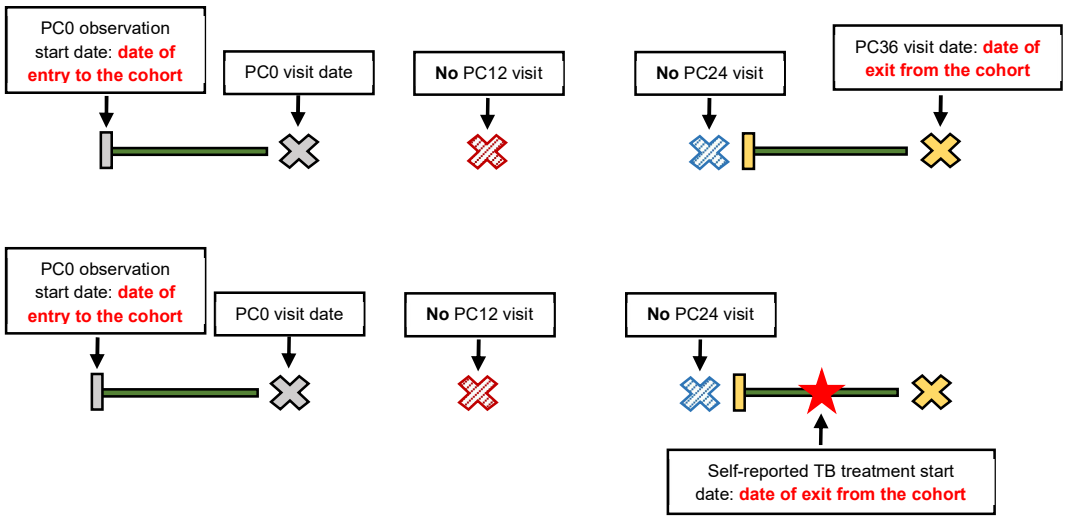

Figure 9: Step 4 - Generating the date of entry to the cohort and the date of exit from the cohort. The date of entry was the PC0 observation start date that was generated 14 months before the PC0 visit. The date of exit was the last PC visit date if no TB treatment was reported. If TB treatment was reported, the date of exit was the date of self-reported TB treatment.

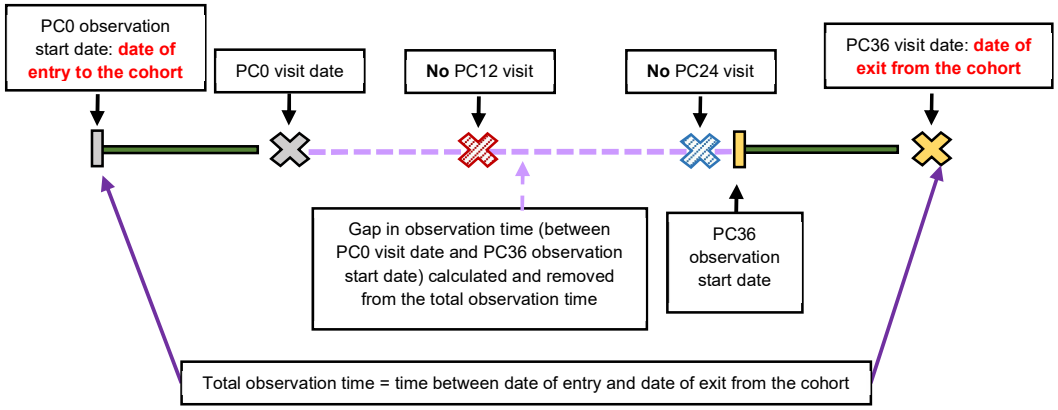

Figure 10: Step 5 – Generating gaps in follow up. The time between the date of entry and the date of exit from the cohort, was the total observation time. Where there were gaps in observation time (e.g. due to missed visits), the gap in observation time was determined as the difference between the PC visit date (after which there was a gap) and the observation start date for the subsequent PC visit. All gaps in observation time for each PC participant were generated by the calendar year/s in which the gaps occurred.

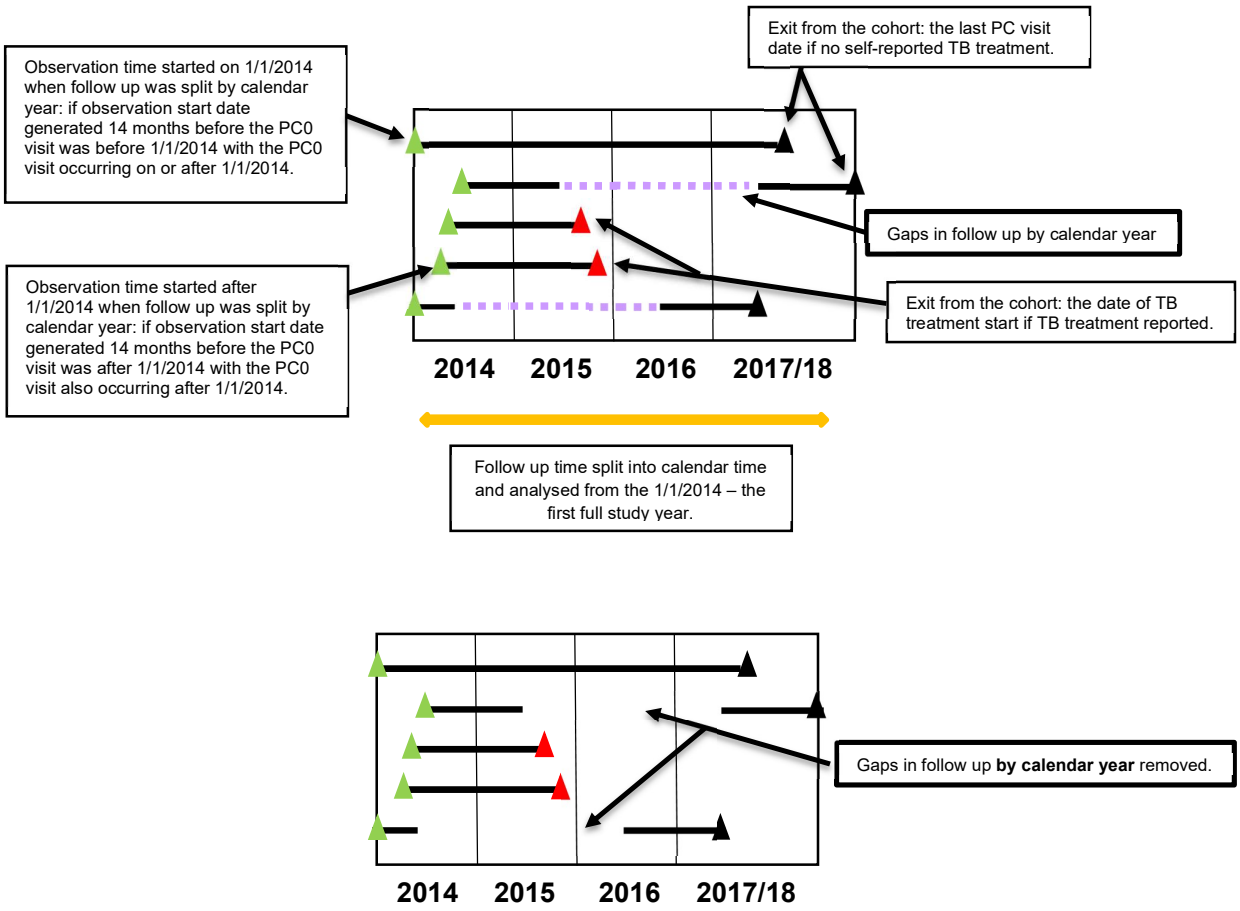

Figure 11: Step 6 – The total observation time generated for each PC participant (time between the date of entry and exit from the cohort) was split into calendar years from 2014 (the first full study year). The calendar periods analysed were 2014, 2015, 2016 and 2017/18 (as follow up in 2018 was only 6 months [PC ended in July 2018], 2017/18 was analysed as one calendar period). Observation time started on or after the 1/1/2014 for 38287/38474 who contributed person-time to the analysis. 53 PC participants were excluded from the analysis because their observation start date generated (14 months before the PC0 visit) and the PC0 visit date occurred before 1/1/2014 with no follow up visits. 134 PC participants who reported TB treatment before 1/1/2014 were also excluded from the analysis, as their date of exit occurred before 1/1/2014. Gaps in follow-up time during which outcome status was unknown, were removed. Gaps were removed according to the calendar year/s in which they occurred such that the observation time for each calendar year was adjusted to account for any gaps in observation time occurring during that year.

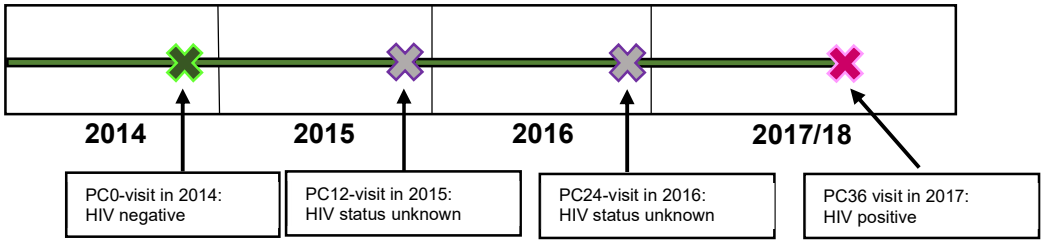

Figure 12-1: HIV status at each PC visit determined using blood HIV testing at each PC visit

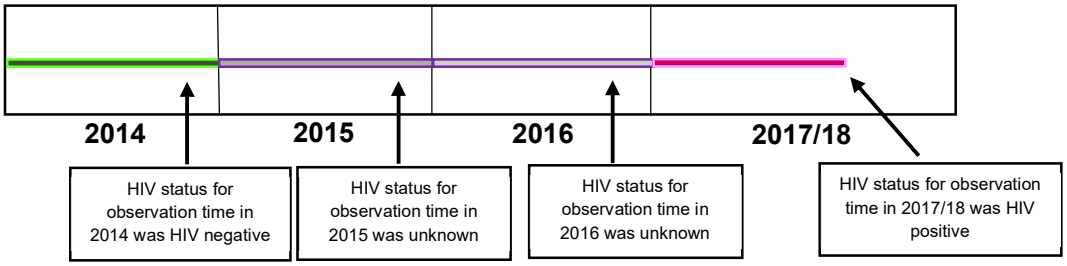

Figure 12-2: The HIV status at the PC visit was assumed to be the HIV status for the whole calendar year in which the PC visit took place and therefore, for the observation time contributed by the PC participant for that calendar year. If HIV status in a calendar year to which the PC participant contributed observation time was HIV positive, all subsequent calendar years to which the PC participant contributed observation time where HIV status was unknown, was imputed as HIV positive. If HIV status in a calendar year to which the PC participant contributed observation time was HIV negative, all preceding calendar years to which the PC participant contributed observation time where HIV status was unknown, was imputed as HIV negative. Analyses stratified by calendar year and HIV status were conducted based on this HIV status assignment.

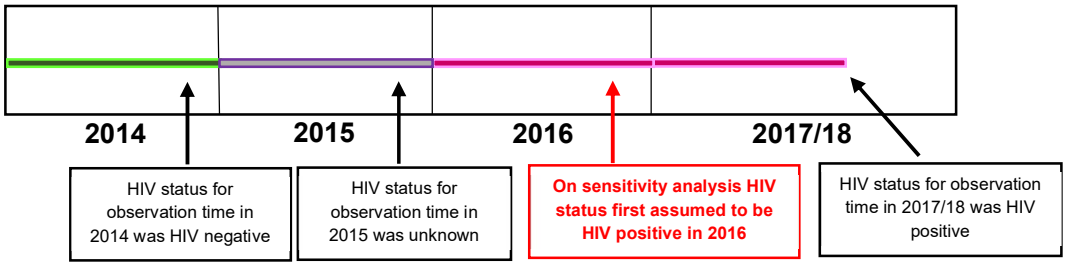

Figure 12-3: Where HIV status in the year preceding a HIV positive result was unknown (i.e. in 2016 in this example), the first sensitivity analysis conducted assumed the missing HIV status was positive

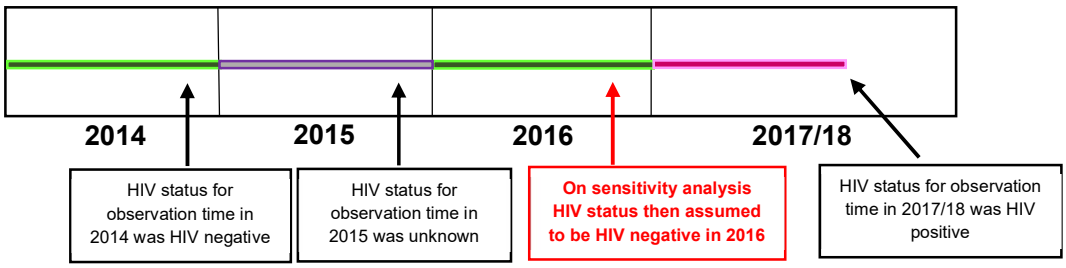

Figure 12-4: Where HIV status in the year preceding a HIV positive result was unknown (i.e. in 2016 in this example), second sensitivity analysis conducted assumed the missing HIV status was negative

Figure 12: Assigning HIV status for each calendar year and sensitivity analyses

The characteristics of PC participants contributing observation time during each calendar year were explored, to determine losses to follow up and comparability of PC participants seen in study arms over time. The rate of self-reported TB (overall and by HIV status) was calculated for each community, each year. Where there were no individuals self-reporting TB treatment for a community in a given calendar year, 0.5 was added to the numerator to generate a rate for the community, as log rates (and geometric means) were used in the analysis. By calendar year, the geometric mean of the rates of self-reported TB treatment for the communities in each arm were generated and then compared between study arms. Arms A and C, and arms B and C were compared; overall and for PLHIV. Cross-arm comparisons were not conducted for HIV negative individuals because there were a small number of events across the study arms when data were disaggregated by community and calendar period. There were no events among HIV negative individuals in six communities in 2014, eight communities in 2015, two communities in 2016 and five communities in 2017/18.

Statistical inferences used the recommended 2-stage approach, adjusting for covariates at Stage-1[14, 15]. Stage-1 used Poisson regression to compute the expected number of individuals with self-reported TB, assuming no intervention effect. Due to the small number of events during later calendar years (especially in 2017/18 in arm A), the total population analysis included only triplet and HIV status as covariates (without adjusting for age and sex). Analyses for PLHIV included triplet alone. At Stage-2, a two-way analysis of variance was conducted on the log (observed/expected number self-reporting TB) in each community, with matched triplet and study arm as factors, to generate the overall rate ratio and 95% confidence intervals for cross-arm comparisons.

The cross-sectional analysis was the secondary analysis. It was conducted to check the robustness of the findings from the cohort analysis. The cohort analysis used longitudinal data on self-reported TB treatment and treatment start month and year, allowing incidence rates to be estimated. However, it may have been biased by errors in reported dates and gaps in follow up between PC visits during which the outcome status was unknown. The

cross-sectional analysis used fewer assumptions. In this analysis each PC visit was treated as an independent cross-sectional sample. All 626 self-reported TB treatment episodes were included in the analysis. Figure 2 summarises the HPTN 071 (PopART) intervention rounds, study arms, PC0 to PC36 visit periods, and the observation period during which self-reported TB treatment was determined (14 months before each PC visit) at each PC visit. HIV status at the PC visit was assumed to be the HIV status during the 14-month eligibility period used to measure the outcome. The characteristics of PC participants seen at each PC visit were explored, to determine losses to follow up and comparability of PC participants seen across the study arms at each PC visit. The proportion self-reporting TB treatment (overall and by HIV status) was calculated for each community at each PC visit. Where there were no individuals self-reporting TB treatment for a community at a PC visit, 0.5 was added to the numerator to generate a proportion for the community. By PC visit, the geometric mean of the proportion self-reporting TB treatment for the communities in each arm was generated and then compared between study arms. Arms A and C, and arms B and C were compared; overall and for PLHIV. Cross-arm comparisons were not conducted for HIV negative individuals because there were a small number of events across the study arms when data were disaggregated by community and PC visits. There were no events among HIV negative individuals in four communities in PC0, four communities in PC12, three communities in PC24 and five communities in PC36.

Statistical inferences used the recommended 2-stage approach, adjusting for covariates at Stage-1. Stage-1 used logistic regression to compute the expected number of individuals with self-reported TB, assuming no intervention effect. Due to the small number of events during later PC visits (especially in Zambia in PC36), the total population analysis included only triplet and HIV status as covariates (without adjusting for age and sex). Analyses for PLHIV included triplet alone. At Stage-2, a two-way analysis of variance was conducted on the log (observed/expected number self-reporting TB) in each community, with matched

triplet and study arm as factors, to generate the overall prevalence ratio and 95% confidence intervals for cross-arm comparisons.

My role: The questionnaire had already been devised by the HPTN 071 study team and data was collected. I developed the research question based on the available data and reviewed the questionnaire and worked up the case definition. I worked up the methods to prepare the data for analysis (in particular the methods employed to prepare the data for the cohort analysis). I undertook all analyses presented.

Objective 4 - To investigate whether TB screening can identify people with TB disease earlier in their clinical course and improve their clinical outcomes.

Hypothesis: TB screening improves the treatment outcomes of people with TB disease (increased treatment success and decreased case fatality). It does this by identifying people with TB disease earlier in their clinical course when they ma y have less severe disease.

Rationale: There is some evidence that TB screening can decrease population-level TB disease prevalence[4, 16, 17]. To achieve this, people with TB in the community may be identified earlier in their clinical course and linked to care. This should improve their clinical outcomes. Therefore, this systematic review was undertaken to synthesise the evidence on the effect of TB screening on the clinical outcomes of people with TB disease. It was specifically conducted to inform the 2021 WHO guidelines on systematic screening for TB disease[5]. This work provides the foundation from which to understand whether the HPTN 071 (PopART) intervention can improve the clinical outcomes of people with TB disease.

Study design: Systematic review

Methods: Studies investigating the effect of any TB screening strategy on TB disease severity and the clinical outcomes of people with TB disease in any population group were included.

Populations, intervention, comparator, case definitions and outcomes: All population groups were included; any risk group (e.g. prisoners, miners, people attending health facilities) and general community populations. The intervention was any provider-initiated TB screening intervention, ranging from using health information/education to encourage appropriate health-seeking behaviours with or without increasing access to diagnostic services, to systematic TB screening using any screening tool (e.g. symptoms, chest radiography, microbiological tests) in a predetermined target group that aimed to identify people with undiagnosed TB disease and link them to TB treatment and care. The comparator was the routine diagnosis of symptomatic people with TB disease who self-presented to health

services (i.e. no TB screening activity). The TB disease case definition was bacteriologically confirmed (culture, Xpert MTB/RIF or smear positive) TB. Table 4 details the outcomes and their definitions.

Search strategy: In 2010, a systematic review undertaken by Kranzer et al 2013[6], synthesised literature published between 1/1/1980 to 13/10/2010 to inform the 2013 WHO TB screening guidelines. To update these TB screening guidelines, the WHO commissioned a series of systematic reviews, including this “clinical outcomes review”, using the same methods used in 2010. First Pubmed, EMBASE, Scopus and the Cochrane Library were searched between 1/11/2010 and 13/4/2020 for primary research articles. This search was conducted by Chaisson et al 2021[10]. The search terms used were broad, covering the concepts of TB and screening (Table 5). The aim of this initial search was to identify any study reporting on TB screening, using any TB screening strategy. Initial title and abstract screens were broad, only requiring the publication to be original research and screening for TB to have occurred. Full texts were reviewed to identify studies with sufficient information on the population screened. All population groups were included (general community populations and all risk groups). All stages of initial article screening process (title, abstract and full texts) were done by two reviewers. Disagreements were resolved by a third reviewer.

Articles from the search conducted by Chaisson et al 2021[10] reporting on screening for all forms of TB were assessed for eligibility in this “clinical outcomes review”. In addition, articles identified in the 2010 Kranzer review were also included. Bibliographies of identified studies were searched, and authors contacted for additional data when needed.

Table 4: TB disease severity and clinical outcomes

Outcome category		**Outcome indicator**
Earlier diagnosis	Disease severity at diagnosis - microbiology	smear positivity among bacteriologically-confirmed people with TB; smear grade; Xpert cycle threshold values; culture grade/colonies; time to culture positivity
	Disease severity at diagnosis - radiology	CXR severity score/grading
	Disease severity at diagnosis - anthropometric	body mass index
Earlier diagnosis and linkage to care	Time to first contact with health services	interval from start of symptoms to first contact with health services
	Time to diagnosis	interval from start of symptoms to diagnosis
	Time to treatment start	interval from start of symptoms to treatment start; time between diagnosis and treatment start
	Pre-treatment loss to follow-up	lost to follow-up between diagnosis and treatment start
Treatment	Treatment outcomes at treatment end	treatment success (cure and completion); lost to follow-up
	Disease outcome at treatment end - morbidity	body mass index; lung function test results; TB recurrence
Deaths	Mortality among screened and unscreened groups	all-cause mortality; TB-specific mortality
	Case fatality among people diagnosed with TB disease	all-cause case fatality; TB-specific case fatality
	Case fatality among people treated for TB disease	all-cause case fatality; TB-specific case fatality

Table 5: Search terms used in Pubmed by Chaisson et al 2021[10] shown below. These were adapted for EMBASE, Scopus and the Cochrane Library.

#1	"tuberculosis"[MeSH Terms]
#2	"tuberculosis"[tw] OR “Pulmonary Consumption”[tw] OR “Consumption, Pulmonary”[tw] OR Phthisis[tw] OR “Tuberculoses”[tw] OR “MDR-TB”[tw] OR “XDR-TB”[tw] OR “MDR TB”[tw] OR “XDR TB”[tw]
#3	#1 OR #2
#4	“Mass Screening”[MeSH Terms] OR “Mass Chest X-Ray”[MeSH Terms] OR "contact tracing"[MeSH Terms] OR “health surveys”[MeSH Terms] OR “Cross-Sectional Studies”[MeSH Terms] OR “Epidemiologic Studies”[MeSH Terms]
#5	“Mass Chest X Ray”[tw] OR “Mass Chest X-Rays”[tw] OR “screenings”[tw] OR “screening”[tw] OR “cross-sectional”[tw] OR “case-detection”[tw] OR “case finding”[tw] OR “contact tracing”[tw] OR “health survey”[tw] OR "prevalence survey"[tw] OR “prevalence studies”[tw] OR "mass radiography"[tw] OR "contact examination"[tw]
#6	#4 OR #5
#7	#3 AND #6
#8	("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))
#9	#7 NOT #8
#10	("2010/11/01"[EDAT] : "3000/12/31"[EDAT] OR "2010/11/01"[CRDT] : "3000/12/31"[CRDT]) OR ("2010/11/01"[PDAT] : "3000/11/31"[PDAT])
#11	#9 AND #10

Eligibility criteria: Only comparative studies were included; both interventional studies (randomised controlled trials and quasi-randomised trials) and observational studies (parallel design and before and after studies).

Exclusion criteria

- No screening for TB disease conducted or screening for MTB infection only
- Data not disaggregated by intervention and comparator group
- No comparator group (including studies where two TB screening strategies were being compared)
- Screened and comparator group represent two different non-comparable populations (e.g. screened miners and comparator the general population)
- Culture, Xpert MTB/RIF or smears not performed
- Only clinical diagnoses reported
- Clinical and microbiological diagnoses grouped together and could not be disaggregated

- No original data (commentary, editorial etc)
- Abstracts only
- Unable to locate full texts of articles

Inclusion criteria

- Original research data
- English, French and Spanish language articles

Study selection, data extraction, risk of bias assessment and evidence synthesis: Study selection, data extraction and risk of bias assessments were undertaken by two independent reviewers. Disagreements were resolved through discussion or, if required, consultation with a third reviewer. The abstracts of all articles were initially searched to identify studies with a comparator group. This review was broad, and confirmed if screening for TB disease took place and classified the time, place, and person characteristics of the comparator population (parallel design and comparator group from the same population/risk group as the screened group; before and after design in a defined population/risk group over defined periods of time). The full texts of studies with valid control populations were reviewed to determine suitability for inclusion. The full texts of articles with no abstracts and where the control group characteristics were also unclear were also reviewed.

Data were extracted into case report forms. Variables extracted included study design, population, calendar period, screening strategy, algorithm for diagnosing people with TB self-presenting to routine health services, TB case definition, participant numbers and outcome data. Methodological quality of cross-sectional studies was assessed across four domains; valid participant selection, valid exposure ascertainment, valid outcome ascertainment, and adequate control for confounders[18]. Quality assessment of cluster randomised trials was undertaken using the Cochrane Risk of Bias tool[19, 20].

Due to the heterogeneity of included studies (populations, screening tools, effect estimates, etc), data synthesis was narrative and stratified by population group (general population and risk groups). For treatment success and on-treatment case fatality calculations, only outcomes of cured, treatment completed, death, treatment failure, lost to follow-up, and not evaluated (including transferred out) were included in the denominator; other outcomes reported, such as still on treatment, were excluded. Smear grade was recategorized, with grades scanty/1+/2+ combined to reflect lower grades and 3+ reflecting higher grades. Sensitivity analysis explored recategorizing smear grades scanty/1+ as lower grade and 2+/3+ as higher grade. Where proportions were reported, 95% confidence intervals around the estimates were calculated.

My role: The PICO questions and eligibility criteria were developed by the Guideline Development Group convened by the WHO. I led the clinical outcomes review. I developed the review protocol, study selection process, and SOPs. I trained my team, who undertook the clinical outcomes review, on the study procedures and undertook as a reviewer the abstract and full text screens and the risk of bias assessment. I synthesised the evidence.

Objective 5 - To investigate the association between how TB disease was diagnosed (TB screening versus self-presentation to health services) and the clinical outcomes (treatment success and case fatality) of people with TB disease on TB treatment in the eight Zambian HPTN 071 (PopART) arm A and B intervention communities.

Hypothesis: TB screening improves the treatment outcomes of people with TB (increased treatment success and decreased case fatality).

Rationale: There is some evidence that TB screening can decrease population-level TB disease prevalence[4, 16, 17]. To achieve this, people with TB in the community may be identified earlier in their clinical course and linked to care. This should improve their clinical outcomes. But there are very limited data on the effect of TB screening on clinical outcomes[6]. Therefore, this study was undertaken to determine the association between TB screening and the clinical outcomes of people with TB disease on TB treatment.

Study design: Cross-sectional study

Methods: This study used data from the Zambian HPTN 071 (PopART) intervention communities alone. Similar data were not available for the South African intervention communities.

In Zambia there were eight intervention communities. Over three intervention rounds spanning 11/2013-12/2017 (with each round being ~15 months in duration), Community HIV care providers (or CHiPs) delivered a door-to-door combined HIV/TB prevention intervention. In both intervention arms, a questionnaire (comprising symptoms [cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month] or household member currently on TB treatment) was used to screen for TB at each intervention round. If screen positive, CHiPs collected and transported sputum for testing at the health centre using Xpert MTB/RIF if HIV positive or HIV status was unknown and smear if HIV negative. Sputum results were returned to the CHiPs. If Xpert or smear positive, CHiPs returned the results to

the individual in the community and linked them to TB treatment at the health centre with follow-up during TB treatment to ensure treatment was started and adherence to treatment.

Information on sputum samples collected by CHiPs was documented in paper presumptive TB registers, kept at the health centres, and maintained by the intervention team in seven communities. These intervention team presumptive TB registers were commenced during Quarter 4 of 2014 and were maintained by the intervention team until the end of the intervention period (December 2017). Table 6 details the information collected in the intervention team presumptive TB registers. One intervention community only had a laboratory register, where information on sputum samples tested with Xpert and smear were documented. This laboratory register served as the intervention team presumptive TB register for that community.

Information on all individuals started on TB treatment was recorded in paper TB treatment registers maintained by the health centre TB clinic. Each health centre had a TB treatment register. The TB clinics were usually run by a TB nurse, with support from volunteers. Table 7 details the information collected in the TB treatment registers.

Table 6: Information collected in the intervention team presumptive TB registers.

Variable name	Variable description
Sputum registration date	Day/month/year Date information entered in the presumptive register Usually complete
Serial Number	Consecutive number starting at 1 each year, given to all individuals who have information entered in the presumptive TB register. Multiple formats for entry used.
Entry point (also called sputum sample source)	Where the sample originated from **If from CHiPs TB screening – it was designated CHiPs or PopART allowing these samples to be identified in the registers.** Other options included outpatient department, ART clinic etc.
Full Name	Forename and surname
Popular name or nickname	
Sex	Male or Female
Age in years	Age at last birthday
Address	Poorly captured
Landmarks	Poorly captured
Phone number	Not available in all registers
Date sputum sent to lab	Day/month/year Poorly captured
Date sputum results received	Day/month/year Poorly captured
Sputum 1 result	Xpert or smear result
Sputum 2 result	Xpert or smear result
Sputum 3 result	Xpert or smear result
HIV result	Reactive, not reactive or blank Very poorly captured
Date TB treatment card opened	Day/month/year For individuals started on TB treatment Very poorly captured
Observations	Usually blank

Table 7: Variables available in the TB register

#	Variable	Variable description
1	Serial number	Numerical value. Starts at 1 at the start of each year and is consecutive.
2	Date of registration	day, month, year that individual was recorded in the TB register. May be different from the date of TB treatment start.
3	TB ID number	Found in several different formats. Site name/number/year Number/year Site name/number Number Meant to be a unique ID for each person with TB starting TB treatment. However, this number was not always available and not always unique.
4	Name	Text
5	Age	In years at last birthday
6	Sex	Male or Female
7	Address and landmarks	***Poorly recorded.*** Often missing, or just the community name or a number. In part this was because communities do not have formal street names and house numbers. Dwellings can be put up on any available plot of land. Most people had telephone numbers recorded, which were used to contact people with TB who needed to be located.
8	Patient type	New - no previous TB treatment Relapse – often used for anyone who previously had any TB treatment Transfer in Treatment after failure Treatment after loss to follow-up Other
10	TB type	Pulmonary (PTB) Extrapulmonary (EPTB)
11	M0 lab results	Sputum result at diagnosis (smear or Xpert) - positive, negative, or blank May include grade (smear/Xpert) – ***Poorly recorded***
12	M2/3 and M5-8 lab results	Usually not filled in Can have negative or positive results (including smear grade)
13	HIV result	Reactive Not reactive Blank
14	ART	Yes No Blank Represents ART started before or during TB treatment ***Poorly recorded***
15	ART start date	Day, month, year ***Poorly recorded***
16	Date of TB treatment start	Day, month, year
17	Regimen	TB treatment regimen
18	Treatment outcome	Cured Treatment completed Treatment failed Died Lost to follow-up Not evaluated (which included transferred out) ***Poorly recorded***
19	Outcome date	Day, month, year

The study communities in Zambia were across four Provinces - Copperbelt, Central, Lusaka, and Southern - which spanned the country (from the border with the Democratic Republic of the Congo in the North to Zimbabwe in the South). Data collection from all intervention community health centres was undertaken in three waves, between January 2017 and September 2019. Intervention team presumptive TB register data from 2014 to 2017 and TB treatment register data from 2014 to 2018 were collected for this work. At each data collection round, the following activities were conducted at the HPTN 071 intervention study community health centres:

1. Presumptive TB registers maintained by the intervention team and TB treatment registers were photographed. Images were immediately downloaded onto a secure encrypted laptop and deleted from the camera data card upon transfer.

2. Photographs of the TB treatment registers taken were printed at the study sites. The registers were printed at the sites to quality control the data. The printed TB treatment register copies were kept in a secure locked trunk, in locked HPTN 071 (PopART) study site offices. Different designated study staff members had access to the office key and the trunk key.

3. Original treatment cards (where available, see Table 8) were located for all people with TB started on TB treatment. These cards were the original patient records. TB treatment register information was usually completed using these treatment cards. The treatments cards were used to identify any missing TB treatment register information (in particular addresses, diagnosis sputum grades, ART start dates and treatment outcomes). Any missing variable values identified using the treatment cards were manually entered into the printed TB treatment register copies using a red pen, which differentiated them from the original information in the TB treatment register.

4. With HPTN 071 (PopART) study staff (community mobilisers and CHiPs), all addresses and locator information for all people in the TB treatment register were reviewed. Based on

this information, all people in the TB treatment registers for six intervention communities (excluding the two large Lusaka Province communities) were designated as living in the HPTN 071 (PopART) study community area, living outside the HPTN 071 (PopART) study community area, and don't know if living in the HPTN 071 (PopART) study community area.

5. All printed TB treatment register copies were taken back to the Zambart head office in Lusaka, where the data were double entered into study databases with entry validation and data cleaning. At Zambart, the printed registers were kept in locked trunks in locked offices, with only designated study staff having access to the offices and trunks. All TB treatment register photographs from the laptop were transferred onto the secure server at Zambart and deleted from the laptop upon transfer.

6. At the Zambart head office in Lusaka, photographs of the intervention team presumptive TB registers were printed. The data were single entered into a study database. The printed presumptive TB registers were kept in locked trunks in locked offices, with only designated study staff having access to the offices and trunks. All photographs from the laptop were transferred onto a secure server at Zambart and deleted from the laptop upon transfer.

Through discussions with the TB focal person at district health offices, additional health centres surrounding study communities known to be attended by study community members were identified. TB treatment register data were captured from three of these additional health centres. Data from all additional health centres could not be collected due to feasibility (especially for the large Lusaka sites) and local, district-specific requirements.

Table 8 outlines the completeness of the TB treatment register data from the intervention community health centres, the availability of treatment cards, additional health centres from which data were collected and specific information relating to communities during the HPTN 071 (PopART) study period. The study activities resulted in the capture of data for 21,826 people started on TB treatment between 2014-2018. Complete TB treatment register data (i.e. with no missing register information – see Table 8) were available for the Zambian

intervention communities from 1/12/2015. Presumptive TB register data were only captured from the study community health centres. The study activities resulted in the capture of data for 51,114 people investigated for TB disease between Quarter 4 of 2014 and December 2017.

Table 8: HPTN 071 (PopART) Zambian intervention communities, completeness of TB treatment register data and patient cards, additional health centres from which data were collected and additional comments

Communities	2014	2015	2016	2017	2018	Comments
Triplet 1A (Kitwe)	Complete	No register.	Complete	Complete	Complete	Very small number of treatment cards found. Rapid growth and urbanisation of community. Data from the TB notification centre for Kitwe was also captured. No treatment outcome data recorded at the notification centre.
Triplet 1B (Kitwe)	Complete	Complete	Complete	Complete	Complete	Address very poorly captured. Data from the TB notification centre for Kitwe was also captured. No treatment outcome data recorded at the notification centre.
Triplet 2A (Ndola)	Complete	Complete	Complete	Complete	Complete	No treatment cards kept. Addresses very poorly captured. No TB corner nurse until 2018 – TB corner run by volunteers. Treatment outcomes poorly recorded.
Triplet 2B (Kabwe)	Aug-Dec only.	Complete	Complete	Complete	Complete	Data from a nearby health centre also captured. Very few treatment cards. Older TB registers and cards destroyed during a storm. Registers in very poor condition with missing pages in most.
Triplet 3A (Lusaka)	Complete	Jan-Apr & Dec only.	Complete	Complete	Complete	Registers in very poor condition over most years. Missing pages in most. Very few treatment cards found. TB corner moved several times, including to different health centres with treatment cards lost during these moves and damage to registers. Addresses very poorly captured. Data represent a large Lusaka community with irregular intervention borders.
Triplet 3B (Lusaka)	Complete	Complete	Complete	Complete	Complete	Data represent a large Lusaka community with irregular intervention borders.
Triplet 4A (Livingstone)	Complete	Complete	Complete	Complete	Complete	Data from a nearby hospital also captured.
Triplet 4B (Livingstone)	Complete	Complete	Complete	Complete	Complete	Data from a nearby hospital also captured. Multiple copies of registers found (due to missing registers which were later found). Information needed to be consolidated. Limited number of treatment cards found. Condition of registers generally poor.

Redefining intervention boundaries for the Lusaka intervention communities: The aim was to include all people with TB starting TB treatment, residing in the intervention community areas, that would have received/would have had the opportunity to receive the HPTN 071 (PopART) intervention. All Zambian communities had areas within their boundaries. Prior to the start of the study, the HPTN 071 (PopART) study team delineated each community into study zones. The intervention was delivered to all households within the HPTN 071 (PopART) zones. For Zambian communities outside the Lusaka Province (six of the eight communities), the zones covered all areas within the community (i.e. the intervention was delivered throughout the community). While communities grew over time, and different healthcare seeking behaviours resulted in people with TB seeking treatment from different health centres, and addresses/landmarks were poorly captured in TB treatment registers, which could not be fully accounted for, the original study intervention zones were easier to delineate. Therefore, when addresses/landmarks were available in TB treatment registers from these communities, it was possible to identify if the dwellings were inside the HPTN 071 (PopART) intervention zones or outside the HPTN 071 (PopART) intervention zones.

In the Lusaka Province intervention communities, the intervention was only delivered to part of the total community population, due to the large size of the communities. When study zones were delineated, they did not always cover all household in a given community area as shown in Figure 13. In some intervention community areas only some of the households received the intervention – using addresses/locator information available in the TB treatment registers, households receiving the intervention could not be clearly separated from those not receiving the intervention in these areas. Therefore, for this analysis, people starting TB treatment whose addresses in the TB treatment register were from these areas were excluded. In some areas within the Lusaka intervention communities, all households received the intervention – people starting TB treatment whose address in the TB treatment register were from these areas were included in the analysis.

1, 2, 3, 4, 5	Areas within the community. Each area is surrounded by a black border
	Did not receive the intervention.
	Received the intervention. Also called HPTN 071 (PopART) intervention zones.

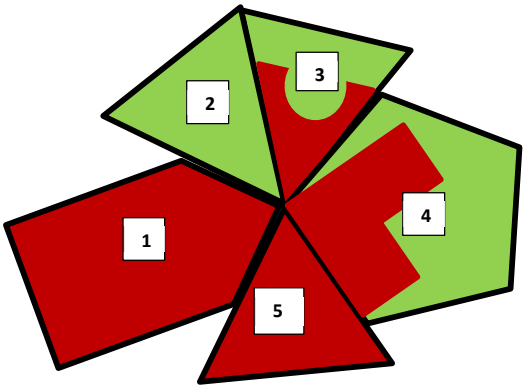

Figure 13: Example showing how intervention boundaries were re-defined for the Lusaka intervention communities. Numbers 1-5 represent areas within the community. All households in areas 1 and 5 received the intervention and any person with TB starting TB treatment, whose address in the TB treatment register was from these areas was included in the analysis. Only some households in areas 3 and 4 received the intervention – these households could not be easily distinguished from those that did not receive the intervention in the areas based on address/locator information in the TB treatment registers. Therefore, any person with TB starting TB treatment, whose address in the TB treatment register was from these areas, was not included in the analysis. No households in area 2 received the intervention. All people with TB starting TB treatment, whose addresses in the TB treatment register were from this area, were excluded from the analysis.

Data linkage: The aims of data linkage were:

1) To determine the proportion of people with TB disease identified through CHiPs TB screening who were started on TB treatment.
2) To categorise all people with TB disease started on TB treatment in the TB treatment register, by the mode of how they were diagnosed (CHiPs TB screen identified, or clinic identified). Once they were categorised, treatment outcomes were compared between the groups using the data available in the TB treatment registers.

Presumptive TB registers were used to identify all CHiPs positive TB results; defined as a documented sputum Xpert MTB/RIF or smear positive result in the intervention team presumptive TB register and sputum sample source documented as CHiPs or PopART. All

people with a CHiPs positive TB result between 1/12/2015 to 31/12/2017 were included in the analysis. The start date mirrored the date from which there was complete TB treatment register data for matching, and the end date, the end of the intervention. TB treatment register data between 1/12/2015 and 31/12/2018 (to allow maximum time for matching) were used for matching.

There was no unique identifier for individuals in the two registers. Therefore, patient names of CHiPs positive TB results identified in the presumptive TB registers were matched to names in the TB treatment registers using the Stata “matchit” command. This command allows automated approximate matching between string variables as detailed in Figure 14.

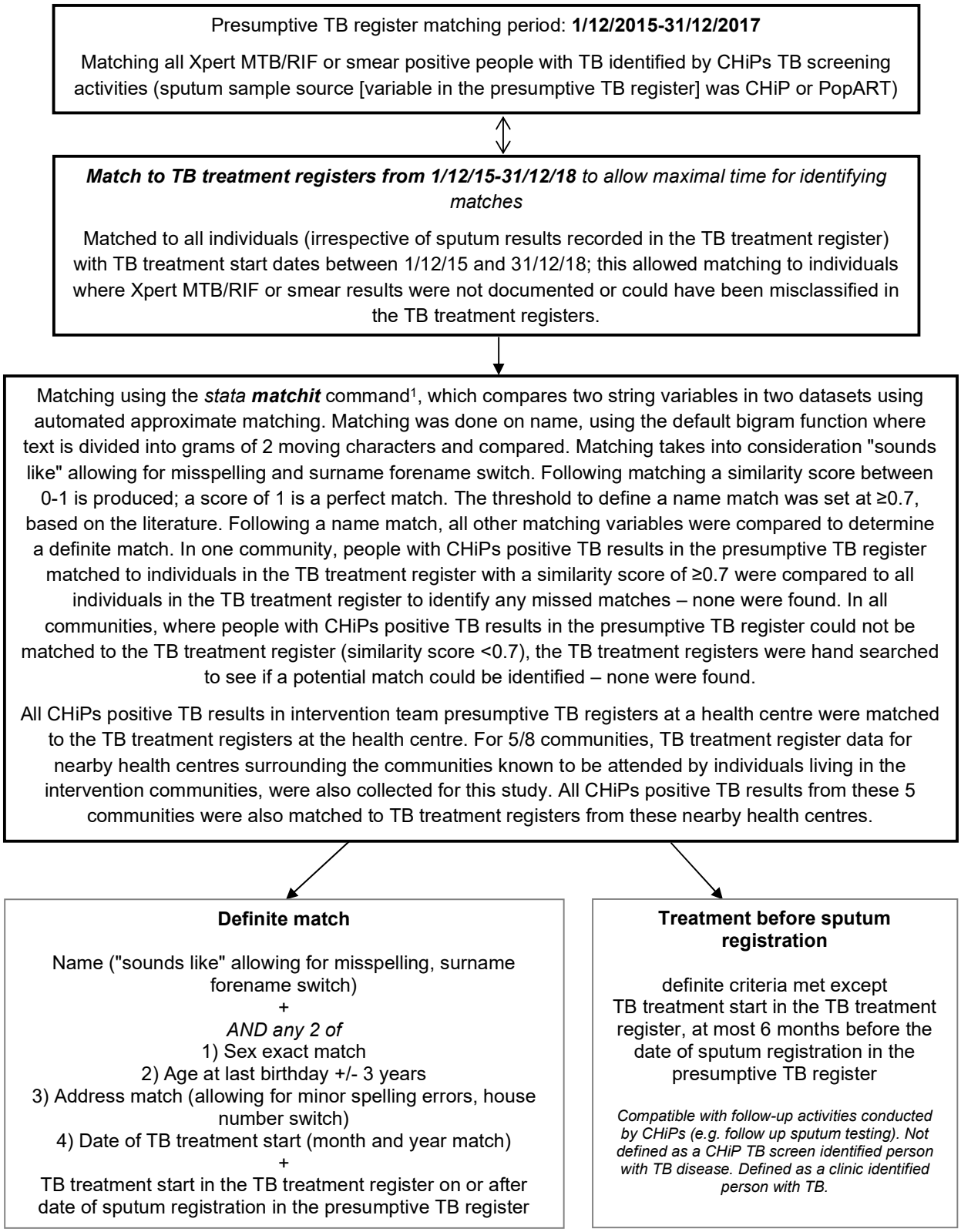

Figure 14: Matching CHiPs positive TB results to TB treatment registers [1]*Julio Raffo, 2015. "MATCHIT: Stata module to match two datasets based on similar text patterns," Statistical Software Components S457992, Boston College Department of Economics, revised 20 May 2020*

A definite match was defined as a name match AND any two of sex, age +/-3 years, address or TB treatment start month/year match AND the treatment start date was the same as or after the sputum registration date. By matching, all individuals in the TB treatment registers were categorised as CHiPs TB screen identified (definite match to a CHiPs positive TB result) or clinic identified (not matched to a CHiPs positive TB result or matched to a CHiPs positive TB result but TB treatment was started in the 6 months before the date of sputum registration in the presumptive TB register); this was the exposure. For the analysis data in the TB treatment register between 1/1/2016 and 31/12/2017 were used. Figure 15 summarises the study processes and the inclusion and exclusion criteria, including the rationale for the primary analysis. The TB case definition for the primary analysis was new, Xpert MTB/RIF or smear positive, adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, who resided within community areas where all households in the area were eligible for the intervention. The TB case definition for the secondary analysis was all (new and previously treated), Xpert MTB/RIF or smear positive, adults, starting TB treatment between 1/1/2016-31/12/2017, who resided within community areas where all households in the area were eligible for the intervention.

Sputum results were classified as high grade (Xpert MTB/RIF medium and high or smear 2+ and 3+) or low-grade (Xpert MTB/RIF low, very low and trace or smear scanty and 1+). Sputum grade was considered a mediator of the association between TB screening and treatment outcomes, as screening aims to identify individuals earlier in their clinical course when sputum-grade may be lower. The study outcomes were treatment success (cured and treatment completed combined) and case fatality (death from all causes while on TB treatment) among all individuals treated. The denominator (all individuals started on TB treatment) included those with missing treatment outcomes, individuals who were lost to follow up during treatment or who transferred out while on treatment.

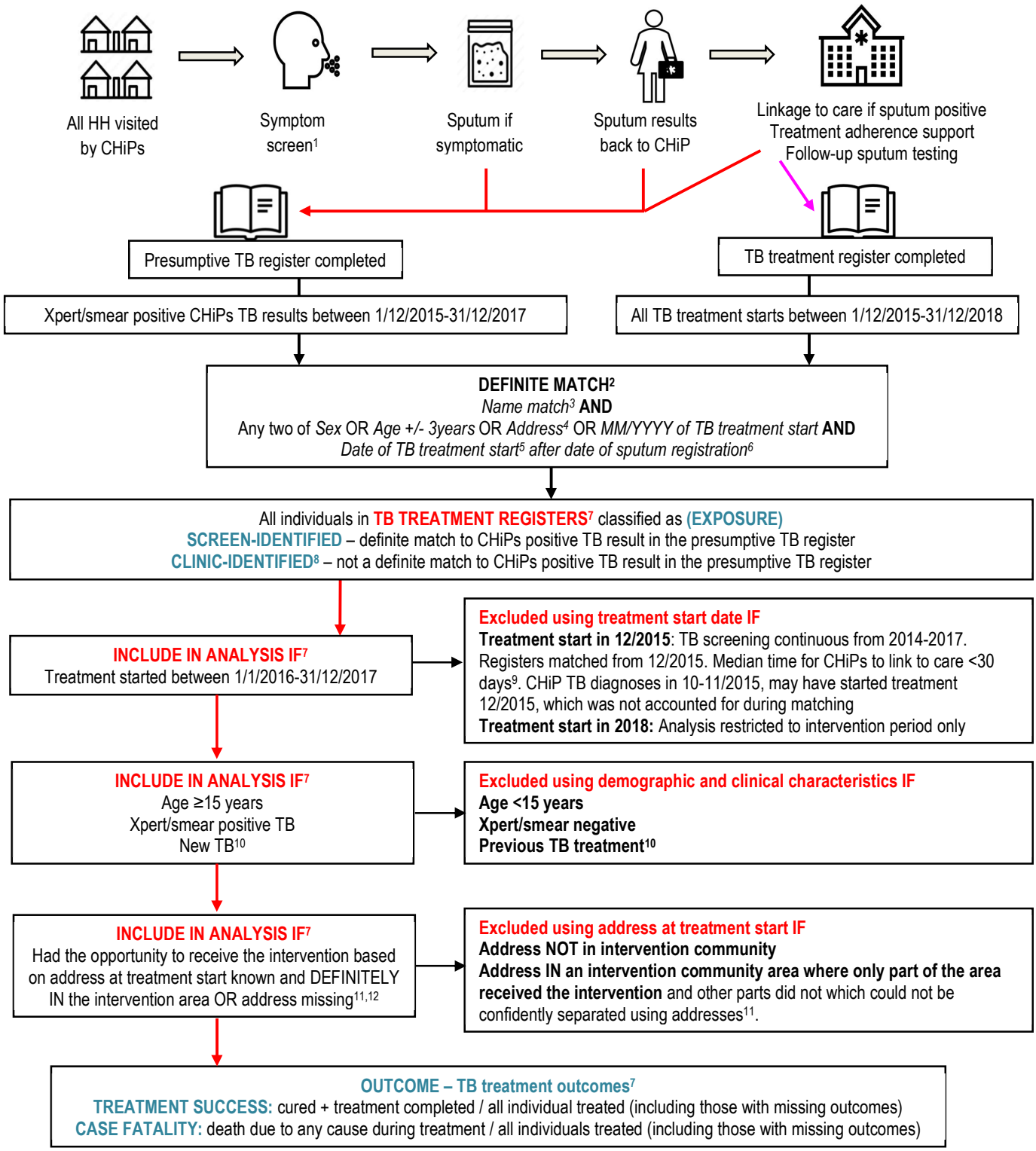

Figure 15: The systematic TB screening intervention, data sources, matching algorithm, exposure, inclusion/exclusion criteria for TB case definition and outcome. HH=household; CHiPs=community HIV-care providers; TB=tuberculosis; [1]TB screening (using symptoms [cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month] or household contact of a person with TB disease) with all households visited at least 3 times between 2014-2017; [2]Matching also identified individuals meeting definite criteria except treatment was started in the 6 months before sputum registration (compatible with follow-up sputum testing, testing symptomatic

people on treatment). These individuals were not considered CHiPs TB screen identified people with TB disease; [3]Matching done using the stata matchit command which allows automated approximate matching between string variables. Matching includes exact matches or "sounds like" and allowing for misspelling and surname forename switch. Matching produces a similarity score between 0-1 (1 is a perfect match). A threshold of ≥0.7 was used to define a match; [4]allowing for minor spelling errors, house number switch; [5]in TB treatment register; [6]in presumptive TB register; [7]Following matching the analysis was restricted to information held in the TB treatment registers; [8]Included those not matched to CHiPs positive TB results in the presumptive TB registers or individuals meeting definite match criteria except TB treatment was started in the 6 months before sputum registration; [9]CHiPs intervention data showed the median time to link to treatment was ~20 days in 7/2015-9/2016 and ~14 days in 10/2016-12/2017; [10]secondary analysis included individuals with new and previous TB treatment; [11]All communities had areas within their boundaries. In the large Lusaka province communities, the intervention was only delivered to part of the community. In some areas, all households received the intervention – people with TB disease starting TB treatment whose addresses were in these areas were included in the analysis. In some areas only some of the households received the intervention - households receiving the intervention could not be clearly separated from those not receiving the intervention in these areas. People with TB disease starting TB treatment whose addresses were in these areas were excluded. Outside the Lusaka province, the intervention was delivered throughout community areas that were clearly demarcated. [12]Individuals with missing addresses (8% of the study sample) – who could not be categorized as living at an address definitely in or not in the intervention community areas - were included in the analysis.

Analysis: The proportion of CHiPs TB screen identified people with TB disease among all individuals started on TB treatment meeting the TB case definitions were summarised. To investigate the association between the mode of TB diagnosis and sputum grade, and between mode of TB diagnosis and treatment success, logistic regression was used. Initial base models adjusted for age, sex, and community. Multivariable analysis consisted of base models and HIV status. Due to the small number of deaths, conditional logistic regression, matched on community, was used to investigate the association between mode of TB diagnosis and case fatality. Initial base models adjusted for age and sex. Multivariable analysis consisted of base models and HIV status.

Data quality: Routine TB (presumptive TB and TB treatment register) data collection commenced in Zambia in January 2017, during the final year of the HPTN 071 (PopART) intervention. Therefore, the data collected were mainly retrospective; the study team were unable to influence/improve the completeness of most data collected. There were missing TB treatment registers for 3/8 (38%) communities (Table 8). This resulted in missing full year/months of data. Efforts were made to identify missing registers, identify treatment cards

to complement available data, and find alternative sources of TB treatment register data (e.g. TB notification centre data for Kitwe). Complete TB treatment register data (i.e. no data missing for whole months) were only available from 1/12/2015. Complete presumptive TB register data were only available from Quarter 4 of 2014. Therefore, data were only matched and analysed for the last 2 years (2016-2017) of the 4-year intervention period. Even where TB treatment register data were complete, register conditions were poor for 3/8 communities (38%; 2 arm B communities and 1 arm A community), with missing pages in registers (Table 8). While poorer conditions predominantly affected older registers (2014-2015 registers), this could have affected linkage between presumptive TB and TB treatment registers.

All routine TB data were collected in three data collection rounds starting in Quarter 1 of 2017; the final intervention year. These study activities, which were planned and expected by the intervention team and health centres, may have contributed to improving the completeness of register data (presumptive TB and TB treatment) from 2017. This may in part have contributed to the observed changes in the proportion of people started on TB treatment identified through CHiPs TB screening between 2016 and 2017 (proportion increased from 11% in 2016 to 19% in 2017 – see Chapter 7). However, our findings were consistent with feedback on TB screening-related activities from the Zambian intervention team and the yield of TB screening determined using CHiPs intervention process data: the proportion of individuals identified with presumptive TB (i.e. had a positive symptom screen) increased from 1.2% in intervention round 2 to 2.7% in intervention round 3, and the yield of TB screening increased from 93 per 100,000 people screened in intervention round 2 to 110 per 100,000 people screened in intervention round 3 (see Chapter 1). This suggests study related activities contributed to the changes observed using routine data.

The completeness of the recorded variable values varied (Table 6-7). Presumptive TB register (Table 6) variables used to identify CHiP positive TB results (name, sputum sample source) were well recorded. Nevertheless, misclassification of sputum sample source was possible. The HPTN 071 (PopART) trial did not consent community members to link CHiPs

intervention process data to health centre data; if this were possible, all CHiP positive TB results identified in presumptive TB registers could have been cross-checked/verified against individuals documented as having a positive sputum result through TB screening activities in the CHiPs intervention process data. Two of the four variables used for matching (address and date of TB treatment start) tended to be poorly recorded in presumptive TB registers. However, for individuals with a CHiP sputum sample source these variables were mostly complete, giving confidence when matching between presumptive TB and TB treatment registers.

Sputum grade and treatment outcomes were poorly recorded in TB treatment registers (Table 7). To try and identify missing variable values, original treatment cards were sought, organised where available and cross-checked against TB treatment registers. Very few/no treatment cards were found for 5/8 (63%) communities. The proportion with treatment success was high (82%; see Chapter 7). Treatment outcomes could not be verified; over-ascertainment of good outcomes (e.g. treatment success documented even if outcomes were unknown) or other types of misclassifications were possible.

This work was restricted to Zambian intervention communities alone, as similar data from the South African intervention communities were not available. Presumptive TB registers were not available from South Africa for this work; National Health Laboratory Services (NHLS; South African laboratory) data, could have been used as the sputum sample source is documented in this data. However, local regulations did not permit NHLS data to be matched with TB treatment registers for this work. Further, as already mentioned, there were shortfalls in TB treatment register data captured through the Electronic TB Registers in South Africa, across multiple communities and multiple calendar years, during the study period. Therefore, TB treatment register data for South Africa were also not available.

My role: I developed the research question. I developed the data dictionary for the study database and trained the study data manager and data capturers on the data dictionary. I

developed all study related SOPs. The study data manager and I photographed all intervention team presumptive TB registers at the health centres, at each data capture round. I worked up the matching algorithm, undertook all matching, and undertook all analyses.

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Chapter 3: Literature review on the effect of increasing antiretroviral therapy coverage on measures of tuberculosis at the population-level.

Overview of objective and methods

The overall objectives and methods are detailed in Chapter 2. In summary, a literature review using systematic methods was undertaken to synthesise the evidence on the impact of antiretroviral therapy (ART) scale-up in sub-Saharan Africa on measures of tuberculosis (TB) at the population-level. The intervention was increasing ART coverage due to scaling-up ART and changes to CD4+ T-lymphocyte thresholds at which ART was initiated. The comparator was lower ART coverage (in the same population at a different point in time or in a different population) or the pre-ART era. The outcomes were TB disease prevalence, TB disease incidence, TB notifications, *Mycobacterium tuberculosis* (MTB) infection incidence or MTB infection prevalence. MEDLINE and EMBASE were searched from inception to the 5th of September 2022 for original research articles. A narrative synthesis was used to summarise the findings.

Results

The search identified 11,772 articles of which 19[1-19] met the eligibility criteria for inclusion (Table 1). Table 2 to Table 4 describe the 19 articles. Of the 19 articles, 18 reported on observational studies[1-18] (Table 2 and Table 3) and one a cluster randomised trial[19] (Table 4). Of the articles reporting on observational studies, four were from Malawi[1-4], seven from South Africa[5-9, 16, 17], two from Zimbabwe[11, 12], one from Eswatini[10], one from Kenya[13], one from Uganda[14] and two combined data published by the World Health Organization (WHO) for sub-Saharan African countries[15, 18].

Table 1: Number of articles identified, screened, assessed for eligibility, and included.

Total number of articles identified (including systematic reviews* and original research articles)	14,961
Number remaining after de-duplication	11,772
Number remaining after title screen	398
Number remaining after abstract screen (including those with no abstracts)	81
Number eligible	19

*no systematic reviews assessing the impact of ART scale-up in sub-Saharan Africa on measures of TB at population-level were identified through this literature review.

Table 2: Articles reporting on observational studies using routinely available data that describe changes to TB notifications and diagnoses coincident with increasing ART coverage.

Author, year, study design, and country	**Methods**
Zachariah 2011[1] Ecological Malawi	**Area:** Thylolo district - rural. HIV prevalence of 20% in 2007. **Study period:** 2002-2009 **ART programme:** Since 2003. ART eligibility CD4+ T-lymphocyte threshold ≤250 cell/μL. **Data sources:** district TB register for 2002–2009 with TB notification standardised per 100,000 population/year. Annual population data from Demographic and Health Survey and census data. ART data from Médecins Sans Frontières and the routine district reporting system. **Outcome:** new and recurrent TB notification rates. **Data analysis:** Described changes to TB notification rates over time.
Kanyerere 2014[2] Ecological Malawi	**Area:** Malawi national data. **Study period**: 2000-2012 **ART programme**: Started in 2004. ART eligibility CD4+ T-lymphocyte threshold ≤250 cell/μL up to 2010 and ≤350 cell/μL thereafter. **Data sources**: TB notifications from NTP reports; ART data from MoH reports. **ART coverage**: all adults and children recorded as alive and retained on ART at the end of each year divided by the total number of PLHIV based on epidemiological projections from UNAIDS. **Outcome:** number of all TB notifications. **Data analysis:** Described changes to ART coverage and TB notifications over time.
Kanyerere 2016[3] Ecological Malawi	**Area**: Malawi national data. **Study period:** 2005-2015 **ART programme**: Started in 2004. ART eligibility CD4+ T-lymphocyte threshold ≤250 cell/μL before 2010, ≤350 cell/μL between 2010-2014, and ≤500 cell/μL thereafter. **Data sources:** TB notifications from NTP reports. ART data from MoH reports. National population estimates from the Malawi National Statistics Office. **ART coverage:** all adults and children recorded as alive and retained on ART at the end of each year divided by the total number of PLHIV based on epidemiological projections from UNAIDS. **Outcome**: all TB notification rates **Data analysis**: Described changes to ART coverage and TB notification rates over time.

Kanyerere 2016[4] Ecological Malawi	**Area:** Malawi national data. **Study period**: 1985-2014 **ART programme:** Started in 2004. ART eligibility CD4+ T-lymphocyte threshold ≤250 cell/μL before 2010, ≤350 cell/μL between 2010-2014, and ≤500 cell/μL thereafter. **Data sources:** TB notifications from NTP reports. ART data from MoH reports. National population estimates from the Malawi National Statistics Office. **ART coverage**: all adults and children recorded as alive and retained on ART at the end of each year divided by the total number of PLHIV based on epidemiological projections from UNAIDS. **Outcome**: all TB notification rates and number of TB notifications. **Data analysis**: Described changes to ART coverage and TB notification rates and TB number over time.
Middelkoop 2011[5] Ecological South Africa	**Area:** Peri-urban township near Cape Town: HIV prevalence of 23% in 2005. **Study period:** 1997-2008 **ART programme:** Started in 2003 through the local clinic and hospital, with scale-up in 2005. From 2004 TB screening for all PLHIV starting ART. **Data sources:** TB notifications from the local TB clinic. ART data from TB registers and the ART database at the health clinic and hospital. Population denominators from the 1996 national census and household census in 2002, 2004, 2006, and 2008. HIV prevalence estimated using the AIDS demographic model for African populations, using 2 HIV prevalence surveys in the communities (2005 and 2008) to parameterise the model. **ART coverage**: proportion of all adult (≥15 years) PLHIV receiving ART each year. **Outcome**: all TB notification rates among adults (≥15 years). **Data analysis:** A priori chose 2005 as the 1st year of ART availability as this was the first year an appreciable number received ART. Described changes to ART coverage and TB notification rates pre-2005 and from 2005.
Hermans 2015[6] Ecological South Africa	**Area:** Cape Town (urban, peri-urban). **Study period:** 2003-2013 **ART programme:** Available since 2001. National programme launched in 2004. ART eligibility CD4+ T-lymphocyte threshold <200 cell/μL from 2004, ≤350 cell/μL in 2012, and ≤500 cell/μL in 2015. **Data sources:** TB notifications from NTP data. Annual population size from Statistics South Africa estimates. Annual HIV prevalence from the Western Cape AIDS and demographic model. Number of people on ART from the Health Information System. **ART coverage**: proportion of all PLHIV each year who were on ART. **Outcome:** all TB notification rates. **Data analysis:** Described changes to ART coverage and TB notification rates over time.
Nanoo 2015[7] Ecological South Africa	**Area:** South Africa national data. **Study period**: 2004-2012 **Data Sources:** Microbiologically confirmed TB data from National Health Laboratory Services. TB notification data from NTP. Population estimates from census data every 5 years, with imputation for interim years. HIV prevalence and ART coverage data from the South African AIDS and demographic model. **Outcome:** microbiologically confirmed (smear, culture, or Xpert MTB/RIF positive) TB incidence, TB notification rates. **Data analysis:** Time series analysis to describe trends in microbiologically confirmed TB incidence and TB notification rates.
Hoogendorn 2017[8] Ecological South Africa	**Area**: Mopani district - rural. Adult HIV prevalence 12%. **Study period**: 2009-2013 **ART programme**: In 2009 a doctor driven centralised service with an ART eligibility CD4+ T-lymphocyte threshold <200 cell/μL. In 2013 this was nurse managed with an ART eligibility CD4+ T-lymphocyte threshold ≤350 cell/μL. **Data sources:** TB notifications from TB registers from 4 public hospitals. ART data and how coverage determined not specified. **Outcome***:* number of extrapulmonary TB notifications. **Data analysis**: Described changes to ART coverage and extrapulmonary TB notifications over time.

Hermans 2019[9] Ecological South Africa	**Area:** Cape Town. HIV prevalence in 2013 19.7%. **Study period:** 1993 and from 2003-2014 **Data source:** TB notifications from the Cape Town Medical Officer of Health report for 1993 and from the Cape Town Metropolitan Electronic TB Registers from 2003. Population estimates from the Cape Town Medical Officer of Health report for 1993 and statistics South Africa (from 2003). Annual HIV prevalence estimates from the South Africa Western Cape AIDS model 2008. **ART coverage:** Calendar years used to assign 4 stages of HIV epidemic: 1993 – minimal HIV; 2003 – early HIV no ART; 2008 – established HIV with early ART – coverage estimated at 29%; and 2013 – established HIV with late ART rollout and ART coverage 63%. **Outcome:** all TB notification rates stratified by gender. **Data analysis:** Described changes to ART coverage and TB notification rates (stratified by gender) by stages of the HIV epidemic.
Kerschberger 2019[10] Ecological Eswatini	**Area**: Shishelweni region – rural. **Study period**: 2009 to 2016 **ART programme**: ART eligibility CD4+ T-lymphocyte threshold changed from <200 cell/μL to <350 cell/μL in 2010, and to <500 cell/μL in 2015. **Data sources**: All TB notifications (excluding those transferring in) from the electronic TB register maintained by Médecins Sans Frontières. ART numbers from the national electronic ART treatment database maintained by the MoH. Population denominators were from projected regional estimates based on a 2007 household census. HIV prevalence estimates used 2 sources - 2011 HIV incidence survey estimates for 20-49 year olds, Demographic and Health Survey data for ≤14 and ≥50 years olds, and an average of the 2 data sources for those aged 15-19 years old. **ART coverage** defined as the mid-year numbers of PLHIV on ART divided by the estimated number of PLHIV. **Outcome**: all TB notification rates. **Data analysis**: Described changes to ART coverage and TB notification rates over time. Using all TB notifications, multivariable analysis was used to determine factors associated with TB.
Takarinda 2016[11] Ecological Zimbabwe	**Area**: Zimbabwe national data. **Study period**: 2000-2013 **ART programme**: started in 2004. ART eligibility CD4+ T-lymphocyte threshold <200 cell/μL from 2004, <350 cell/μL from 2011 and <500 cell/μL from 2014. **Data sources**: TB notifications from WHO website. Number of PLHIV and number of PLHIV on ART from UNAIDS data. Total population size from census in 2002 and 2012 and between 2002-2012 population figures were based on an annual average growth of 1.1%. For 2013 used national population projection statistics. **ART coverage:** proportion of PLHIV each year, who were on ART. **Outcome**: all TB notification rates. **Data analysis:** Described changes to ART coverage and TB notification rates over time.
Takarinda 2020[12] Ecological Zimbabwe	**Area**: Zimbabwe national data. **Study period**: 2000-2018 **ART programme**: started in 2004. ART eligibility CD4+ T-lymphocyte threshold <200 cell/μL from 2004 up to 2010, <350 cell/μL from 2011-2013, <500 cell/μL from 2014 to mid-2016 and irrespective of CD4+ T-lymphocyte threshold from mid-2016. IPT scale-up started in 2011. **Data sources**: TB notifications from WHO website. National population size from 2002 and 2012 national census data with projections based on these for years without figures. Annual estimated number of PLHIV from UNAIDS projections. Annual number on ART from national programme reports from WHO. Annual number on IPT from the Zimbabwe Demographic Health Information System. **ART coverage**: annual number of PLHIV on ART divided by the annual estimated number of PLHIV. **IPT coverage**: annual number of PLHIV receiving IPT divided by the annual number of PLHIV on ART. **Outcome**: all TB notification rates. **Data analysis**: Described changes to ART coverage and TB notification rates over time.

Yuen 2014[13] Ecological Kenya	**Area**: Kenya national data. **Study period**: 2006-2012 **ART programme**: started in 2004. ART eligibility CD4+ T-lymphocyte threshold ≤200 cell/μL until 2007, ≤250 cell/μL up to 2010 and ≤350 cell/μL thereafter. **Data Sources**: TB notifications from NTP data. HIV prevalence from 2007 and 2012 Kenya AIDS Indicator Survey, with a constant rate of change in HIV prevalence assumed between surveys. ART data from the National AIDS and STI programme data. Population estimates from 1999 and 2009 Kenya census with constant annual growth in population size assumed between surveys. **ART coverage:** proportion of PLHIV each year, who were on ART. **Outcome**: all TB notification rates among adults ≥15 years. **Data analysis**: Described changes to ART coverage and TB notification rates over time.
Zawedde-Muyanja 2019[14] Ecological Uganda	**Area**: Kampala and 8 surrounding districts. Estimated HIV prevalence of 9%. **Study period**: 2009-2017 **ART programme**: ART eligibility CD4+ T-lymphocyte threshold ≤250 cell/μL in 2009-2011, <350 cell/μL in 2012, <500 cell/μL in 2014, and irrespective of CD4+ T-lymphocyte count in 2016. **Data sources**: TB notifications from quarterly reports submitted to the NTP. Population estimates from national census data from 2002 and 2014, with adjustments for the intervening periods. HIV prevalence from AIDS indicator surveys in 2005 and 2011 and CDC data for 2015. HIV prevalence adjusted for the intervening periods. Number of people alive and on ART from the Annual AIDS control programme report. **ART coverage**: number of PLHIV alive and on ART divided by the number of PLHIV. **Outcome**: all TB notification rates. **Data analysis**: modelled the average annual percentage change in TB notification rates using a Poisson generalized linear model.
Surie 2018[15] Ecological sub-Saharan Africa	**Area**: sub-Saharan Africa. **Study period**: 2010-2015 **Data sources**: TB notifications, number tested for HIV, and number HIV positive from WHO. HIV prevalence estimates for those aged 15-49 years and ART coverage from UNAIDS. Population estimates for those aged 15-49 years from UNDP. **Inclusion/exclusion for all 47 countries considered:** Data quality considered adequate if HIV prevalence estimate available and ≥75% of people with TB had been tested for HIV. If <4 years of data meeting adequate quality criteria – excluded. After calculating HIV stratified TB notification rates, countries excluded if >50% year on year variation in estimates, which could be due to data quality issues or too few people with TB to make rate calculations meaningful. **Outcome**: all TB notification rates. **Data analysis**: Described changes to ART coverage and TB notification rates over time. For each country the average annual percent change in TB notification rates (stratified by HIV status) was calculated based on the corresponding 2010 and 2015 notification rates and assuming a constant annual percent change during this period. Across the countries, the median annual average change in TB notification rates were compared between PLHIV and those HIV negative.

TB=tuberculosis, ART=antiretroviral therapy; PLHIV=people living with HIV; NTP=National TB programme; MoH=Ministry of Health; UNAIDS=Joint United Nations Programme on HIV/AIDS; WHO=World Health Organization; AIDS=Acquired Immune Deficiency Syndrome; IPT=Isoniazid Preventive Therapy; STI=Sexually Transmitted Infections; UNDP=United Nations Development Programme; All information on ART programmes is as presented in the original manuscripts.

Table 3: Observational studies that investigated the association between ART coverage and measures of TB at the population-level.

Author, year, study design, and country	Methods
Middelkoop 2010[16] Cross-sectional South Africa	**Area**: peri-urban township. ART roll out commenced in 2005. The estimated ART coverage among PLHIV was 5% in 2004; 13% in 2005 and 21% in 2008. TB screening when PLHIV started on ART. **Baseline TB prevalence survey:** in 2005. TB prevalence 3% (treated and untreated TB) in the community. **Study survey:** used the same methods as the 2005 survey. *Date* – June to December 2008. *Population* – Households in the community enumerated and 1500 resident ≥15 years randomly selected (10% of the community). *Procedures* – questionnaire; 2 sputum samples for smear and culture; anonymised HIV testing. *TB case definition* – 1) treated TB = self-reported current treatment; 2) untreated TB = no treatment AND 2 positive smears *or* 2 positive cultures *or* smear and culture positive on separate specimens. **Outcome**: TB prevalence (all and by treatment status). **Analysis**: logistic regression to examine changes in overall TB prevalence between the two surveys, after adjusting for individual-level covariates.
Tomita 2019[17] Population-based cohort South Africa	**Area**: Demographic and Health Survey area in rural KwaZulu-Natal. **Study period**: 2009-2015. **ART programme and coverage**: ART programme started in 2004. By 2009 the average ART coverage across communities was 30%. Following changes to ART eligibility thresholds in 2010, the average ART coverage in 2012 was 52%. **Data sources**: TB data from annually collected Demographic and Health Survey information on self-reported TB in the last 12 months. ART data from ARTemis (the ART Evaluation and Monitoring System). ART data were linked to the Demographic and Health Survey data and the proportion of all PLHIV receiving ART (ART coverage) calculated for each community. **Outcome**: self-reported TB in the last 12 months in adults ≥15 years who took part in the survey at least once between 2009-2015. **Analysis**: the association between community ART coverage and self-reported TB investigated using multi-level random intercepts models with individual-, household-, and community-level covariates.
Boah 2021[18] Ecological African countries	**Area**: African countries – 54 countries. **Study period**: 2000-2018 **Data sources**: WHO data for estimated TB incidence, TB treatment coverage and treatment success. The World Bank world development indicator database for the population size ≥15 years and GDP per capita. UNAIDS data for HIV prevalence and ART coverage. **Outcome:** WHO estimated TB incidence **Variables**: the exposure was ART coverage (defined as the proportion of PLHIV of all ages who received ART). Covariates in the model were population size, economic (GDP), biologic (HIV prevalence) and TB programme performance (treatment coverage and success) indicators. TB programme performance was benchmarked against STOP TB partnership targets. Treatment coverage was categorised as 1 if coverage was ≥70% and 0 if not. Treatment success was categorised as 1 if ≥85% and 0 if not. The outcome was WHO estimated TB incidence. **Analysis**: a fixed-effects regression model of longitudinal data was used to assess the association between ART coverage and changes in estimated TB incidence in the countries from 2000 to 2018.

TB=tuberculosis, ART=antiretroviral therapy; PLHIV=people living with HIV; WHO=World Health Organization; UNAIDS=Joint United Nations Programme on HIV/AIDS; GDP=gross domestic product.

Table 4: Trials

Author, year, study design, country	Methods
Havlir, 2019[19] Cluster randomised trial Uganda and Kenya	**Area:** 32 rural communities. **Study period**: 2013-2017 **Community selection and randomisation**: 54 communities chosen based on criteria including presence of a government clinic that provided ART. Communities were pair-matched based on geographic region, population density, number of trading centres, variety of occupations, and mobility patterns. The best-matching 16 pairs were randomly assigned to one of two study arms. **Intervention arm**: baseline HIV testing at health fair. Then annual HIV testing and ART start irrespective of CD4+ T-lymphocyte count (universal testing and treatment [UTT]). 3 intervention (UTT) rounds during the study period. **Control arm**: baseline HIV testing at health fair only. No repeated HIV testing during the trial. ART started throughout study period for PLHIV as per national guidelines (CD4+ T-lymphocyte threshold ≤350 cells/μL until 2014 then <500 cells/μL). **Outcome**: Post-hoc analysis assessed the effect of the intervention on TB notifications. **Analysis**: compared TB notification rates in the intervention and control arm, in the 3rd study year.

ART=antiretroviral therapy; PLHIV=people living with HIV; TB=tuberculosis;

Of the 18 articles representing observational studies, 15 articles used routine TB data (TB notifications or laboratory data on bacteriologically confirmed TB) as the outcome (Table 2)[1-15]. All were ecological, describing at the population-level changes to TB notification rates, numbers notified or diagnoses over time, as estimated ART coverage changed due to the availability of ART through routine ART programmes, and changes in the eligibility (CD4+ T-lymphocyte threshold for ART) over time. Of the 15 articles, four were from Malawi[1-4], five from South Africa[5-9], one from Eswatini[10], two from Zimbabwe[11, 12], one from Kenya[13], one from Uganda[14], and one used data published by the WHO for sub-Sharan African countries[15]. Of the four articles from Malawi, three reported on overlapping time periods, using similar data sources and methods[2-4]. Likewise in each of South Africa[6, 9] and Zimbabwe[11, 12], two articles reported on overlapping time periods using similar data sources and methods. Table 5 summarises the findings from the articles reporting on TB notification rates[1, 3, 5, 6, 9-15], TB numbers notified[2, 4] or TB diagnoses[7] over time.

Table 5: Changes to routinely available data (TB notification rates, TB numbers notified and TB diagnoses) coincident with increasing ART coverage in 15 articles, reporting on 11 separate studies (all ecological) from sub-Saharan Africa.

Country	Author; year outcome	National or regional; study period	ART programme start	ART coverage[1] & years	Peak CNR shown	Decrease TB - all[2]	Decrease TB - PLHIV[2]	Decrease TB - HIV negative[2]	Comments
Malawi	Zachariah 2011[(1)] CNR	Regional; rural 2002-2009	2003	11% end of 2006	yes peak - 2005	New: 33% (95%CI 27-39%; between 2005-2009) Recurrent: 25% (95%CI 9-49%; between 2006-2009)	-	-	
	Kanyerere 2014[(2)] TB number	National 2000-2012	2004	<0.5% to 41% 2000-2012	yes peak - 2003	28%[4] (between 2003-2012)	30%[4] (between 2007-2011)	10%[4] (between 2007-2011)	Overlapping data
	Kanyerere 2016[(3)] CNR	National 2005-2015	2004	2.4% to 52.2% 2005-2015	yes peak - 2006	49% (95%CI 42-56%)[5] (between 2006-2015)	43% (95%CI 40-46%)[5] (between 2007-2015)	26% (95%CI 16-38%)[5] (between 2008-2015)	
	Kanyerere 2016[(4)] TB number	National 1985-2014 CNR/ART 2005-2014	2004	<5% to 45.3% 2005-2014	yes peak - 2003	37%[4] (95%CI 36-38%)[5] (between 2003-2014)	-	-	
SA	Middelkoop 2011[(5)] CNR	Township; peri-urban 1997-2008	2003	1% to 21% 2003-2008	yes peak - 2005	22% (95%CI 20-23%)[6] (between 2005-2008) 183 per 100,000 per year[7] (between 2005-2008)	578 (95%CI -697 to -459) per 100,000 per year (between 2005-2008)	143 (95%CI -195 to -95) per 100,000 per year (between 2005-2008)	
	Hermans 2015[(6)] CNR	Regional; urban and peri-urban 2003-2013	From 2001, national programme in 2004	9% to 63% 2003-2013	yes peak 2008-2010	16% (95%CI 14-17%) (between 2010-2013)	21% (95%CI 19-23%) (between 2010-2013)	9% (95%CI 7-11%) (between 2010-2013)	Overlaps with Hermans 2018 Decreased CNR when ART coverage 30-40%
	Nanoo 2015[(7)] Lab confirmed	National 2004-2012	not specified	~1% to 28% 2004-2012	yes[3] peak 2008	9%[3] (95%CI 7-11%)[5] (between 2008-2012)	-	-	
	Hoogendorn 2017[(8)] TB number	Regional; rural 2009-2013	unclear; 2009 programme small	5% to 41% 2009-2013	No	13% (95%CI 11-15%)[4] (between 2009-2013)	-	-	

	Hermans 2019[9] CNR	Regional; urban and peri-urban 1993; 2003-2014	2004	4 periods: Minimal HIV; no ART; early ART; late ART	Yes 2010	female - 26% (95%CI 23-29%)[5] male - 16% (95%CI 14-18%)[5] (between 2010-2014)	female - 32% (95%CI 30-33%)[5] male - 17% (95%CI 16-18%)[5] (between 2010-2014)	female - 23% (95%CI 18-27%)[5] male - 15% (95%CI 12-18%)[5] (between 2010-2014)	Overlapping data with Hermans 2015 Data stratified by gender
Eswatini	Kerschberger 2019[10] CNR	Region; rural 2009-2016	not specified	22% to 83% 2009-2016	no	80% (95%CI 78-82%)[6] (between 2009-2016)	83% (95%CI 82-84%)[6] (between 2009-2016)	67% (61-72%)[6] (between 2009-2016)	Comparing 2016 with 2009, the effect of calendar year on declining TB was higher in PLHIV (aRR 0.13, 95%CI: 0.10–0.17) than in HIV negative people (aRR 0.32, 95%CI 0.24-0.44)
Zimbabwe	Takarinda 2016[11] CNR	National 2000-2013	2004	<0.5% to 48% 2004-2013	yes peak - 2003	56% (95%CI 52-60%)[6] (between 2003-2013)	-	-	Overlapping data
	Takarinda 2020[12] CNR	National 2000-2018	2004	<1% to 88% 2004-2018	yes peak - 2004	66% (95%CI 62-70%)[5] (between 2004-2018)	-	-	
Kenya	Yuen 2014[13] CNR	National 2006-2012	2004	7%-37% (2006-2012)	yes peak 2004-2007	-	by 28-44% (between 2007-2012)	by 11-26% (between 2007-2012)	Upper estimate - assumes HIV prevalence in people with TB without HIV status same as people with HIV results; lower estimates - assume same as general population.
Uganda	Zawedde-Munyanja 2019[14] CNR	Regional; urban/peri-urban 2009-2017	2008 large scale provision of ART	20% to 51.5% (2009-2017)	No	Average annual change -3.5% (95%CI -3.7 to -3.3%)	Average annual change -5.0%	Average annual change -2.6%	
SSA	Surie 2018[15] CNR	National; 23/47 countries met eligibility criteria 2010-2015	n/a	median absolute increase from 2010-2015 25% (IQR 16-31%)	no details	-	median average annual change -5.7% (IQR -6.9 to -1.7%)	median average annual change -2.3% (IQR -4.2 to -0.1%)	CNR among PLHIV decreased more in countries with higher ART coverage

SA=South Africa; CNR=TB notification rate; ART=antiretroviral therapy; PLHIV=people living with HIV; 95%CI=95% confidence interval; Lab=laboratory; IQR=interquartile range; aRR=adjusted rate ratio; SSA=sub-Saharan Africa; [1]among all PLHIV - calculated using available data when not provided in the text if possible; [2]comparing highest with lowest values unless otherwise indicated; [3]incidence (per 100,000 population) of bacteriologically confirmed TB (smear, Xpert and culture) using laboratory data; [4]TB numbers only, not TB notification rates; [5]95% confidence interval calculated using data available in the manuscript; [6]Proportion and 95% confidence interval calculated using data available in the manuscript; [7]CI reported as -183 to -183

The ART programmes started in ~2004, where this was reported. Outcomes were measured between ~4 to 14 years, following the start of ART programmes. Irrespective of the outcome or method of analysis, studies consistently showed a decrease in TB notification rates[1, 3, 5, 6, 9-15], numbers notified[2, 4, 8] or TB diagnoses[7] over time, that was coincident with an increase in ART coverage. Where data were stratified by HIV status[2, 3, 5, 6, 9, 10, 13-15], the decreases in TB measures were greater among people living with HIV (PLHIV) than those who were HIV negative.

Three further observational studies tried to quantify the association between ART coverage and measures of TB at the population-level (Table 6)[16, 17]. In one South African township, TB prevalence surveys were conducted in 2005 and 2008 as ART coverage increased from 13% to 21%, during the early phase of an ART programme[16]. There was an ~50% decrease in the overall odds of prevalent TB between 2005 and 2008. When stratified by HIV status, a decrease in odds of prevalent TB between 2005 and 2008 was only observed among PLHIV. Data from a general population cohort, in another South African study, measured self-reported TB in the previous 12 months, by use of a survey questionnaire, among adults living in communities in a rural Demographic and Health Survey area[17]. ART coverage for the communities, measured by linking ART data to survey data, increased from 30% to 53% over the study period due to changes in the ART eligibility CD4+ T-lymphocyte threshold. After adjusting for individual-, household- and community-level covariates, the study found each 1% increase in ART coverage was associated with a 2% decrease in the odds of self-reported TB. A third study used WHO estimated TB incidence for 54 African countries over an 18-year period[18]. After adjusting for population-level covaries (population size, economic, biological and TB programme performance), each 1% increase in ART coverage was associated with an ~4 per 100,000 population decrease in estimated TB incidence.

Table 6: The association between increasing ART coverage and population-level measures of TB in three observational studies from sub-Saharan Africa

Country; design	Author; year; outcome	National or regional; study period	ART programme start	ART coverage[1] years	Decrease in TB measure - all	Decrease in TB PLHIV	Change in TB HIV negative	Association
South Africa Cross sectional	Middelkoop 2010[16] Prevalence	Regional; peri-urban 2005 and 2008	2004	13% in 2005 21% in 2008	1.6% in 2008[2] 3% in 2005[2]	3.6% in 2008[2] 9.2% in 2005[2]	1% in 2008[2] 1.2% in 2005[2] No change (p=0.90)	Adjusted for age, sex, education, household number; alcohol use, smoking mine worker and HIV status. overall aOR 2008 vs 2005 0.53 (95%CI 0.28-0.97; p=0.05). PLHIV aOR 0.35 (95%CI 0.15-0.80; p=0.01)
South Africa Ecological	Tomita 2019[17] self-reported TB in last 12m	Regional; rural 2009-2015	2004	30% to 52% 2009-2012	-	-	-	ART coverage aOR 0.98 (95%CI 0.97-0.99). Each 1% increase in ART was associated with a 2% decrease in the odds of TB. Adjusted for individual (age, gender, married, HIV status, ART status and year), household (income) and community (HIV prevalence, urban/rural) level variables.
African countries Ecological	Boah 2021[18] WHO estimated TB incidence	National; 54 countries 2000-2018	n/a	not given	average annual % change -2.28% (IQR -2.52 to -2.04%)	-	-	Association between ART coverage and TB incidence (per 100,000 population) between 2000-2018 - model adjusting for population size, economic (GDP), biology (HIV prevalence) and TB programme indicators (treatment coverage and success); ART coverage (%) β -3.97 (SE 1.13; p=0.001)

ART=antiretroviral therapy; TB=tuberculosis; PLHIV=people living with HIV; aOR=adjusted odds ratio; WHO=World Health Organization; GDP=gross domestic product; IQR=interquartile range; SE=robust standard error; [1]among all PLHIV; [2]treated and untreated TB

Table 7: Trials reporting on changes to TB notifications with universal testing and treatment for HIV (UTT)

Country; design	Author; year; outcome	Study sites and period	Intervention	Control	Association
Uganda and Kenya CRT	Havlir 2019[19] TB notifications	32 rural communities 2013-2017	Baseline HIV testing at health fair and annual testing with universal ART over 3 intervention rounds	Baseline HIV testing at health fair and ART as per national guidelines.	TB notifications during 3rd study year in intervention vs control arms among PLHIV: RR 0.41 (95%CI 0.19-0.86) No difference among those HIV negatives

CRT=cluster randomised trial; TB=tuberculosis; ART=antiretroviral therapy; PLHIV=people living with HIV; RR=rate ratio; 95%CI=95% confidence interval

One cluster randomised HIV treatment as prevention trial in Uganda and Kenya, the Sustainable East Africa Research in Community Health (SEARCH) trial, assessed the impact of universal testing and treatment for HIV (UTT) over three intervention rounds compared with baseline HIV testing alone (with no repeat HIV testing) and ART started according to national guidelines (the control), on HIV incidence[19]. A post-hoc analysis assessed the impact of UTT on TB notification rates. Among PLHIV, the TB notification rate in the third year of the intervention was 59% lower (rate ratio 0.41 [95% confidence interval 0.19-0.86]) in the UTT arm compared to the control arm. While formal comparisons were not made during the second year of the intervention, the data showed a steep fall in TB notification rates in the second intervention year compared to the first year among PLHIV in the intervention arm (i.e. following the roll-out of UTT in the first intervention year); TB notification rates among PLHIV in the control arm remained relatively steady over this time. Among those HIV negative, there was no difference in the TB notification rates.

Discussion

HIV is one of the strongest risk factors for incident TB disease[20-23]. In sub-Saharan Africa, the TB epidemic is mainly driven by the generalised HIV epidemic; the proportion of people with TB disease who are also living with HIV is high[24]. Among PLHIV taking ART, the risk of incident TB is substantially reduced[25-27]. This has given rise to optimism about the potential role of ART in TB control. However, it cannot be assumed that the individual-level effect of ART among PLHIV taking ART will necessarily translate to a population-level impact among all PLHIV - which includes those in and not in HIV care, also taking into consideration adherence to ART and losses to follow-up during treatment - or to the population as a whole.

This literature review aimed to synthesise the available evidence to date, to address if increasing ART coverage could control TB. It primarily identified observational ecological

studies, that explored changes to population-level measures of TB during periods of increasing ART coverage under routine programmatic conditions[1-15, 18]. The observational design of most studies was unsurprising, as ART has been part of routine clinical care for PLHIV in sub-Saharan Africa for nearly two decades. The findings consistently showed overall TB notifications and diagnoses decreased over time[1-15]. When stratified by HIV status, these decreases were greater among PLHIV than those who were HIV negative[2, 3, 5, 6, 9, 10, 13-15]. The changes coincided with the scale-up of ART. These consistent findings were compatible with an ART associated impact; decreases in TB disease incidence among PLHIV directly due to ART, could contribute to decreased *Mycobacterium tuberculos*is (MTB) transmission, resulting in decreased TB disease incidence among those HIV negative and PLHIV. The direct and indirect effect of ART on PLHIV would be expected to result in a larger impact among PLHIV than those who are HIV negative. But, despite the consistency in findings, these observations were hypothesis generating alone, and cannot be assumed to represent a causal association. It is possible that the observed decreases were a result of other changes that have occurred over time such as improvements in socio-economic conditions, TB programmes or the scale-up of isoniazid preventive therapy.

Three observational studies tried to quantify the association between ART coverage and TB[16-18]. Using different study design and outcomes, the findings suggest an association between increasing ART coverage under routine programmatic conditions and decreases in population-level measures of TB. While these studies adjusted for some potential confounders, residual confounding cannot be excluded, and the observed association cannot be taken to infer causation. However, taken together, the data do suggest that ART may in part play a role in the observed decline in reported TB measures.

Routine ART programmes depend on PLHIV seeking care themselves. Even with the availability of universal ART (i.e. universal treatment with ART irrespective of CD4+ T-lymphocyte count)[28], the median CD4+ T-lymphocyte count at ART initiation remains low at ~350-400 cells/μL[29-31]. A high proportion of PLHIV still present with severe

immunosuppression (CD4+ T-lymphocyte counts <200 cells/μL). In populations with high HIV prevalence, how to test and treat all PLHIV early to achieve the health benefits of universal ART, remains a challenge. UTT aims to address this: using a community-based approach, everyone in a target population is tested repeatedly for HIV (i.e. screened for HIV), with PLHIV linked to HIV care for immediate ART start (universal treatment) and adherence to treatment promoted[32, 33]. It represents an intensive intervention, which should result in large swathes of PLHIV in a population being commenced on ART, at potentially high CD4+ T-lymphocyte counts. Indeed, several HIV treatment as prevention trials have demonstrated that UTT was feasible, can help meet ambitious Joint United Nations Programme on HIV/AIDS (UNAIDS) HIV targets, and control HIV[32, 33].

Mathematical modelling also suggests that UTT could substantially impact HIV-associated TB[34]. Modelling predicts that with annual HIV testing and immediate ART start, an ~50% decrease in HIV-associated TB incidence could be achieved, when full ART coverage is reached[34]. In the SEARCH trial, an HIV treatment as prevention trial, post-hoc analysis found a 59% decrease in TB notification rates in the UTT arm compared to the control arm in the third year of the intervention (i.e. after two full intervention rounds)[19]. While formal comparisons were not made during the second year, the data also showed steep reductions in TB notification rates in the intervention arm during the second year, following the roll-out of UTT. While the findings need cautious interpretation, when taken together with the totality of the observational data, they suggest that ART scale-up could play an important role in TB control. A UTT based approach, should rapidly increase ART coverage, allowing the TB control benefits of ART to be realised quickly, as seen in the SEARCH trial[19]. TB notification rates among those HIV negative were not significantly different between the SEARCH trial arms[19], but given the short trial duration, it is plausible that sufficient time had not elapsed to capture changes to TB disease incidence as a consequence of changes to MTB transmission.

The longer-term impact of UTT on TB disease incidence remains unclear. Mathematical modelling predicts that with annual HIV testing and immediate ART start, after a steep initial fall in HIV-associated TB incidence, incidence subsequently falls more slowly[34]. This is because PLHIV on ART live longer. Their risk of TB disease, while lower than when not on ART, does not return to that of those who are HIV negative[22, 35-37]. This gives PLHIV on ART a high cumulative lifetime risk of TB. Therefore, predicted decreases in longer-term HIV-associated TB incidence with UTT were slow, requiring PLHIV on ART to age and die and HIV incidence to fall[34]. Further considerations include the infectiousness of PLHIV with TB disease, which plausibly could increase on ART as CD4+ T-lymphocyte counts recover or levels are maintained, relative to PLHIV not on ART[38, 39]. This could increase MTB transmission from PLHIV with TB disease. The observational data to date do not support this theory (i.e. a levelling off or rise in TB notifications/diagnoses have not been observed with increasing CD4+ T-lymphocyte thresholds for ART initiation). But how UTT, where the CD4+ T-lymphocyte count among PLHIV starting ART could be much higher than among those routinely presenting to HIV care, affects the infectiousness of TB disease among PLHIV, remains unclear. This important knowledge gap should be addressed through studies measuring the longer-term trends in TB notifications and the infectiousness of PLHIV starting ART by CD4+ T-lymphocyte count, in the universal ART era.

Most studies aimed to describe the effect of increasing ART coverage on TB disease incidence (mainly using TB notifications as a proxy measure). Only a single study investigated the effect of increasing ART coverage on TB disease prevalence[16]. The effect of ART on TB disease incidence and TB disease prevalence (which is influenced by both disease incidence and its duration) may vary. In the absence of ART, HIV infection is more strongly associated with TB disease incidence than TB disease prevalence[40]. This is because, while TB disease incidence among PLHIV is higher than those who are HIV negative, its duration is shorter (with rapid disease progression resulting in earlier treatment initiation or death)[40, 41]. With increasing ART coverage, TB disease incidence among PLHIV

(and overall, if PLHIV contribute a substantial proportion of TB disease incidence as is the case in sub-Saharan Africa) is expected to fall; results from this review consistently showed decreases in reported TB incidence-related measures. But the effect on TB disease prevalence may be variable and is unclear. If TB disease among PLHIV on ART resembles TB disease among those who are HIV negative (which is typically more infectiousness and has a longer duration)[38, 39], the effect of increasing ART coverage on TB disease prevalence may depend on the balance between the change in incidence and duration/infectiousness. Alternatively, routine TB screening through ART programmes may result in earlier diagnosis, shortening the duration of disease and therefore increasing the effect on TB disease prevalence. There is insufficient data from this review to examine any differential effect of ART on different measures of TB at the population-level.

There were several limitations to this literature review. Only two databases were searched. One reviewer undertook all study related activities. Only English language articles were included. Therefore, some relevant articles may have been missed. Risk of bias and publication bias were not assessed.

In conclusion, this literature review primarily identified observational studies, reporting on changes to population-level measures of TB with increasing ART coverage under routine programmatic conditions in sub-Saharan Africa. Studies consistently showed that increasing ART coverage, including UTT, was associated with decreased measures of population-level TB, and that TB notifications and diagnoses decreased coincident with increasing ART coverage. Decreases were greater among PLHIV than those who were HIV negative. Study limitations prevent causal inferences and findings should be interpreted cautiously (i.e. we cannot say ART caused these changes and therefore could control TB). But the totality of the evidence suggests that ART may in part explain the findings and could therefore contribute in the fight to END-TB.

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Chapter 4: The effect of general-population systematic tuberculosis screening on case notification rates

RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	159168	**Title**	Dr
First Name(s)	Lilanganee		
Surname/Family Name	Telisinghe		
Thesis Title	Can universal testing and treatment for HIV and community-wide active case finding for tuberculosis control the African TB epidemic?		
Primary Supervisor	Professor Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	IJTLD		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For the systematic review, I developed the research question, worked up the eligibility, inclusion, and exclusion criteria, and the approach to undertaking this review. I undertook all title, abstract, and full text screens. I extracted the data. I worked up the methods to analyse the extracted data, so that they could be compared across studies, and summarised the findings. I drafted and edited the systematic review manuscript sections. For the mathematical modelling work in this manuscript, I developed the questions to be addressed and approached Pete Dodd, an expert in the field of TB mathematical modelling at Sheffield University to collaborate. Pete Dodd and Debebe Shaweno undertook the mathematical modelling. We reviewed the outputs together to interpret the mathematical model findings and put the empirical findings from the systematic review in context with the model findings. Pete Dodd wrote the mathematical modelling manuscript sections; I edited this and drafted and edited the sections that put the review and model outputs in context.

SECTION E

Student Signature	L. Telisinghe
Date	28/02/2024

Supervisor Signature	Helen Ayles
Date	18/03/2024

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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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.

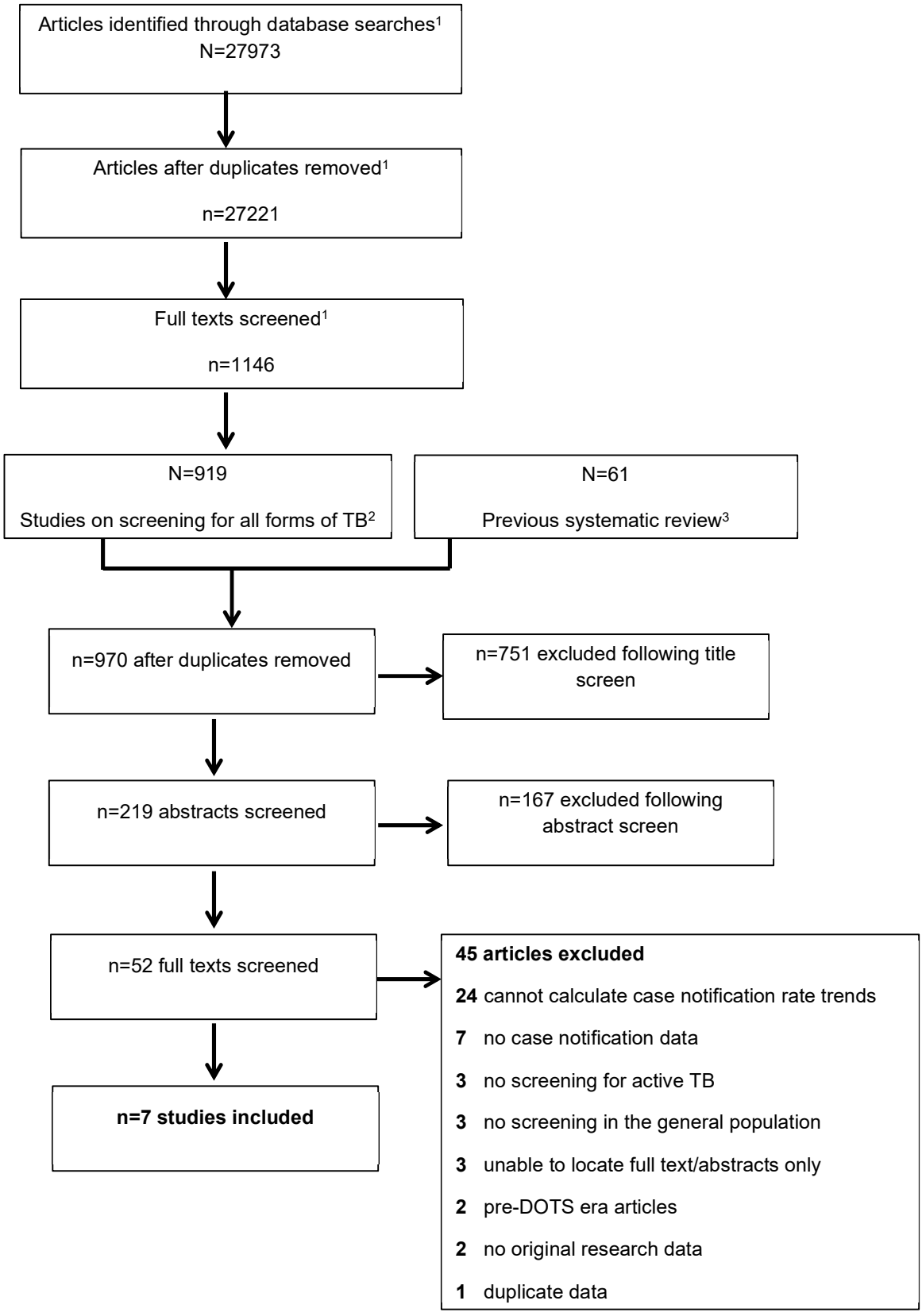
4. **Case notification rates relative to baseline following the end of screening.** All ratios (y-axis) represent annualised TB case notifications rates, relative to the baseline notification rate (i.e. case notification rate in the year prior to the start of screening). Solid line denotes all TB and 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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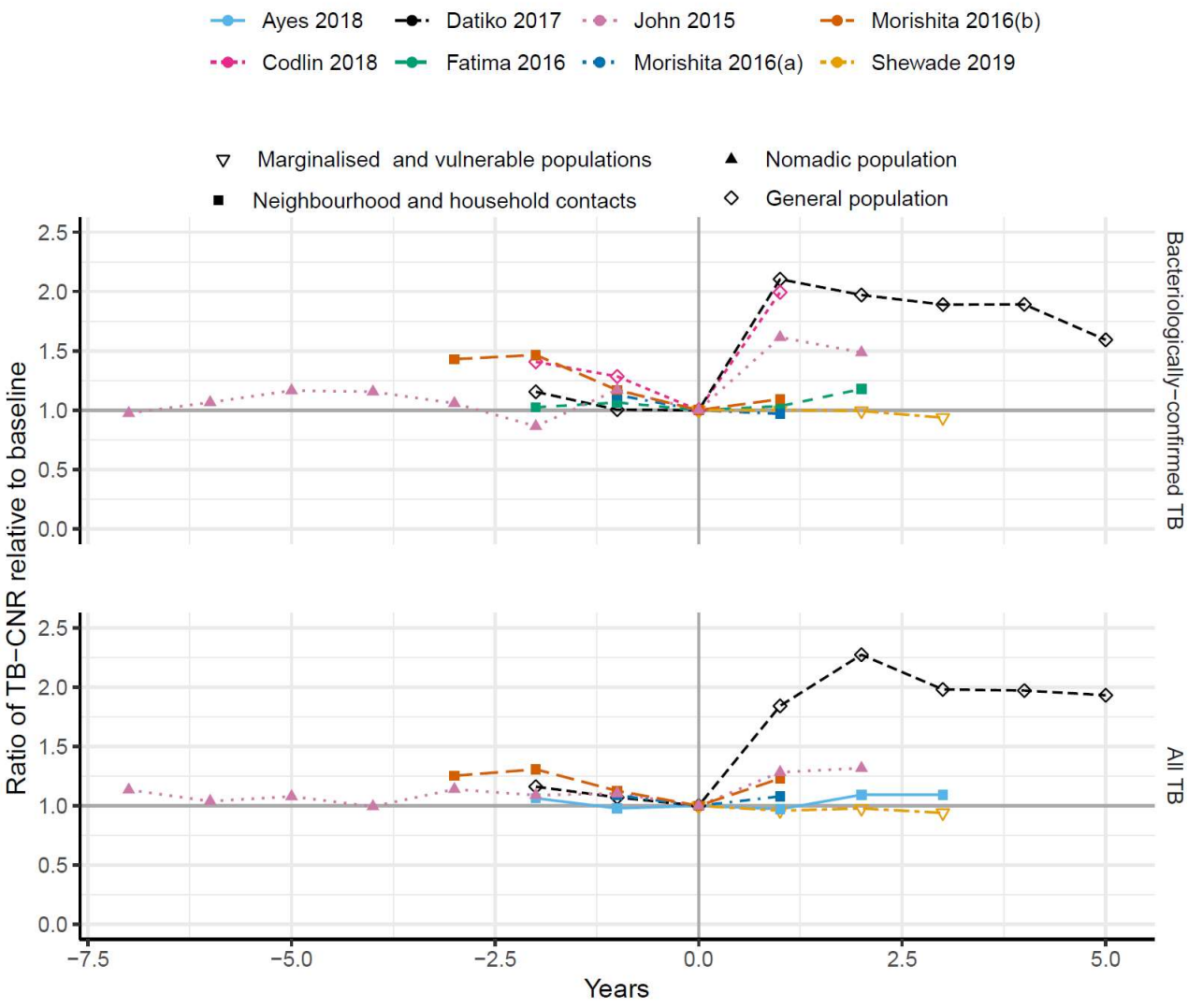

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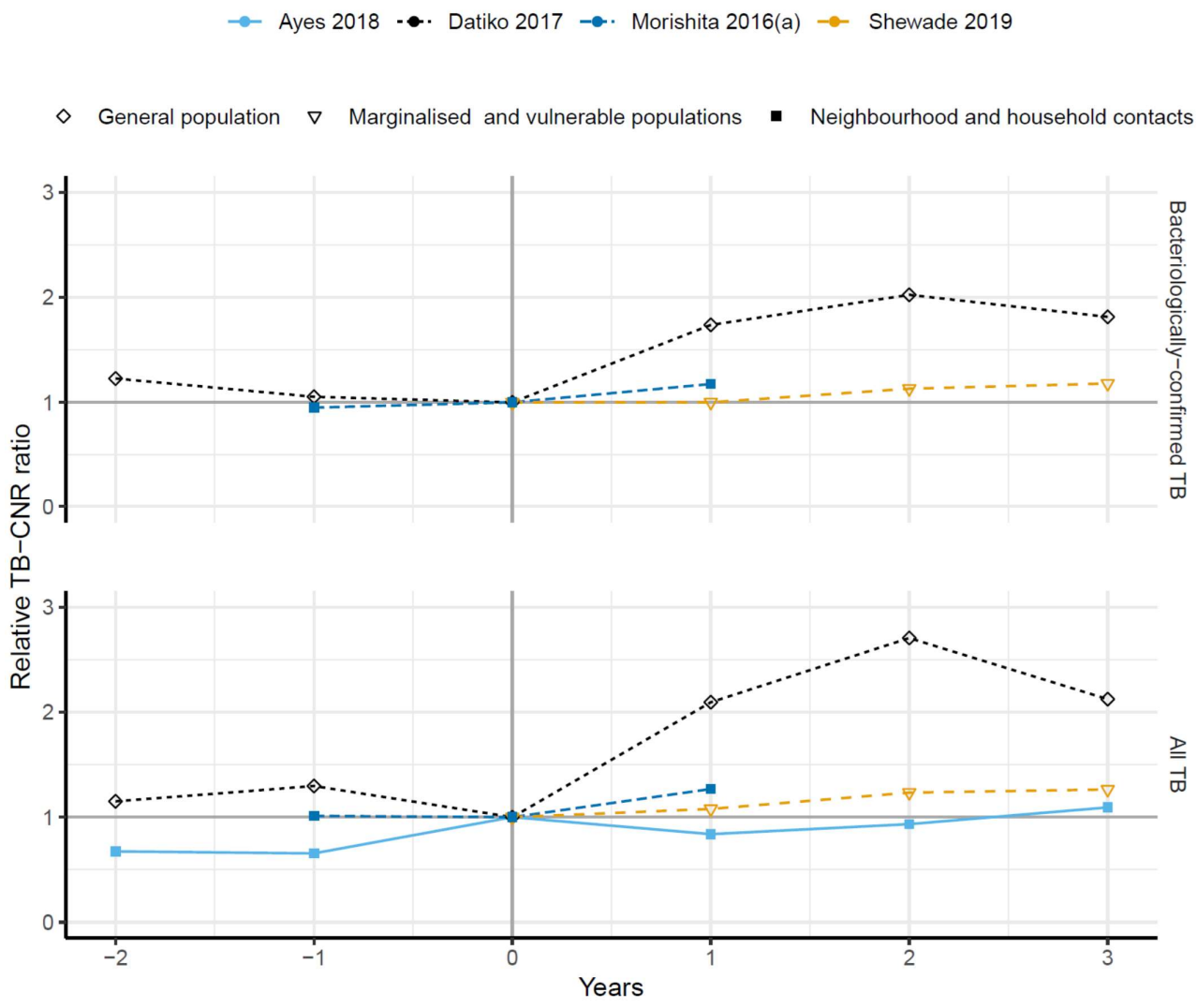

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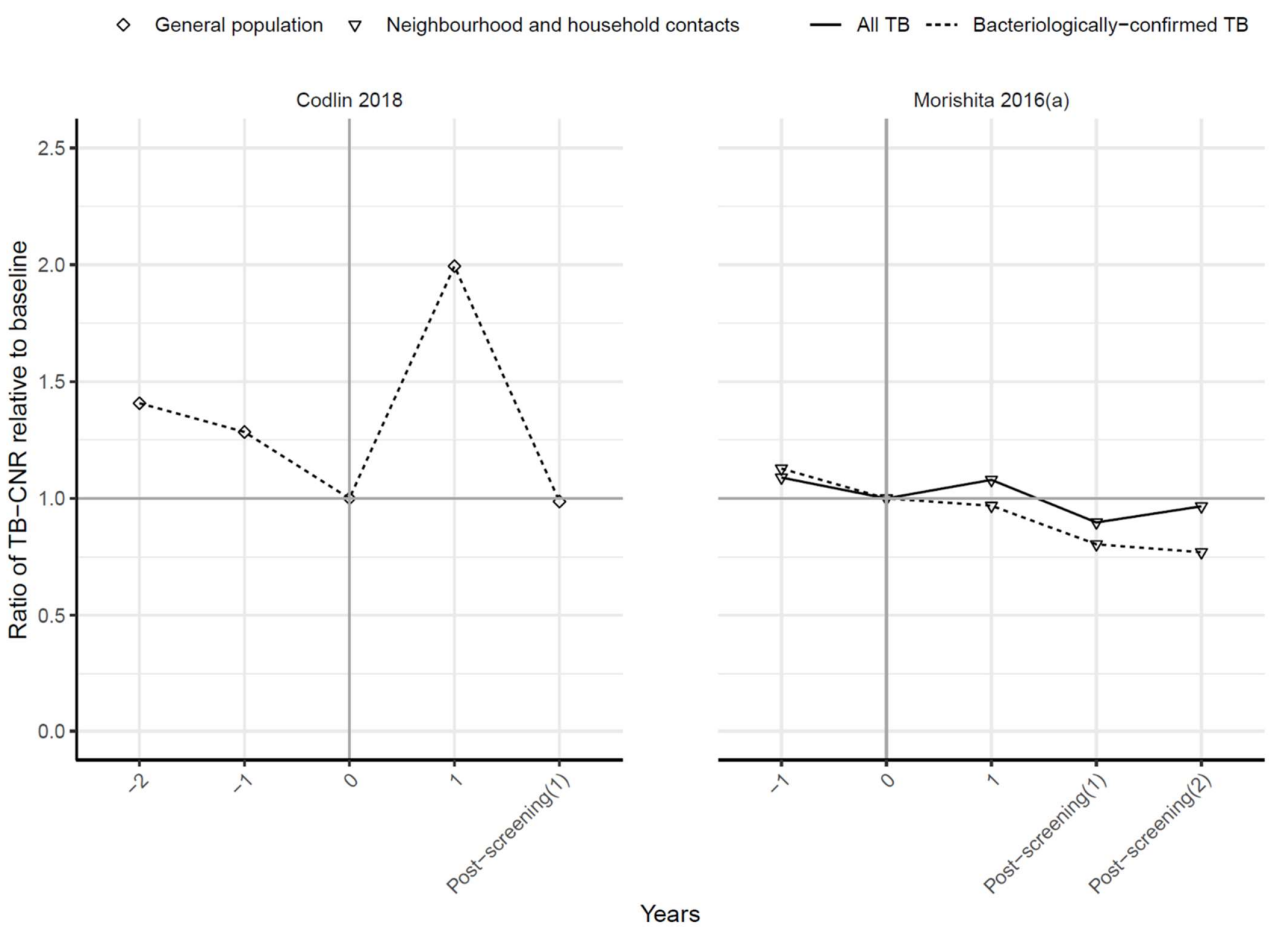

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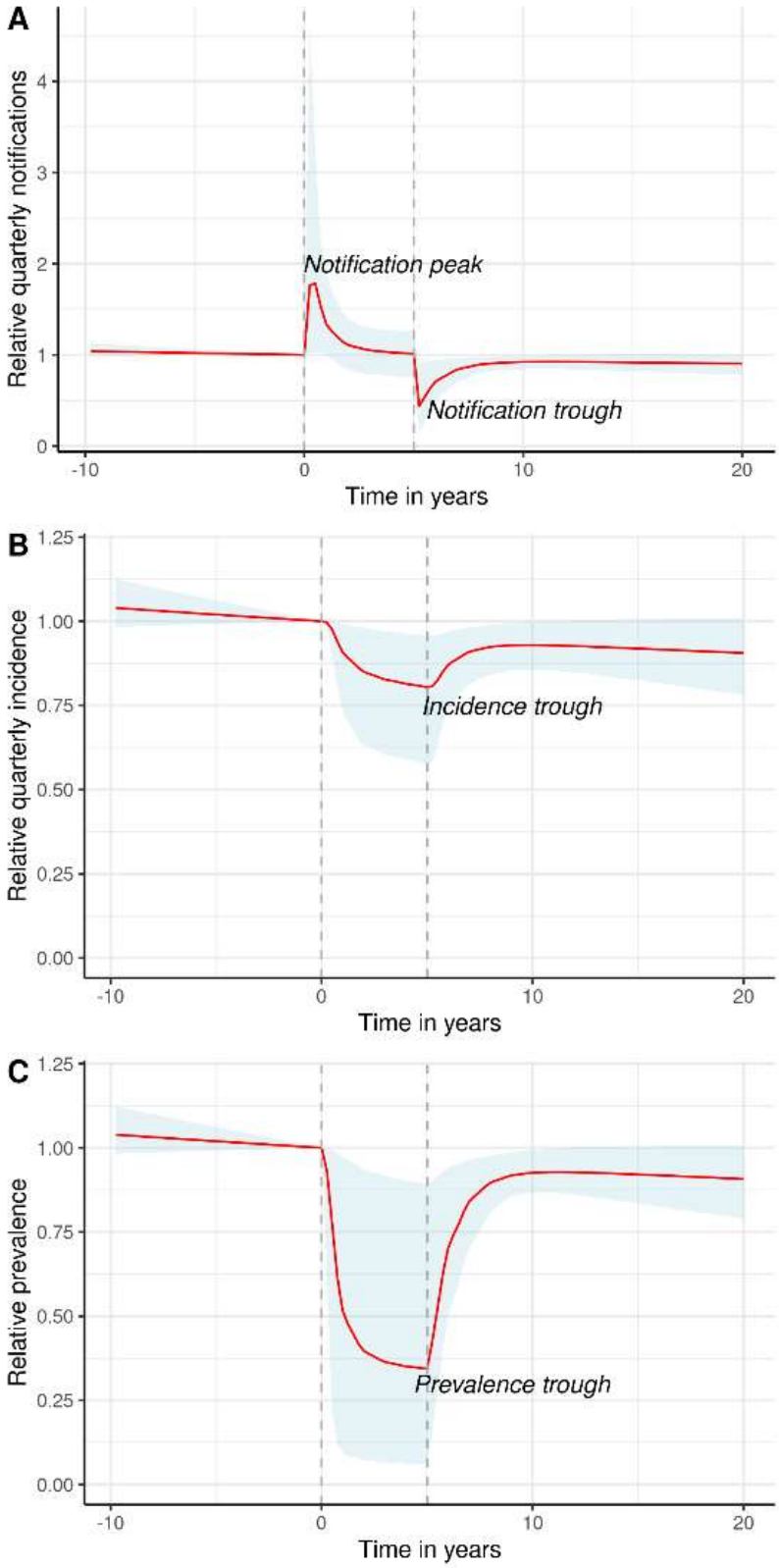

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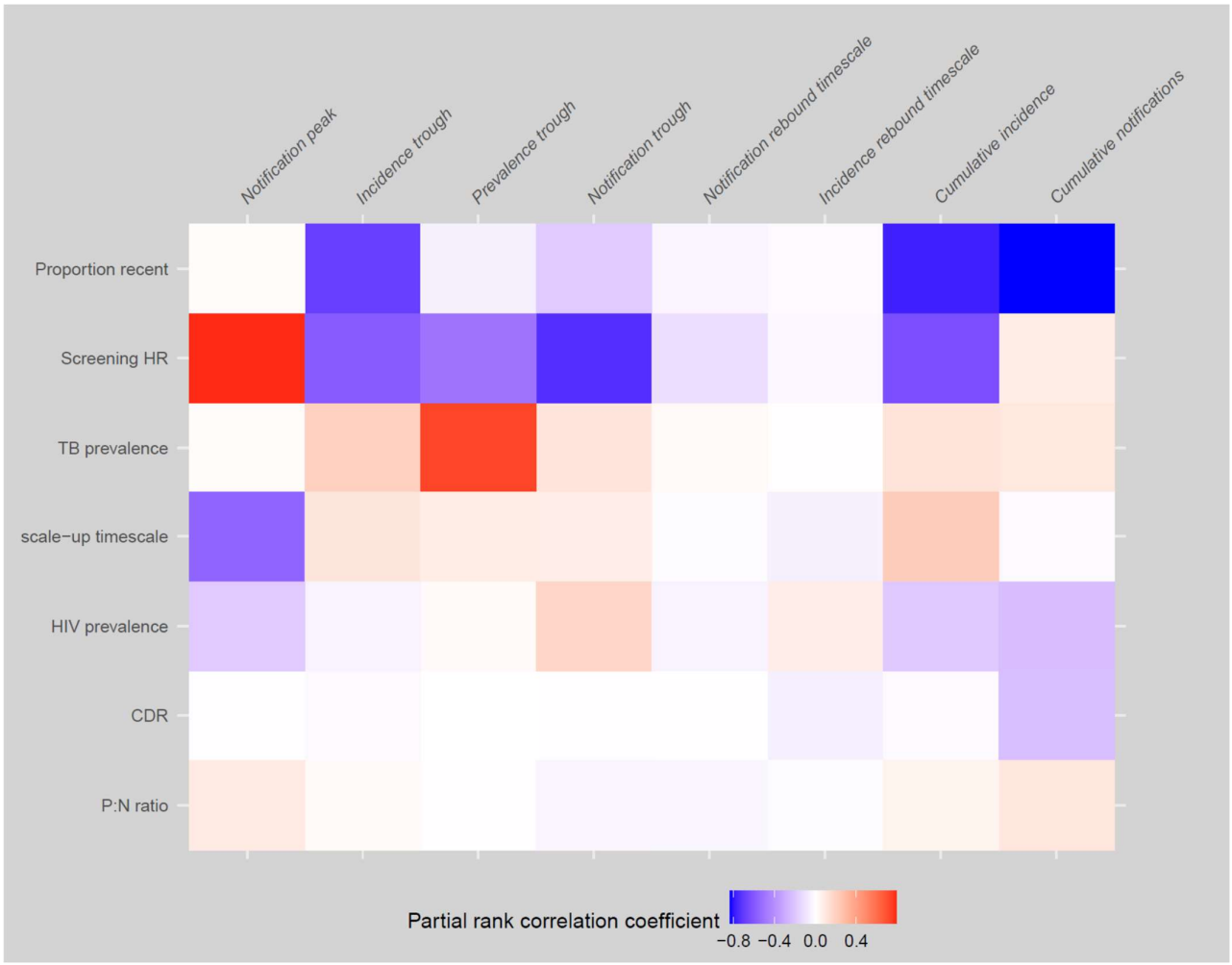

Figure 6 in list above

The effect of systematic screening of the general population on TB case notification rates
Supplementary data

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[3]School of Health and Related Research, The University of Sheffield, Sheffield, UK

Appendix 1: Search terms

Search terms used in Pubmed are shown below. These were adapted for EMBASE, Scopus and the Cochrane Library.

#1	"tuberculosis"[MeSH Terms]
#2	"tuberculosis"[tw] OR “Pulmonary Consumption”[tw] OR “Consumption, Pulmonary”[tw] OR Phthisis[tw] OR “Tuberculoses”[tw] OR “MDR-TB”[tw] OR “XDR-TB”[tw] OR “MDR TB”[tw] OR “XDR TB”[tw]
#3	#1 OR #2
#4	“Mass Screening”[MeSH Terms] OR “Mass Chest X-Ray”[MeSH Terms] OR "contact tracing"[MeSH Terms] OR “health surveys”[MeSH Terms] OR “Cross-Sectional Studies”[MeSH Terms] OR “Epidemiologic Studies”[MeSH Terms]
#5	“Mass Chest X Ray”[tw] OR “Mass Chest X-Rays”[tw] OR “screenings”[tw] OR “screening”[tw] OR “cross-sectional”[tw] OR “case-detection”[tw] OR “case finding”[tw] OR “contact tracing”[tw] OR “health survey”[tw] OR "prevalence survey"[tw] OR “prevalence studies”[tw] OR "mass radiography"[tw] OR "contact examination"[tw]
#6	#4 OR #5
#7	#3 AND #6
#8	("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))
#9	#7 NOT #8
#10	("2010/11/01"[EDAT] : "3000/12/31"[EDAT] OR "2010/11/01"[CRDT] : "3000/12/31"[CRDT]) OR ("2010/11/01"[PDAT] : "3000/11/31"[PDAT])
#11	#9 AND #10

Appendix 2: TB case notification rate/number data as reported in n=7 studies included in the systematic review

All TB – screened group

Bacteriologically-confirmed TB – screened group

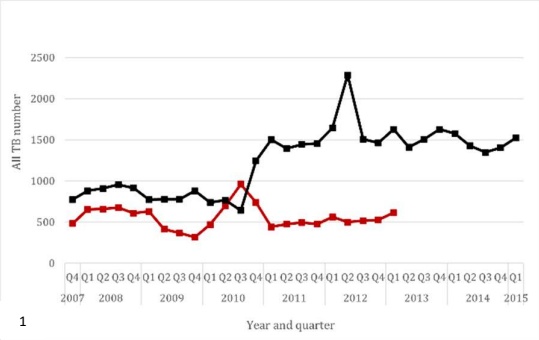
All TB – group screened 2nd

Bacteriologically-confirmed TB – group screened 2nd

All TB – control group

Bacteriologically-confirmed TB – control group

All TB *OR* all and bacteriologically-confirmed TB



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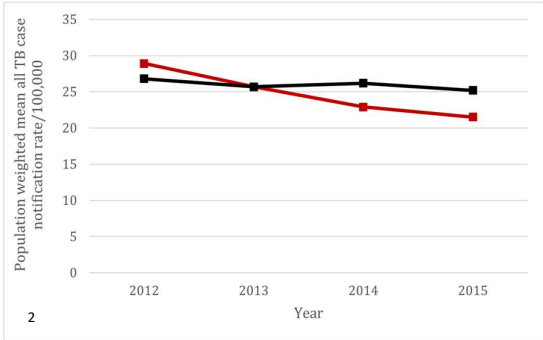

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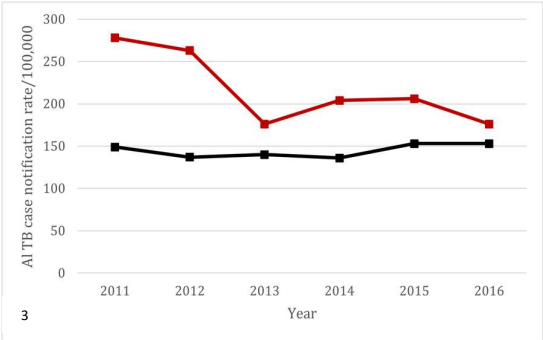

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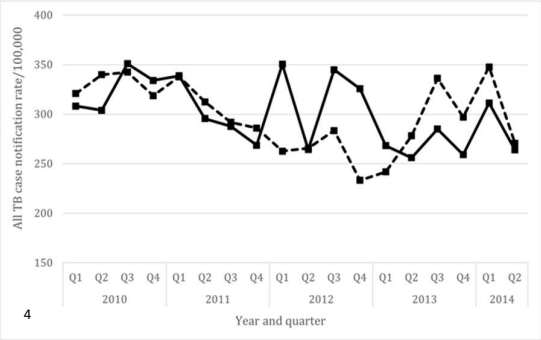

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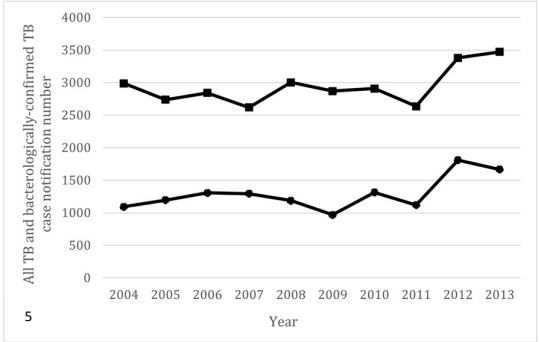

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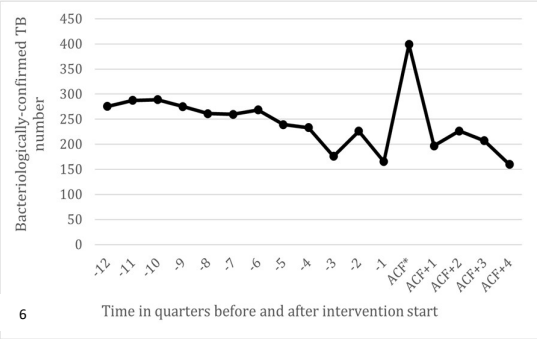
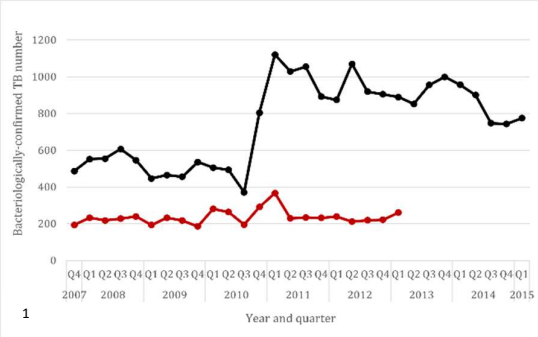
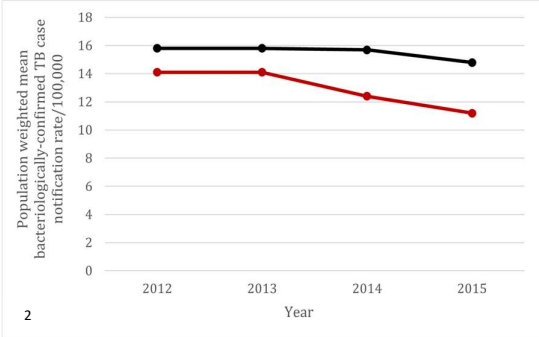
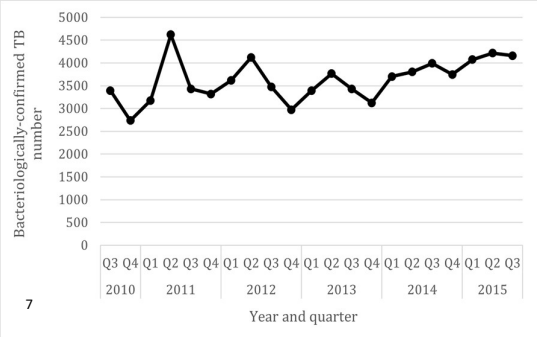
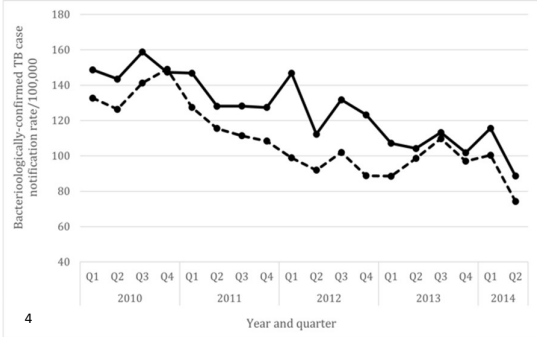
Bacteriologically-confirmed TB











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Appendix 3: Mathematical modelling – supplementary methods and results

Supplementary methods

Model structure

We used a standard compartmental TB transmission model structure to model the adult (15+ years of age) population (Figure 1). Code for this analysis is available on GitHub at: https://github.com/Debebe/ACFnotif

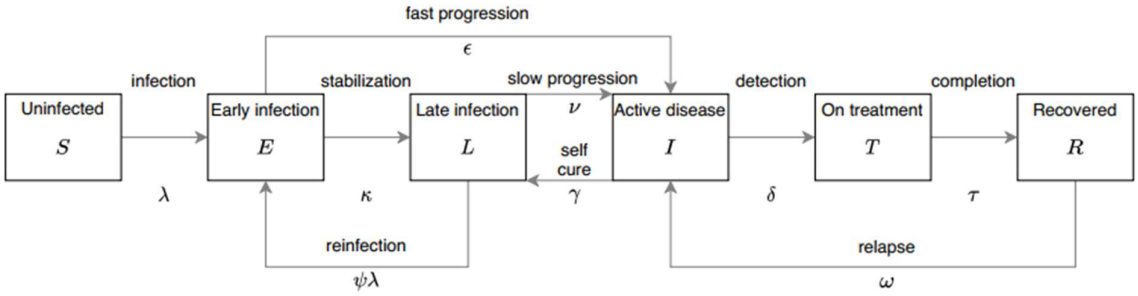

Figure 1. Compartmental TB Model structure. Individuals in each compartment are subjected to natural mortality at rate μ. Those in the I compartment are subjected to additional mortality from active TB disease, μ_t. To keep the population constant, the total number of individuals who die from each compartment at each time step are placed back in the uninfected compartment, as a birth. Model structure is replicated to represent HIV-infection status.

Differential equations and model initialization

The system of ordinary differential equations governing the system represented in Figure 1 is given below, where $i = 1,2$ represents HIV-uninfected and HIV-infected, respectively. The impact of screening was captured by introducing a screening hazard ratio (HR), π, that represents the ratio of the case detection hazard (δ) under screening to the case detection hazard under the counterfactual of standard practice (passive case finding). A HR of 1 represents no screening taking place. The screening HR was parameterised using gamma distribution but its values constrained to be greater than or equal to 1 to represent improved case-finding under screening compared to passive case finding (counterfactual).

The model was initialised heuristically by specifying the initial force-of-infection (λ_0) as a prior distribution parameterised using a gamma distribution (see Table 1). The initial TB prevalence is generated as the ratio of the initial force-of-infection and effective contact rate; the initial prevalence of latent infection (LTBI) was taken to be $1 - exp(-\lambda_0/\mu_1)$, with ad hoc choices that 5% of LTBI was initially fast latent, that the prevalence of treatment was ⅔ that of untreated TB, and that the prevalence of the 'recovered' state was that of treatment multiplied by the probability of unsuccessful treatment (θ). Transients from this initial state decayed in <10 years for reasonable parameter choices.

$$\frac{dS_i}{dt} = \mu_i N_i + \mu_{tbi} I_i + (1-\theta)\tau T_i - (\lambda_i + \mu_i) S_i$$
$$\frac{dE_i}{dt} = \lambda_i S_i + \lambda_i (1-\psi_i) L_i - (\mu_i + \kappa + \varepsilon_i) E_i$$
$$\frac{dL_i}{dt} = \kappa E_i + \gamma_i I_i - (\mu_i + \nu_i + \lambda_i (1-\psi_i)) L_i$$
$$\frac{dI_i}{dt} = \varepsilon_i E_i + \nu_i L_i + \omega_i R_i - (\mu_i + \mu_{tbi} + \gamma_i + \delta_i) I_i$$
$$\frac{dT_i}{dt} = \delta_i I_i - (\tau + \mu_i) T_i$$
$$\frac{dR_i}{dt} = \theta\tau T_i - (\omega_i + \mu_i) R_i$$

Force of Infection

The rate at which susceptible individuals acquire new infection is captured using the force of infection formulated as follows:

$$\lambda_i = \sum_{j=1}^{n} \frac{\beta_{i,j} \eta_j I_j}{N_j}$$

The indices *i* and *j* run from 1 to 2 representing the HIV negative and HIV positive strata. In the model, the proportion of infectious TB captured as η_j varies by HIV status and so does the force of infection. The proportion with infectious TB among HIV positives is modelled as 0.78 times the proportion in HIV negative TB patients[1]. The force of infection assumes random mixing between HIV-infected and HIV-uninfected populations.

Progression rates

In the model, HIV infected individuals have an increased risk developing incident TB both from progression and relapse. We achieved this by introducing a single incidence ratio (IRR) parameter that multiplies TB progression parameters (reactivation, fast progression and relapse) among HIV-uninfected individuals.

Proportion of cases detected and treated are used to generate the HIV-specific hazard of detection, under a competing hazards assumption. We considered TB disease duration for untreated TB that correspond to a mean duration of 1.5 years in the HIV uninfected population and 0.35 years in the HIV-infected population[1] for an average CDR of 0.68 (see Table 1).

Screening intervention and scale-up

In reality, intervention efforts take some time to attain maximum rollout from the start of the intervention. We quantified the dynamics of intervention scale-up by introducing a scale-up factor formulated as

$\varphi = 1 - exp(-\frac{max(\Delta t,0)}{sut})$,

where φ is a scale-up factor, *sut* is the scale-up timescale parameterised using a gamma distribution (Table 1) and Δt represents time since intervention initiation. The dynamic screening HR, π_t used in our model is then:

$$\pi_t = \pi\varphi + 1 - \varphi$$

This parameterisation delays the immediate peaking of notification in simulated data upon initiation of screening in a model, and represents the HR that increases asymptotically to π over a timescale *sut*.

Prior distributions

Parameters and their distributions used in our model are presented in the table below. We increased beta used in our model by a factor of 2 relative to a prior from literature, as our interest was TB epidemiology in higher burden settings and because this parameter is likely to be strongly context dependent. We parameterised screening HR as a gamma distributed prior but added 1 to ensure HR of screening is greater than or equal to 1.

Table 1. Priors and sources of model parameters.

Parameters	Descriptions	Distribution	Source
μ_t	TB mortality rate, year^{-1}	LN(-1.58,0.088)	Ragonnet[2]
γ	TB self-cure rate, year^{-1}	LN(-1.68, 0.18)	Ragonnet[2]
ε	Fast progression rate, year^{-1}	LN (-2.37, 0.32)	Ragonnet[2]
κ	Stabilization rate, year-1	LN (0.62, 0.068)	Ragonnet[2]
υ	Reactivation rate, year^{-1}	LN (-6.89, 0.58)	Ragonnet[2]
$\beta/2$	Effective contact rate**, year^{-1}	LN (1.68, 0.37)	Dodd[3]
ψ	Partial protection	B(77.9, 20.7)	Andrews[4]
CDR_n	CDR in HIV negative	B (65.3, 32.4) *	Corbett[1]
CDR_h	CDR in HIV positive	B (83.07, 11.54) *	Corbett [1,5]
π	Screening hazard ratio	G(1,0.25)+1	Assumed

sut	Screening scale-up time	G(1, 0.75)	Assumed
λ_0	Initial force- of-infection	G(scale=0.025, shape=2)	Houben[6]
μ_{HR}	Natural mortality HR	LN(1.08, 0.20)	Haastrecht[7]
μ_{tHR}	TB mortality HR	LN(1.8, 0.04)	Corbett[8]
α	Incidence rate ratio for TB in PLHIV	G(5.38, 0.53)	Corbett[8]
ω	Relapse rate, year^{-1}	LN (-3.95, 0.27)	Crampin[9]
P_0	HIV prevalence	B(1,9)	Assumption (mean 10%)

** We double the parameter generated from this distribution to generate the higher TB incidences relevant to settings where screening may be considered. *Is transformed into case detection rate as $\delta = \frac{CDR(\mu + \mu t + \gamma)}{1-CDR}$.

$\mu_{2\square} = \mu_{1\square}\mu_{HR\square}$ and $\mu_{t2\square} = \mu_{t1\square}\mu_{tHR\square}$, where $\mu_{2\square}$ and $\mu_{1\square}$ represent natural mortality rates in HIV positives and HIV negatives respectively. Similarly, TB related mortality in HIV infected, $\mu_{t2\square}$ is the product of TB related mortality in HIV-uninfected, $\mu_{t1\square}$ and TB mortality HR.

G- Gamma, N=Normal, LN- LogNormal, B-Beta

Supplementary results

Baseline epidemiologic characteristics

Figure 2 presents baseline epidemiologic characteristics of TB and HIV in our model. TB prevalence and TB incidence are rates per 100,000 population, and 'proportion recent' is the percentage of total incident TB (including HIV positives) that is from fast progression disease. HIV prevalence is a proportion of the total population with HIV infection in our model. Baseline TB characteristics including prevalence, incidence, CDR, P:N ratio, and 'proportion recent' are the weighted averages of HIV positive and HIV negative populations in the model. IRR here quantifies the relative incidence of TB generated by the model in HIV positive population compared to HIV negative population. The unit for scale-up timescale is years.

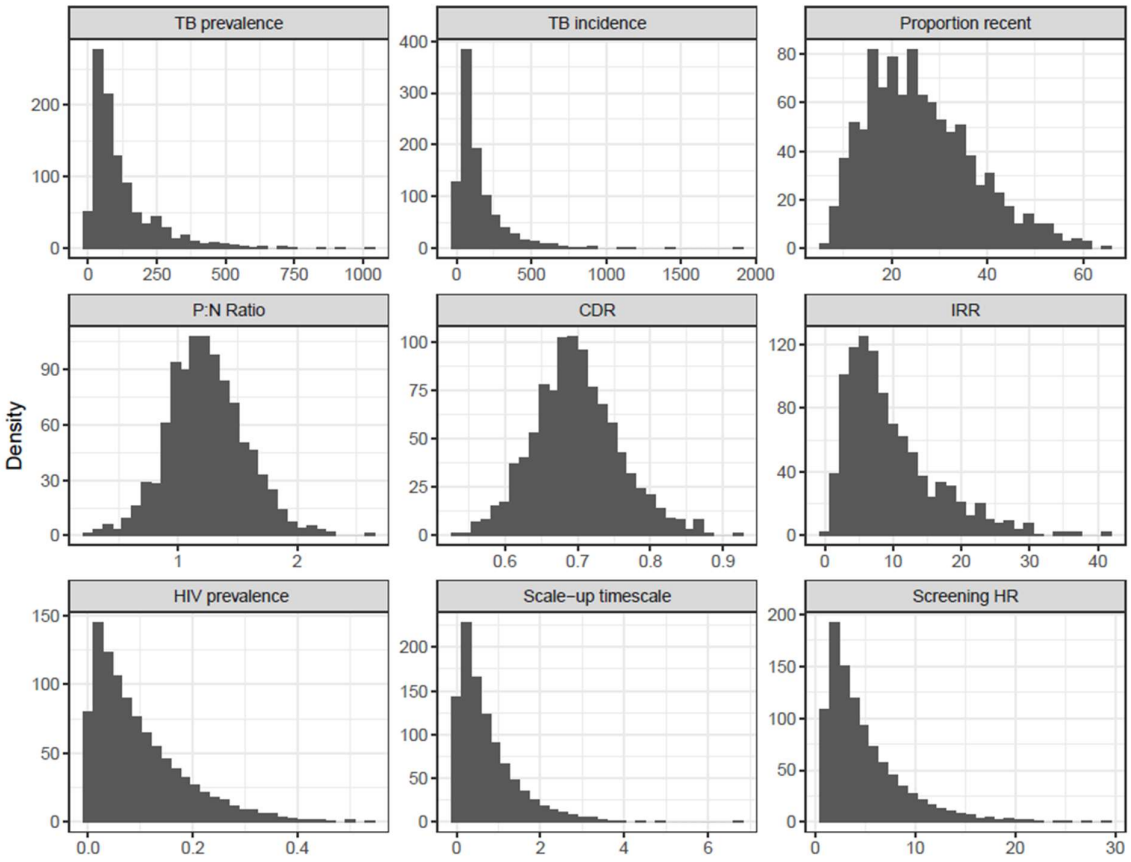

Figure 2- Baseline TB-HIV epidemiology

Rebound times

Rebound in notifications, incidence and prevalence occur immediately after termination of screening. Notifications and prevalence show exactly the same growth rate with an estimated median rate of 1.3 per year after the trough, while incidence rebounds with a much lower rate estimated at median of 0.07 per year. The doubling time for notification and prevalence was 6 months, while it takes about 9 years for trough relative incidence to double.

Relationship between incidence, prevalence and notifications

The average (median) relative notification at peak is 1.7 (1.3, 2.4), while the median relative incidence and prevalence at trough are 0.82 (0.74, 0.88) and 0.28 (0.16, 0.48) respectively. See figure 3 below for the relationship between these variables.

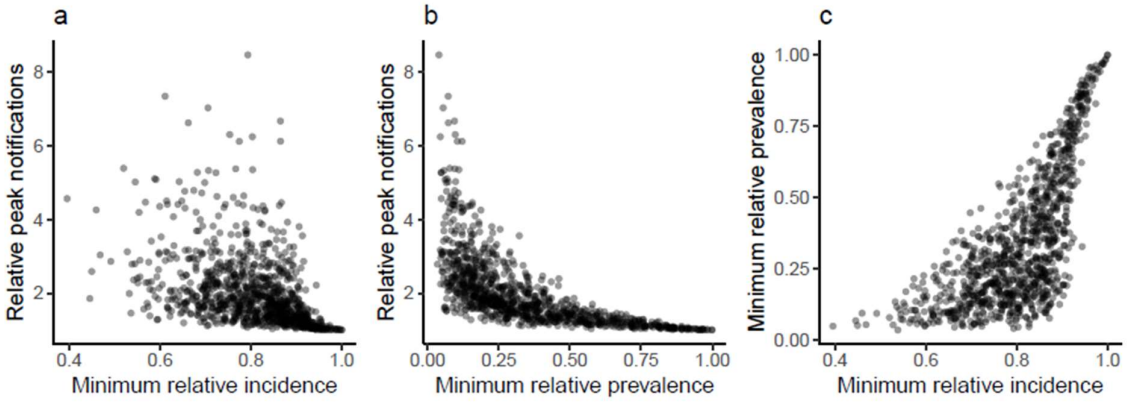

Figure 3: Relationship between peak notifications, and trough incidence and prevalence.

The relationship between screening HR and peak notifications, trough notifications and trough incidence are presented using a panel of scatter plots in figure 4. The height of the peak notifications has a linear relationship with screening HR (panel a). Likewise, the depth of notifications and incidence also depend on the extent of screening coverage (panels b and c), although the impact is lower on incidence compared to notifications.

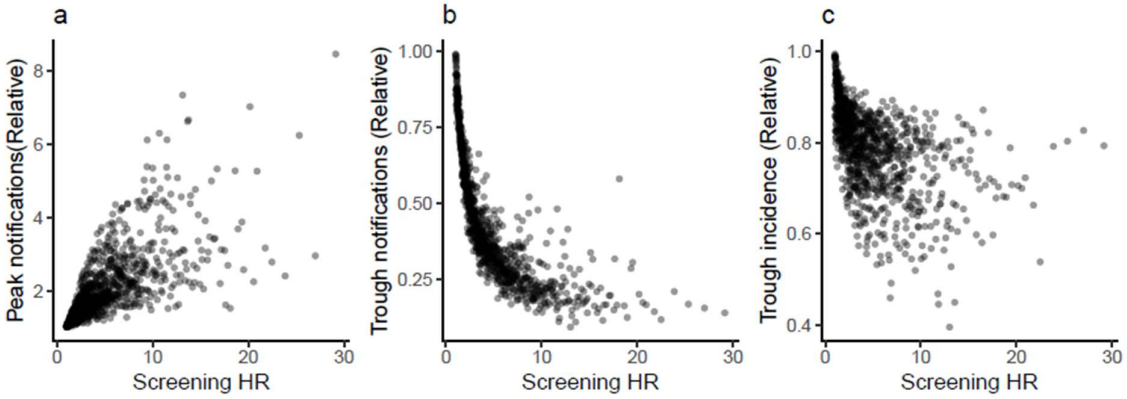

Figure 4: Relationship between baseline epidemiologic characteristics and peak and trough notifications.

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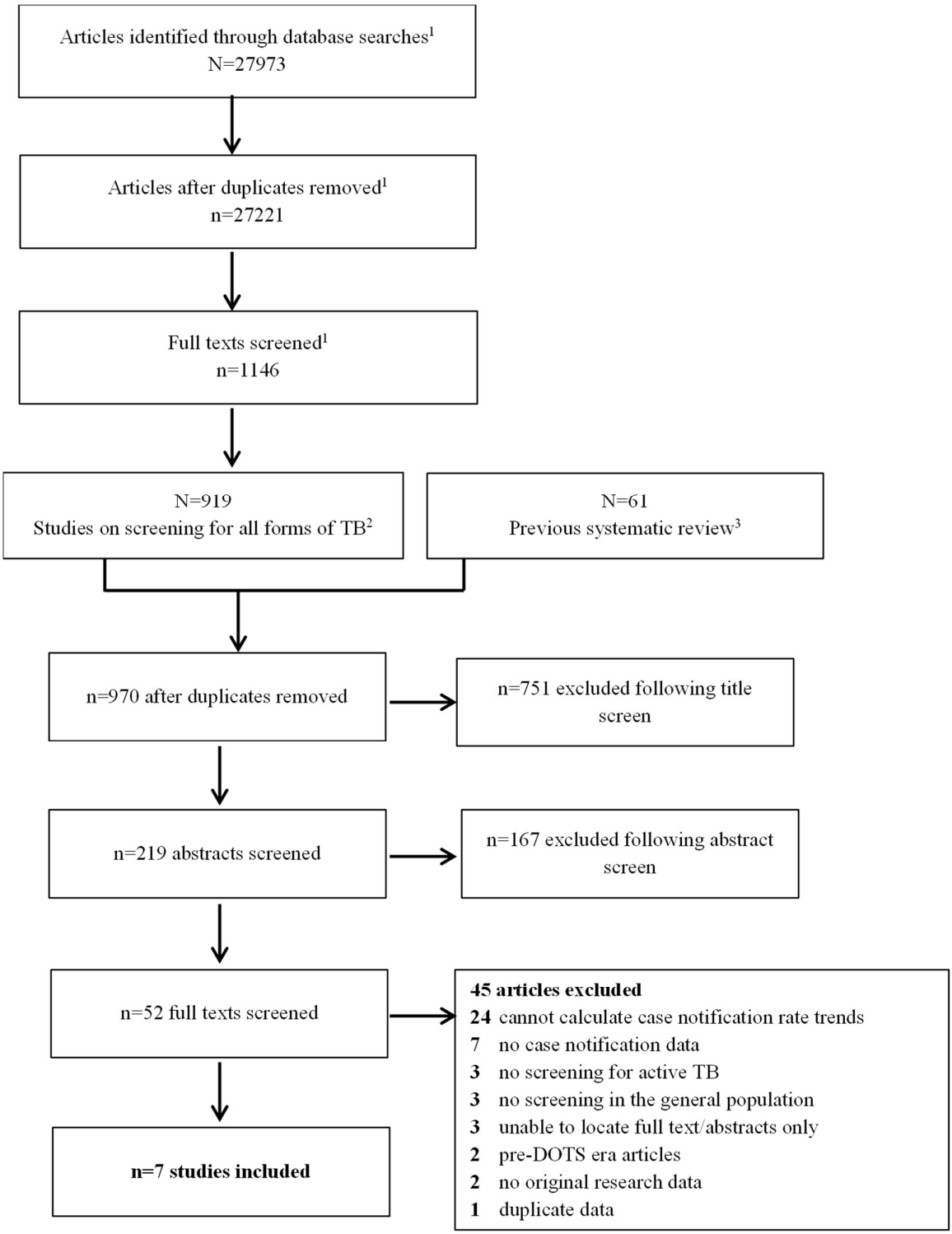
Appendix 4: PRISMA flow diagram of review process



[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

Chapter 5: The incidence of self-reported tuberculosis treatment with community-wide universal testing and treatment for HIV and tuberculosis screening in Zambia and South Africa: A planned analysis of the HPTN 071 (PopART) cluster-randomised trial

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	159168	**Title**	Dr
First Name(s)	Lilanganee		
Surname/Family Name	Telisinghe		
Thesis Title	Can universal testing and treatment for HIV and community-wide active case finding for tuberculosis control the African TB epidemic?		
Primary Supervisor	Professor Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLOS Medicine
Please list the paper's authors in the intended authorship order:	L. Telisinghe, S. Floyd, D. MacLeod, A. Schaap, R. Dunbar, J. Bwalya, N. Bell-Mandla, E. Piwowar-Manning, D. Donnell, K. Shaunaube, P. Bock, S. Fidler, R. J. Hayes and H. M. Ayles
Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the research question based on the available data and reviewed the questionnaire and worked up the case definition. I worked up the methods to prepare the data for analysis (in particular the methods employed to prepare the data for the cohort analysis). I undertook all analyses presented. I drafted and edited the manuscript.

SECTION E

Student Signature	L. Telisinghe
Date	28/02/2024

Supervisor Signature	Helen Ayles
Date	18/03/2024

Full title: The incidence of self-reported tuberculosis treatment with community-wide universal testing and treatment for HIV and tuberculosis screening in Zambia and South Africa: A planned analysis of the HPTN 071 (PopART) cluster-randomised trial

Short title: Impact of TB screening and UTT for HIV on self-reported TB incidence

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Abstract

Background: HIV is a potent risk factor for TB. Therefore, community-wide universal testing and treatment for HIV (UTT) could contribute to TB control, but evidence for this is limited. Community-wide TB screening can decrease population-level TB prevalence. Combining UTT with TB screening could therefore significantly impact TB control in sub-Saharan Africa, but to our knowledge there is no evidence for this combined approach.

Methods and results: HPTN 071 (PopART) was a community-randomised trial conducted between November 2013 to July 2018; 21 Zambian and South African communities (with a total population of ~1 million individuals) were randomised to arms A (community-wide UTT and TB screening), B (community-wide universal HIV testing with treatment following national guidelines and TB screening), or C (standard-of-care). In a cohort of randomly-selected adults (18-44 years) enrolled between 2013-2015 from all 21 communities (total size 38,474; 27,139 [71%] female; 8,004 [21%] HIV positive) and followed-up annually for 36 months to measure the population-level impact of the interventions, data on self-reported TB treatment in the previous 12 months (self-reported TB) were collected by trained research assistants and recorded using a structured questionnaire at each study visit. In this prespecified analysis of the trial, self-reported TB incidence rates were measured by calendar year between 2014 and 2017/18. A p-value ≤0.05 on hypothesis testing was defined as reaching statistical significance. Between January 2014 and July 2018, 38,287 individuals were followed-up: 494 self-reported TB during 104,877 person-years. Overall incidence rates were similar across all arms in 2014 and 2015 (0.33-0.46/100 person-years). In 2016 incidence rates were lower in arm A compared to C overall (adjusted rate ratio [aRR] 0.48 [95% confidence interval (95%CI) 0.28-0.81; p=0.01]), with statistical significance reached. In 2017/18, while incidence rates were lower in arm A compared to C, statistical significance was not reached (aRR 0.58 [95%CI 0.27-1.22; p=0.13]). Among people living with HIV (PLHIV) incidence rates were lower in arm A compared to C in 2016 (RR 0.56 [95%CI 0.29-1.08; p=0.08]) and 2017/18 (RR 0.50 [95%CI 0.26-0.95; p=0.04]); statistical

significance was only reached in 2017/18. Incidence rates in arms B and C were similar, overall and among PLHIV. Among HIV-negative individuals there were too few events for cross-arm comparisons. Study limitations include the use of self-report which may have been subject to under-reporting, limited covariate adjustment due to the small number of events, and high losses to follow-up over time.

Interpretation: In this study, community-wide UTT and TB screening resulted in substantially lower TB incidence among PLHIV at population-level, compared to standard-of-care, with statistical significance reached in the final study year. There was also some evidence this translated to a decrease in self-reported TB incidence overall in the population. Reduction in arm A but not B suggests UTT drove the observed effect. Our data support the role of UTT in TB control, in addition to HIV control, in high TB/HIV burden settings.

Words: 475/500

Author summary

Why was this study done?

- Tuberculosis (TB) is a leading cause of sickness and death worldwide. In sub-Saharan Africa, TB is mainly driven by the HIV-epidemic.
- Between 2013-2018, the HPTN 071 cluster-randomised trial was conducted in 21 Zambian and South African communities. There were 3 study arms: 1) arm A which received universal testing and treatment for HIV (UTT) and TB screening; 2) arm B which received universal HIV testing (with antiretroviral therapy according to national guidelines) and TB screening; and 3) arm C the control.
- As part of the trial, a cohort of 38,474 adults aged 18-44 years were enrolled from all communities at the start and followed up annually over 36 months.

What did the researchers do and find?

- All cohort members were asked if they had been started on TB treatment in the last 12 months (self-reported TB), at each annual visit (maximum of 4 visits). We investigated the effect of the interventions on self-reported TB incidence.
- We found a decrease in self-reported TB incidence among people living with HIV in arm A compared to arm C. There was also some evidence this translated to a decrease in self-reported TB incidence overall in the population in arm A compared to arm C.
- Self-reported TB incidence was similar in arms B and C, overall in the population and among people living with HIV.
- We could not determine the effect of the interventions on self-reported TB incidence among those who were HIV negative, due to the small number of events.

What do these findings mean?

- The decrease in self-reported TB incidence in arm A (which received community-wide UTT and TB screening) but not arm B (which received community-wide HIV testing with antiretroviral therapy according to national guidelines and TB screening) suggests the UTT component of the intervention drove the changes observed in arm A.
- Our data support the role of UTT in TB control in sub-Saharan Africa.

Background

Tuberculosis (TB) is a leading infectious cause of morbidity and mortality worldwide[1]. Sub-Saharan Africa has some of the highest TB incidence and mortality rates, which are mainly driven by the generalised HIV epidemic[1,2]. While current TB control measures have gradually decreased population-level TB incidence in the region, steeper reductions are needed to meet the ambitious World Health Organization (WHO) End TB Strategy milestones and targets: compared to 2015, a 50% and 90% reduction in TB incidence by 2025 and 2035 respectively[1]. However, the best approach to control TB in sub-Saharan Africa is unknown.

At the individual-level, antiretroviral therapy (ART) decreases the risk of incident TB among people living with HIV (PLHIV) who take ART[2]. ART roll-out started in ~2004 in sub-Saharan Africa, with the $CD4^+$ T-lymphocyte threshold for ART initiation and therefore ART coverage increasing over time. In 2015, WHO recommended “universal ART” (i.e. starting ART irrespective of $CD4^+$ T-lymphocyte count) for PLHIV[3]. Several observational studies have tried to determine the potential for ART to control TB, both in the total population and among all PLHIV (those in and not in HIV/ART-care), where the individual-level effect of ART among PLHIV taking ART may not necessarily translate to the population-level impact needed for TB control. Several routine programmes have observed decreases in TB notification rates/diagnoses coincident with routine ART scale-up over time[4-15]. Three further observational studies using different study designs and outcomes, found an association between increasing ART coverage under routine programmatic conditions and decreases in population-level measures of TB[16-18]. While it is plausible that ART use may in part explain these observations, it is not possible to conclude based on these observational findings alone, that ART can control TB in sub-Saharan Africa.

In sub-Saharan Africa, the HIV testing landscape is also changing. The Joint United Nations Programme for HIV/AIDS (UNAIDS) targets, include 95% of PLHIV knowing their status and

95% of those diagnosed receiving ART[19]. To meet these goals, countries must go beyond providing ART only to those seeking HIV-care. One approach is universal HIV testing (i.e. repeated HIV testing of whole populations), combined with linkage-to-care and support to initiate universal ART, along with treatment adherence support. This intervention is called Universal Testing and Treatment for HIV (or UTT). Several trials have shown that UTT can be implemented effectively, help meet UNAIDS targets, and decrease population-level HIV incidence[20]. Mathematical modelling also predicts that with annual HIV testing and universal ART, the HIV-associated TB incidence could decrease by ~50% once full coverage is reached[21]. But to date, these predictions have not been robustly investigated.

To control TB, WHO also recommends systematic TB screening in general populations with high TB prevalence[22]. TB screening aims to, irrespective of HIV-status, identify and treat people with infectious undiagnosed TB early, decreasing the background TB transmission risk[22]. Therefore, combining UTT and TB screening could achieve large, rapid, and sustained decreases in population-level TB incidence; but empirical data supporting this combined approach are lacking.

HPTN 071 (PopART) was a cluster-randomised HIV treatment as prevention trial conducted in Zambia and the Western Cape of South Africa; the intervention package included community-wide UTT and systematic TB screening[23,24]. The primary outcome of the trial, HIV incidence, was measured in a cohort of adults aged 18-44 years who were followed-up for 36 months. The effect of the HPTN 071 (PopART) interventions on HIV incidence and other key secondary outcomes have already been published[24-26]. During follow-up, cohort members were also asked if they initiated TB treatment (self-reported TB). Here we investigated the effect of the intervention on self-reported TB incidence at population-level, a planned secondary analysis of the trial.

Methods

Ethical approval for the trial was obtained from the London School of Hygiene and Tropical Medicine, UK, University of Zambia, and Stellenbosch University South Africa. The trial design has been described in detail elsewhere and is briefly summarised here (also see S1_CONSORT_checklist)[23-25,27].

Population

Twenty-one urban and peri-urban communities (12 Zambian and 9 South African; total population ~1 million), with high HIV prevalence (10-25%), high TB case notification rates (≥400/100,000 population), and population ≥20,000 were purposively selected. A community was the catchment population of a health centre and communities were geographically distinct. Communities were matched into triplets (groups of 3 communities), based on geography and HIV prevalence, giving 4 Zambian and 3 South African triplets. The communities in each triplet were then randomised to one of 3 study arms (2 intervention arms [A and B] and a standard-of-care arm [C]), using restricted randomisation to ensure balance across arms by population size, baseline ART coverage, and HIV prevalence.

Intervention

In arms A and B, between November 2013 and June 2015, a door-to-door, community-wide, HIV/TB prevention intervention was delivered by trained community health workers (Appendix-S1-3). Between July 2015 and December 2017, 2 further intervention rounds were delivered. At each intervention round, all households in the intervention communities were visited and offered the study intervention. In both arms universal HIV testing using rapid tests was offered, with linkage-to-care if HIV-positive. ART initiation was universal in arm A from 2013. In arm B, ART initiation followed national guidelines, which switched to universal treatment in 2016 (Zambia in April and South Africa in October). In both arms, a symptom questionnaire (any one of cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month) was used to screen for TB. If symptomatic, sputum was collected and tested according to national guidelines (using Xpert MTB/RIF and smear).

If sputum positive, individuals were linked to TB treatment. Arm C, the control, received the standard-of-care, through routine services. This included mainly passive TB case finding for people attending health centres. Provider-initiated TB symptom screening was conducted for PLHIV attending ART care. HIV counselling and testing was available at health centres for those seeking HIV care services and those identified as having presumptive TB.

Outcome

To measure trial outcomes, a Population Cohort (PC) was established between November 2013 and March 2015 (Appendix-S3). One adult aged 18-44 years was randomly-selected from a random sample of households in all 21 communities at baseline (called PC0). The cohort was followed-up at 12, 24 and 36 months (called PC12, PC24 and PC36 respectively). PC36 ended in July 2018.

Our primary outcome was self-reported TB measured in a closed cohort enrolled at PC0. At each PC-visit (PC0 to PC36), trained research assistants administered a structured questionnaire using electronic data capture devices. All PC-participants were asked: 1) if they had been told they had TB in the preceding 12 months; 2) if yes, did they start TB treatment (specified as the preceding 12 months in PC12-36, but not at PC0); and 3) if yes, the month and year of treatment start (Table-1). At PC0, self-reported TB was defined as starting TB treatment in the 14 months before the PC-visit (duration calculated using month/year of PC-visit and treatment start date). A 14-month eligibility period (rather than 12 months) was used to allow for errors in recalling months. For PC12-36, in addition to this, individuals unable to recall treatment start month/year were also included in the case definition, as the question specified if treatment was started “in the last 12 months”. At each PC-visit blood was collected and tested in the laboratory to determine HIV-status.

Statistical methods (also see Appendix-S4)

Two approaches were used to analyse data: cohort (primary analysis) and cross-sectional (secondary analysis).

Cohort analysis: Because self-reported TB was determined over the 14 months before each PC-visit, for each PC-participant, an observation start date 14 months before each PC-visit was generated, representing the date from which their observation time for each PC-visit began. To determine incidence, the analysis used the first self-reported TB event observed for each participant. Where month and year of treatment start was known, the day was imputed as 15. Where the date was unknown (only ~10% of those self-reporting TB between PC12-36, where PC-participants who could not recall the month/year of TB treatment start were also included in the case definition; Table-1), it was imputed as the mid-point between the PC-visit with self-reported TB and the preceding PC-visit if there were 2 consecutive PC-visits, or 7 months before the PC-visit with self-reported TB if no consecutive PC-visits. Entry to the cohort was the observation start date generated 14 months before the PC0-visit. Time-at-risk was calculated from the PC0 observation start date until self-reported TB or the last PC-visit, whichever came first. Not all PC-participants were seen at each PC-visit. Therefore, there were gaps in observation time between PC-visits and the observation start date of the subsequent PC-visit, during which outcome status was unknown. These gaps in follow-up were not included in the time-at-risk.

TB screening, by diagnosing and linking people with TB to treatment, should initially increase self-reported TB[28]. When TB transmission and therefore incidence falls, self-reported TB should decrease[28]. UTT should decrease self-reported TB among PLHIV and overall[15]. Therefore, to investigate patterns and exclude initial rises in self-reported TB due to TB screening, time-at-risk was split into calendar year and analysed by year, starting in 2014; the first year during which the intervention was rolled out. As follow-up in 2018 was only 6 months, 2017/18 was analysed as one calendar period.

HIV-status at each PC-visit was assumed to be the HIV-status for the whole year in which the PC-visit took place. Where there were discordant HIV-results (positive and negative) for a year (because 2 PC-visits occurred in 1 year), HIV-status was assumed to be positive. Where HIV-status was unknown in the year before a positive result, sensitivity analysis

explored assuming HIV-status was positive (as the observation period for a PC-visit extends into the preceding year) or negative in the preceding year.

The rate of self-reported TB (overall and by HIV-status) was calculated for each community, each year; 0.5 was added to the numerator if no individuals self-reported TB. The geometric means of these rates were then compared between study arms.

Cross-sectional analysis: Each PC-visit was treated as an independent cross-sectional sample, giving 4 independent cross-sectional samples. All PC-participants seen at a PC-visit, contributed to the analysis for that visit. HIV-status at the PC-visit was assumed to be the HIV-status during the 14-month eligibility period used to measure the outcome. The proportion self-reporting TB (overall and by HIV-status) at each PC-visit was calculated for each community; 0.5 was added to the numerator if no individuals self-reported TB. The geometric means of these proportions were then compared between study arms.

Rate ratios (RR)/prevalence ratios (PR): Arms A and C, and arms B and C were compared; overall and for PLHIV. Cross-arm comparisons were not conducted for HIV-negative individuals due to the very small number of events when data were disaggregated by community and calendar period/PC-visit. Statistical inferences used the recommended two-stage approach, adjusting for covariates at Stage-1[29]. Stage-1 used Poisson regression for the cohort analysis and logistic regression for the cross-sectional analysis, to compute the expected number of individuals with self-reported TB, assuming no intervention effect. Due to the small number of events during later calendar years/PC-visits, the total population analysis included triplet and HIV-status as covariates (without adjusting for age and sex). Analyses for PLHIV included triplet alone. At Stage-2, a two-way analysis of variance was conducted on the log(observed/expected number self-reporting TB) in each community, with matched triplet and study arm as factors, to generate the overall RR (cohort analysis) and PR (cross-sectional analysis) and 95% confidence intervals (CIs) for cross-arm comparisons. A p-value ≤0.05 on hypothesis testing was defined as reaching statistical

significance. All analyses were undertaken in Stata version-15 (Stata Corporation, Texas, USA).

Results

PC-participant characteristics and self-reported TB at PC-visits

In total, 38,474 individuals were enrolled at PC0 (Appendix-S5; Appendix-S6). The majority (27,139/38,474 [71%]) were female, 15,225/38,474 (40%) were aged 18-24 years, and 8,004/38,474 (21%) were PLHIV. Baseline characteristics were similar across study arms at PC0. Of those enrolled at PC0, 27,948/38,474 (73%) were seen at least once during follow-up. The characteristics of those only seen at PC0 (i.e. had no follow-up PC-visits) and those seen at least once during follow-up were similar (Appendix-S7). By PC-visit, 25,290/38,474 (66%), 21,678/38,474 (56%) and 20,422/38,474 (53%), were seen at PC12, PC24 and PC36 respectively; the proportions seen at each PC-visit were similar across study arms. Despite losses to follow-up at each PC-visit, the characteristics of those seen (overall and among PLHIV [Appendix-S8]) were similar across study arms. Further, the characteristics of those seen were similar to those who were not seen (Appendix-S7). The self-reported TB case definition (Table-1; Appendix-S9) was met by 279/38,474 (0.73%) at PC0, 142/25,290 (0.56%) at PC12, 160/21,678 (0.74%) at PC24, and 105/20,422 (0.51%) at PC36. The 686 events at all PC-visits were from 628 PC-participants; 573/628 (91%) only self-reported TB at 1 PC-visit. The proportion self-reporting TB was higher in South Africa than in Zambia and among PLHIV than those HIV-negative. Among PLHIV, the proportion self-reporting TB fell from 2.4% in PC0 to 1.3% in PC36.

Cohort analysis

To measure incidence rates, the first self-reported TB event for each participant was used. Between January 2014 and July 2018, 38,287/38,474 (>99%) provided person-time, with 494 events observed. The proportion contributing person-time each year and their

characteristics were similar across study arms, both overall (Figure-1; Table-2; Appendix-S10) and among PLHIV (Appendix-S8).

The overall incidence of self-reported TB was 0.53/100 person-years (154 self-reported TB/28,847 person-years) in 2014; 0.46/100 person-years (112/24,151) in 2015, 0.64/100 person-years (136/21,193) in 2016, and 0.47/100 person-years (92/19,544) in 2017/18. While self-reported TB incidence (geometric mean across communities) showed year-on-year fluctuations, there were some discernible patterns (Figure-2; Appendix-S11; Table-3a). Incidence was similar across study arms in 2014 and 2015 (Table-4). Over time, incidence in arm C increased, from 0.41 in 2014 to 0.59 and 0.51/100 person-years in 2016 and 2017/18 respectively. In arm A, incidence decreased from 0.44 in 2014 to 0.27 and 0.29/100 person-years in 2016 and 2017/18 respectively; the adjusted RR compared with arm C was 0.48 (95%CI 0.28-0.81; p=0.01) in 2016 and 0.58 (95%CI 0.27-1.22; p=0.13) in 2017/18. In arm B incidence varied, ranging between 0.33-0.55/100 person-years; incidence in arms B and C was similar at all time-points.

Among PLHIV, overall self-reported TB incidence was 1.76/100 person-years (77 self-reported TB/4,385 person-years) in 2014, 1.39/100 person-years (69/4,977) in 2015, 1.68/100 person-years (76/4,528) in 2016, and 1.14/100 person-years (51/4,493) in 2017/18. In 2014 and 2015, incidence in arms C and A was similar (Figure-2; Appendix-S11; Table-3a; Table-4). In arm C, incidence decreased gradually from 1.71/100 person-years in 2014 to 1.48 and 1.42/100 person-years in 2016 and 2017/18 respectively. In arm A, decreases in incidence were large and sustained, from 1.87/100 person-years in 2014 to 0.83/100 person-years in 2016, and 0.70/100 person-years in 2017/2018; the RR compared to arm C was 0.56 (95%CI 0.29-1.08; p=0.08) in 2016 and 0.50 (95%CI 0.26-0.95; p=0.04) in 2017/18. In arm B, incidence decreased slightly from 1.43/100 person-years in 2014 to 1.38/100 person-years in 2016. Incidence in arms B and C was similar over this period. In 2017/18, incidence in arm B fell to 1.11/100 person-years, showing separation from arm C; the RR compared to arm C was 0.78 (95%CI 0.41-1.50; p=0.43). Sensitivity analysis, changing the HIV-positive

case definition, did not alter findings. Among those HIV-negative (Appendix-S11), the number of events was very low, with null events in multiple communities, over multiple calendar years; self-reported TB incidence varied over time across study arms.

Cross-sectional analysis

All 686 events were used to determine the proportion self-reporting TB at each PC-visit. In arms C and B, the overall proportion (geometric mean across communities) followed a similar variable pattern (Figure-2; Appendix-S12; Table-3b; Table-5). In arm A, the proportion self-reporting TB decreased steadily at each PC-visit. The adjusted PR compared with arm C was 0.44 (95%CI 0.23-0.85; p=0.02) at PC24 and 0.58 (95%CI 0.30-1.10; p=0.09) at PC36. The estimated coefficient of between-community variation k was in the range of approximately 0.0-0.20 between PC12 and PC36, after accounting for between-arm and between-triplet variation (Appendix-S13).

Among PLHIV, the proportion self-reporting TB in arms A and B was similar to arm C at PC0 and PC12 (Figure-2; Appendix-S12; Table-3b; Table-5). Between PC12 and PC36 the proportions in arm A, decreased steadily. The PR compared with arm C was 0.54 (95%CI 0.30-0.99; p=0.05) at PC24 and 0.48 (95%CI 0.23-0.99; p=0.05) at PC36. In arm B, while the proportions gradually decreased between PC12 and PC36, the proportions in arms B and C were similar at these PC-visits. Among those HIV-negative (Appendix-S12), the number of events at PC-visits was very low with null events in multiple communities. Self-reported TB incidence varied over time across study arms.

Discussion

In this pre-planned analysis of a large cluster-randomised trial in sub-Saharan Africa, compared to standard-of-care, we found a decrease in self-reported TB incidence among PLHIV following the roll-out of community-wide UTT and systematic TB screening in arm A, which received the full intervention package from the start. There was also some evidence that this translated to a decrease in self-reported TB incidence overall in the population,

although confidence intervals around some effect estimates with less follow-up time/lower sample sizes were wide and crossed 1. There were insufficient events to determine if the intervention had an effect on self-reported TB incidence among those HIV-negative.

With TB screening, we anticipated large initial increases in self-reported TB in the intervention arms[28], which we did not see. Decreases in self-reported TB incidence after the first intervention round among PLHIV in arm A suggests UTT was the main driver of the intervention effect. Our findings were in keeping with mathematical modelling predictions of the impact of UTT on HIV-associated TB incidence[21].

To date, 4 large HIV treatment as prevention trials have been conducted[30]. It is unlikely that trials of their scale and scope will ever be conducted again. Of these, only 1 trial other than HPTN 071 (PopART), the Sustainable East Africa Research in Community Health (SEARCH) trial, evaluated the impact of UTT on TB[31]. However, this was a post-hoc analysis, which therefore requires cautious interpretation. Nonetheless, the TB notification rate ratio in the intervention (UTT) compared to the control arm among PLHIV was 0.41 (95%CI 0.19-0.86); there was no effect among those HIV-negative. Our results confirm these preliminary findings and support the role of UTT in TB control in sub-Saharan Africa.

Self-reported TB should reflect TB notifications, which for small geographic areas typically show year-on-year fluctuations as seen with data from the standard-of-care (Arm C) communities[32]. These fluctuations were mainly among HIV-negative individuals (due to the small number of events). Among PLHIV, there were discernible trends across all arms, with limited fluctuation, and results consistent between the cohort and cross-sectional analysis, lending weight to the robustness of the findings. Self-reported treatment was used as the outcome, rather than “told they had TB” (i.e. potential diagnoses), as the questionnaire was designed to determine treatment starts. The outcome was based on self-report[18,33-36]. Research staff were extensively trained and supervised, with in-built prompts and skip patterns in electronic data capture likely to limit errors in questioning and documenting

responses. Misclassification through under-reporting due to stigma or social-desirability bias was possible but would be expected to be similar across study arms[37,38]. In a cohort study this should not bias the RR, with the ratio representing the intervention effect on underlying TB incidence. If the intervention changed TB-stigma, the direction of the effect given the community-engagement and participatory nature of the trial, would likely reduce stigma and therefore under-reporting in intervention communities. Self-reported TB in standard-of-care communities would be lower, as a proportion of true treatment starts, with impact under-estimated. Treatment for other conditions being erroneously reported as TB[37,38] was unlikely because TB knowledge was common across communities, data collection was structured, with information sharing during the process through in-built prompts and repeated in the same closed cohort over time, and information on TB treatment (which takes 6-8 months) was only collected for the 12 months preceding a PC-visit. Misclassification of TB preventive therapy (TPT) use as TB treatment was also unlikely as PC-participants were specifically asked about TPT use at each PC-visit, research staff were trained on how to administer the TB treatment versus TPT questions, and TPT use by routine services was suboptimal during the study period. Any possible over-reporting would also be expected to be similar across study arms biasing the RR in a cohort study towards the null.

Using self-reported TB in PC as the outcome in our study had some strengths. Measuring the impact of interventions on TB incidence is usually not feasible, but this is the critical outcome for drawing causal inferences about TB control interventions. In well-functioning health systems, where nearly all people with TB are diagnosed, treated and events captured through quality-assured routine surveillance systems, TB notifications can be used as a proxy for TB incidence[39]. But this is not the case in sub-Saharan Africa and the availability and quality of TB notification data varied substantially across study community health centres. Further, people with TB living in study communities often started TB treatment outside community health centres, and therefore using health centre data would have

underestimated TB notifications. These care seeking behaviours also varied by community. When using self-reported TB in the PC, while some under-reporting was possible, the estimated impact should, nonetheless, reflect the minimum impact of the intervention on underlying TB incidence.

When national guidelines for ART initiation recommended a CD4 cell threshold of <500 cells/μL, the self-reported TB incidence among PLHIV in intervention arm B (where ART start followed guidelines) and the standard-of-care arm was similar. While we do not have CD4 data for PC-participants, the proportion of PLHIV with viral suppression was higher in arm A than B, and in both intervention arms than the standard-of-care arm[24]. After national guidelines changed to universal ART in 2016, self-reported TB incidence in arm B showed a non-significant decrease compared to the standard-of-care arm. But there was insufficient follow-up to determine if effects were sustained. Nonetheless this, together with findings from arm A, suggest that universal HIV testing alongside universal ART was critical to achieving intervention benefits quickly. Going forward, identifying models of universal HIV testing and linkage-to-care that are acceptable, cost-effective, and reflect the local TB/HIV epidemiology will be important, if countries want to translate trial findings to local benefits.

Despite large decreases in self-reported TB incidence in arm A compared to standard-of-care communities, absolute incidence in arm A remained high (geometric means ~300/100,000 overall and ~800/100,000 among PLHIV). The trial duration was short, and therefore we were unable to determine the longer-term impact of sustained UTT. Mathematical modelling predicts that following an initial steep drop in HIV-associated TB incidence with UTT, incidence will subsequently fall more slowly[21]. This is because PLHIV on ART live longer[2]. While ART decreases their risk of incident TB it does not return it to that of HIV-negative individuals, giving a relatively high cumulative lifetime risk of TB[2]. This is coupled with the background risk of TB among those HIV-negative, who contribute >30% of all incident TB in sub-Saharan Africa[1]. Therefore, scale-up of other TB prevention interventions, such as TPT in risk groups (e.g. PLHIV) as recommended by WHO, is needed

to prevent TB at the individual-level, which may also translate to population-level benefits[40]. While systematic TB screening, is recommended by WHO in high TB prevalence settings[22], we found no evidence that this increased the proportion of individuals who reported starting TB treatment. Possible explanations include the low sensitivity of symptom screening for prevalent TB[22], and the use of sputum smear in the diagnostic algorithm, which has lower sensitivity than other diagnostic methods[41]. Screening with chest-radiographs, and the routine wide-spread use of GeneXpert MTB/RIF for TB diagnosis may overcome some of these limitations[22,41].

Limitations of our study include limited covariate adjustment due to the small number of events and high losses to follow-up over time. While residual confounding and selection bias cannot be excluded, the characteristics of individuals seen, and proportions seen at each calendar year/PC-visit did not differ by study arm. The cohort analysis used longitudinal data on self-reported TB and treatment start dates, allowing incidence rates to be estimated. However, it may have been biased by errors in reported dates and gaps in follow-up between PC-visits where outcome status was unknown. But conclusions from the cross-sectional analysis (based on fewer assumptions and done to check the robustness of the cohort analysis findings) were very similar, supporting the overall findings. HIV-status was determined at each PC-visit and not at TB treatment start; therefore, some misclassification was likely. However, findings were similar using different approaches to classifying HIV-status and so the effect of any misclassification was likely to be small. HIV-status was defined using all available HIV data (prevalent and incident), to capture the full effect of the interventions on self-reported TB incidence among PLHIV. However, because UTT was shown to decrease HIV incidence, this may have decreased the comparability between PLHIV across study arms. But the degree of any bias was likely to be very small because HIV incidence was very low (~1.4 per 100 person years) compared with prevalence (~18%) and therefore, the number of people with incident HIV at follow-up was very small compared with those who were HIV positive at baseline. Further the intervention effect on HIV

incidence in arm A compared to arm C was very modest (7% reduction in HIV incidence), and the characteristics of PLHIV at each calendar year/PC-visit did not differ by study arm. PC-participants were aged 18-44 years at enrolment; therefore, findings cannot be generalised to the population as a whole.

In conclusion, in this cluster-randomised trial in sub-Saharan Africa, compared to standard-of-care, we found a decrease in self-reported TB incidence among PLHIV following the roll-out of community-wide UTT and systematic TB screening in arm A, which received the full intervention package from the start. There was also some evidence that this translated to a decrease in self-reported TB incidence overall in the population. UTT could contribute to controlling TB in addition to HIV in high TB/HIV burden settings.

Author contribution:

Study design: LT, SF, RJH, HMA

Data analysis: LT with input from SF and RJH.

Drafted manuscript: LT

Edited manuscript: LT, SF, DM, AS, RD, JB, NBM, EPM, DD, KS, PB, SF, RJH, HMA

Approved final draft: LT, SF, DM, AS, RD, JB, NBM, EPM, DD, KS, PB, SF, RJH, HMA

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Table-1: Number and proportion meeting the case definition of self-reported TB treatment by Population Cohort visit, in the cohort enrolled at PC0 (N=38474) from all 21 HPTN 071 (PopART) communities

		PC0 N=38474	PC12 N=25290	PC24 N=21678	PC36 N=20422
Self-reported being told they had TB AND starting TB treatment‡	Yes	361/38474 (0.94%)	164/25290 (0.65%)	177/21678 (0.82%)	110/20422 (0.54%)
Duration between visit date and MM/YYYY of TB treatment startʃ[ŦŦ]	missing¶	67/361 (18.56%)	21/164 (12.80%)	17/177 (9.60%)	12/110 (10.91%)
	≤14 months*	279/361 (77.29%)	121/164 (73.78%)	143/177 (80.80%)	93/110 (84.55%)
	>14 months*	15/361 (4.16%)	22/164 (13.41%)	17/177 (9.60%)	5/110 (4.54%)
Total meeting the case definition of self-reported TB treatment	Yes†¥	279/38474 (0.73%)	142/25290 (0.56%)	160/21678 (0.74%)	105/20422 (0.51%)
Total meeting case definition by country	Zambia	114/19724 (0.58%)	37/12331 (0.30%)	46/10927 (0.42%)	34/10945 (0.31%)
	South Africa	165/18750 (0.88%)	105/12959 (0.81%)	114/10751 (1.06%)	71/9477 (0.75%)
Total meeting case definition by HIV-status$	Negativeɸ	79/29130 (0.27%)	43/17669 (0.24%)	67/15294 (0.44%)	43/15111 (0.28%)
	Positive	192/8004 (2.40%)	84/5086 (1.65%)	75/4579 (1.64%)	60/4758 (1.26%)
	Not determined	8/1340 (0.60%)	15/2535 (0.59%)	18/1805 (1.00%)	2/553 (0.36%)

TB=tuberculosis; PC=Population Cohort; MM/YYYY=month and year of TB treatment start ‡**Question asked:** "in the last 12 months, have you been told that you have TB" with response options of yes, no and don't know. If response was yes, **Question asked:** at PC0 "have you started TB treatment" and at PC12-36 "have you started TB treatment in the last 12 months" with response options of yes, no and don't know; ʃIf response was yes to "in the last 12 months, have you been told that you have TB" AND yes to "have you started TB treatment/ have you started TB treatment in the last 12 months", **Question asked:** "When did you start TB treatment? Please give the month and year?"; ŦDenominator is number of people self-reporting being told they have TB in the last 12 months and starting TB treatment; ¶unable to calculate duration due to missing month and year of TB treatment start; *number of months between self-reported TB treatment start month and year, and, visit date; †At PC0, self-reported TB treatment included individuals reporting TB treatment start in the 14 months before the PC-visit. For PC12-36, self-reported TB treatment was defined as individuals reporting TB treatment start in the 14 months before the PC-visit AND individuals who were unable to recall treatment start month/year (as the question at PC12-36 specified if treatment was started "in the last 12 months"); ¥Proportion of participants meeting the self-reported TB case definition who could recall the month and year of TB treatment start only (overall, by country, by HIV status) shown in Appendix-S9 $HIV-status based on laboratory testing. ɸAmong those HIV-negative, there were no events in multiple communities when data were disaggregated by community (at PC0 there were no events in 4 communities, at PC12 there were no events in 6 communities, at PC24 there were no events in 3 communities and at PC36 there were no events in 7 communities).

Table-2: Characteristics of Population Cohort participants contributing person time to the cohort analysis from all 21 HPTN 071 (PopART) communities in 2014 (the first study year), by study arm

		2014		
		A	B	C
Total N		12616¶ (33%)*	13347¶ (35%)*	12297¶ (32%)*
Country	Zambia	6465 (51%)	6389 (48%)	6736 (55%)
	SA	6151 (49%)	6958 (52%)	5561 (45%)
Community HIV prevalence[x]		18%	19%	19%
Community size[Ø]		34,273	40,535	31,068
Sex	Male	3578 (28%)	3890 (29%)	3655 (30%)
	Female	9004 (72%)	9417 (71%)	8583 (70%)
Age/years[‡]	18-24	5045 (40%)	5162 (39%)	4960 (40%)
	25-29	2771 (22%)	2867 (21%)	2585 (21%)
	30-34	2137 (17%)	2278 (17%)	2058 (17%)
	35-39	1453 (12%)	1705 (13%)	1535 (13%)
	40-44	1175 (9%)	1295 (10%)	1096 (9%)
HIV-status[†]	Positive	2071 (18%)	2215 (18%)	2099 (18%)
	Negative	9745 (82%)	10320 (82%)	9372 (82%)

PC=Population Cohort; SA=South Africa; ND=not determined; All percentages rounded to the nearest whole number, where possible; ¶denominator for all column percentages shown in the column (unless otherwise indicated); *denominator is the total number contributing person time each year (row percentage); *Geometric mean of estimated community HIV prevalence among the population aged 18-44 years using HIV prevalence estimates at PC0 which were standardised using the population structure of the communities; ØGeometric mean of estimated minimum population size, based on census conducted by the study team in 2013; ‡age in years at PC0; †Measured in the study cohort with HIV-status based on laboratory HIV-testing.

Table-3

3a: The rate of self-reported TB treatment by study arm and calendar year in the cohort analysis from all 21 HPTN 071 (PopART) communities

	Total population Rate* (d/pyrs)			PLHIV Rate* (d/pyrs)			HIV negative Rate* (d/pyrs)		
Self-reported TB	Arm A	Arm B	Arm C	Arm A	Arm B	Arm C	Arm A	Arm B	Arm C
2014	0.44 (45/9473)	0.46 (56/9985)	0.41 (53/9389)	1.87 (26/1397)	1.43 (22/1526)	1.71 (29/1463)	0.12 (12/7392)	0.21 (20/7755)	0.15 (15/7202)
2015	0.37 (40/7865)	0.33 (33/8161)	0.40 (39/8124)	1.17 (24/1590)	1.31 (23/1624)	1.14 (22/1764)	0.16 (14/5894)	0.12 (9/6208)	0.16 (15/5921)
2016	0.27 (31/6827)	0.55 (49/7643)	0.59 (56/6722)	0.83 (17/1453)	1.38 (27/1554)	1.48 (32/1521)	0.21 (13/5093)	0.29 (20/5820)	0.34 (22/4878)
2017/18	0.29 (23/6305)	0.36 (34/7064)	0.51 (35/6175)	0.70 (11/1458)	1.11 (20/1552)	1.42 (20/1483)	0.20 (12/4684)	0.20 (13/5371)	0.21 (15/4567)

TB=tuberculosis; PLHIV=people living with HIV; d=total number self-reporting TB treatment; pyrs=person years; PC=Population Cohort; d/prys=total number self-reporting TB treatment/total number of person years contributed by PC-participants during each calendar year (2014, 2015, 2016 and 2017/2018) in each study arm; *rate calculated as the geometric mean of the cluster rates in each arm expressed per hundred person years;

3b: The proportion self-reporting TB treatment by study arm and Population Cohort visit in the cross-sectional analysis from all 21 HPTN 071 (PopART) communities

	Total population %† (d/N)			PLHIV %† (d/N)			HIV negative %† (d/N)		
Self-reported TB	Arm A	Arm B	Arm C	Arm A	Arm B	Arm C	Arm A	Arm B	Arm C
PC0	0.53 (77/12671)	0.57 (82/13404)	0.81 (120/12399)	2.20 (55/2583)	1.95 (56/2734)	2.48 (81/2687)	0.14 (20/9594)	0.19 (22/10235)	0.24 (37/9301)
PC12	0.41 (48/8234)	0.41 (45/8572)	0.48 (49/8484)	1.26 (27/1661)	1.58 (31/1660)	1.40 (26/1765)	0.21 (15/5781)	0.16 (12/6210)	0.18 (16/5678)
PC24	0.31 (37/6938)	0.64 (55/7873)	0.84 (68/6867)	0.98 (21/1459)	1.58 (26/1608)	1.82 (28/1512)	0.22 (15/4931)	0.37 (24/5691)	0.42 (28/4672)
PC36	0.27 (22/6623)	0.43 (46/7416)	0.49 (37/6383)	0.63 (10/1549)	1.45 (28/1637)	1.33 (22/1572)	0.19 (12/4873)	0.19 (16/5587)	0.20 (15/4651)

TB=tuberculosis; PLHIV=people living with HIV; %=proportion; †proportion calculated as the geometric mean of the cluster proportions in each arm; d=total number self-reporting TB treatment; N=total number seen at each PC-visit; PC=Population Cohort; d/N= total number self-reporting TB treatment/total number of PC-participants seen at each PC-visit (PC0, PC12, PC24 and PC36) in each study arm;

Table-4 The effect of the HPTN 071 (PopART) intervention on the incidence rate of self-reported TB treatment, by calendar year among Population Cohort participants

		2014			2015			2016			2017/18		
Population	**Adjusted for**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Arm A vs C													
Total population	triplet	1.08	(0.51-2.30)	0.83	0.91	(0.36-2.32)	0.83	0.47	(0.28-0.78)	0.007	0.57	(0.28-1.14)	0.10
	triplet and HIV	1.10	(0.52-2.33)	0.78	0.97	(0.37-2.59)	0.95	0.48	(0.28-0.81)	0.01	0.58	(0.27-1.22)	0.13
PLHIV	triplet	1.10	(0.49-2.47)	0.81	1.02	(0.52-2.01)	0.94	0.56	(0.29-1.08)	0.08	0.50	(0.26-0.95)	0.04
PLHIV*	triplet	1.13	(0.52-2.46)	0.74	1.03	(0.50-2.14)	0.92	0.55	(0.28-1.05)	0.06	0.50	(0.26-0.95)	0.04
Arm B vs C													
Total population	triplet	1.13	(0.53-2.42)	0.72	0.84	(0.33-2.14)	0.68	0.93	(0.56-1.55)	0.77	0.71	(0.35-1.42)	0.30
	triplet and HIV	1.11	(0.53-2.35)	0.76	0.95	(0.36-2.54)	0.92	0.97	(0.57-1.64)	0.90	0.72	(0.34-1.52)	0.35
PLHIV	triplet	0.84	(0.37-1.89)	0.64	1.15	(0.59-2.26)	0.66	0.93	(0.48-1.80)	0.82	0.78	(0.41-1.50)	0.43
PLHIV*	triplet	0.95	(0.44-2.07)	0.89	1.25	(0.60-2.59)	0.52	0.92	(0.48-1.77)	0.79	0.78	(0.41-1.50)	0.43

TB=tuberculosis; RR=rate ratio; 95%CI=95% confidence interval; PLHIV=people living with HIV; *HIV-status based on the sensitivity analysis: If HIV-positive for a calendar year and HIV-status was not determined in the preceding year, HIV-status in the preceding year assumed to be positive

Table-5 The effect of the HPTN 071 (PopART) intervention on the proportion self-reporting TB treatment, by Population Cohort visit, among Population Cohort participants

		PC0			PC12			PC24			PC36		
Population	**Adjusted for**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Arm A vs C													
Total population	triplet	0.66	(0.37-1.19)	0.15	0.87	(0.40-1.87)	0.70	0.36	(0.20-0.64)	0.002	0.56	(0.31-1.02)	0.06
	triplet and HIV	0.68	(0.38-1.20)	0.17	0.92	(0.41-2.07)	0.83	0.44	(0.23-0.85)	0.02	0.58	(0.30-1.10)	0.09
PLHIV	triplet	0.89	(0.50-1.58)	0.66	0.90	(0.47-1.72)	0.73	0.54	(0.30-0.99)	0.05	0.48	(0.23-0.99)	0.05
Arm B vs C													
Total population	triplet	0.69	(0.38-1.25)	0.20	0.87	(0.40-1.87)	0.69	0.76	(0.42-1.35)	0.31	0.89	(0.49-1.63)	0.69
	triplet and HIV	0.67	(0.38-1.18)	0.15	0.99	(0.44-2.21)	0.97	0.87	(0.45-1.69)	0.66	0.91	(0.48-1.73)	0.76
PLHIV	triplet	0.78	(0.44-1.40)	0.38	1.13	(0.59-2.16)	0.68	0.87	(0.48-1.58)	0.62	1.09	(0.53-2.26)	0.80

TB=tuberculosis; PC=Population Cohort; PR=prevalence ratio; 95%CI=95% confidence interval; PLHIV=people living with HIV;

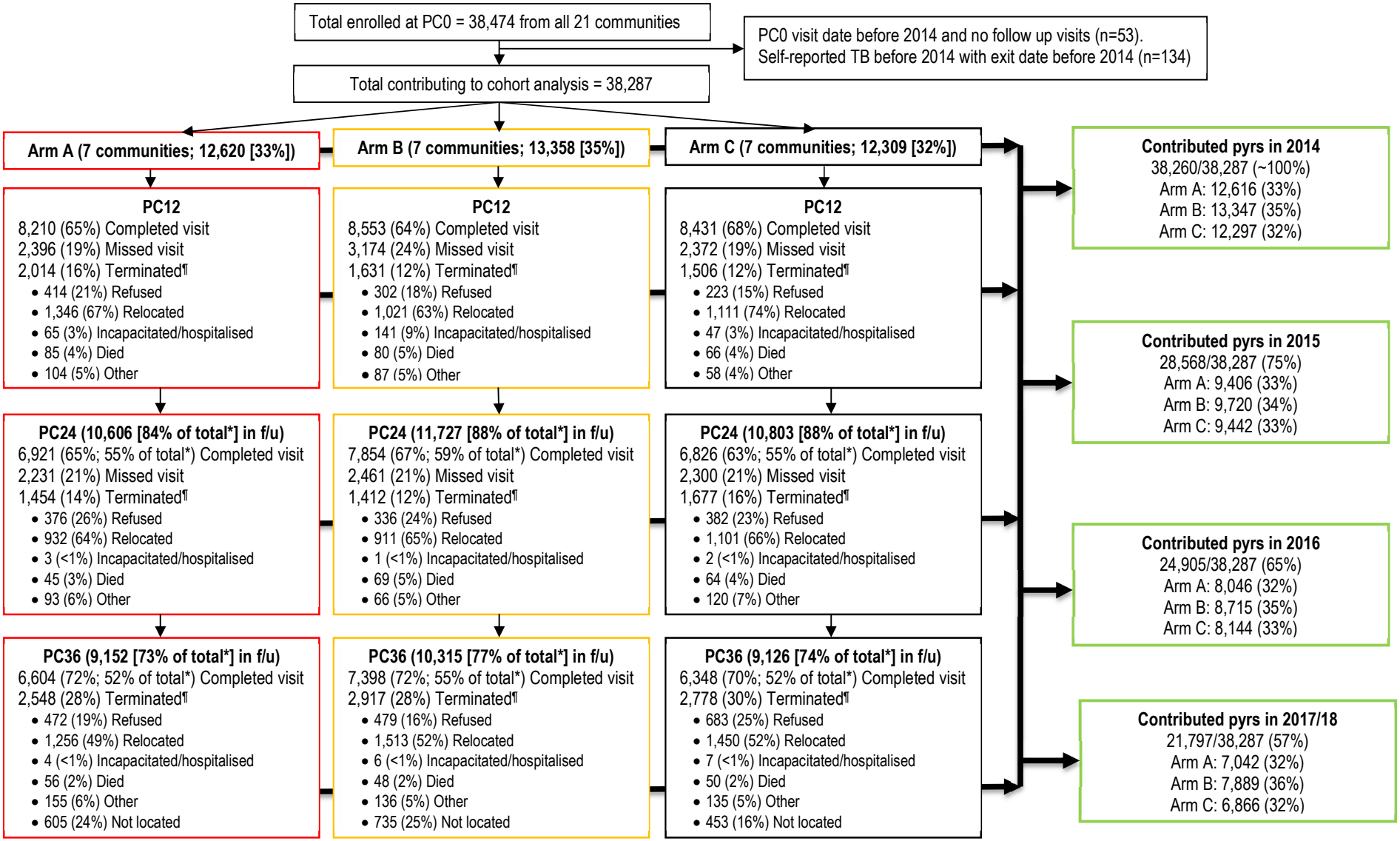

Total enrolled at PC0 = 38,474 from all 21 communities
PC0 visit date before 2014 and no follow up visits (n=53).
Self-reported TB before 2014 with exit date before 2014 (n=134)
Total contributing to cohort analysis = 38,287
Arm A (7 communities; 12,620 [33%])
Arm B (7 communities; 13,358 [35%])
Arm C (7 communities; 12,309 [32%])
PC12
8,210 (65%) Completed visit
2,396 (19%) Missed visit
2,014 (16%) Terminated¶
• 414 (21%) Refused
• 1,346 (67%) Relocated
• 65 (3%) Incapacitated/hospitalised
• 85 (4%) Died
• 104 (5%) Other
PC12
8,553 (64%) Completed visit
3,174 (24%) Missed visit
1,631 (12%) Terminated¶
• 302 (18%) Refused
• 1,021 (63%) Relocated
• 141 (9%) Incapacitated/hospitalised
• 80 (5%) Died
• 87 (5%) Other
PC12
8,431 (68%) Completed visit
2,372 (19%) Missed visit
1,506 (12%) Terminated¶
• 223 (15%) Refused
• 1,111 (74%) Relocated
• 47 (3%) Incapacitated/hospitalised
• 66 (4%) Died
• 58 (4%) Other
PC24 (10,606 [84% of total*] in f/u)
6,921 (65%; 55% of total*) Completed visit
2,231 (21%) Missed visit
1,454 (14%) Terminated¶
• 376 (26%) Refused
• 932 (64%) Relocated
• 3 (<1%) Incapacitated/hospitalised
• 45 (3%) Died
• 93 (6%) Other
PC24 (11,727 [88% of total*] in f/u)
7,854 (67%; 59% of total*) Completed visit
2,461 (21%) Missed visit
1,412 (12%) Terminated¶
• 336 (24%) Refused
• 911 (65%) Relocated
• 1 (<1%) Incapacitated/hospitalised
• 69 (5%) Died
• 66 (5%) Other
PC24 (10,803 [88% of total*] in f/u)
6,826 (63%; 55% of total*) Completed visit
2,300 (21%) Missed visit
1,677 (16%) Terminated¶
• 382 (23%) Refused
• 1,101 (66%) Relocated
• 2 (<1%) Incapacitated/hospitalised
• 64 (4%) Died
• 120 (7%) Other
PC36 (9,152 [73% of total*] in f/u)
6,604 (72%; 52% of total*) Completed visit
2,548 (28%) Terminated¶
• 472 (19%) Refused
• 1,256 (49%) Relocated
• 4 (<1%) Incapacitated/hospitalised
• 56 (2%) Died
• 155 (6%) Other
• 605 (24%) Not located
PC36 (10,315 [77% of total*] in f/u)
7,398 (72%; 55% of total*) Completed visit
2,917 (28%) Terminated¶
• 479 (16%) Refused
• 1,513 (52%) Relocated
• 6 (<1%) Incapacitated/hospitalised
• 48 (2%) Died
• 136 (5%) Other
• 735 (25%) Not located
PC36 (9,126 [74% of total*] in f/u)
6,348 (70%; 52% of total*) Completed visit
2,778 (30%) Terminated¶
• 683 (25%) Refused
• 1,450 (52%) Relocated
• 7 (<1%) Incapacitated/hospitalised
• 50 (2%) Died
• 135 (5%) Other
• 453 (16%) Not located
Contributed pyrs in 2014
38,260/38,287 (~100%)
Arm A: 12,616 (33%)
Arm B: 13,347 (35%)
Arm C: 12,297 (32%)
Contributed pyrs in 2015
28,568/38,287 (75%)
Arm A: 9,406 (33%)
Arm B: 9,720 (34%)
Arm C: 9,442 (33%)
Contributed pyrs in 2016
24,905/38,287 (65%)
Arm A: 8,046 (32%)
Arm B: 8,715 (35%)
Arm C: 8,144 (33%)
Contributed pyrs in 2017/18
21,797/38,287 (57%)
Arm A: 7,042 (32%)
Arm B: 7,889 (36%)
Arm C: 6,866 (32%)

Figure-1: Consort flow diagram showing the Population Cohort participants from all 21 HPTN 071 (PopART) communities that contributed person time to the cohort analysis.

PC=Population Cohort; f/u=follow-up; pyrs=person years; ¶1 person with unknown termination reason at PC12; 42 people with unknown termination reason at PC24 (5 [<1%] in arm A; 29 [2%] in arm B; and 8 [<1%] in arm C); *denominator the total enrolled in that arm at PC0

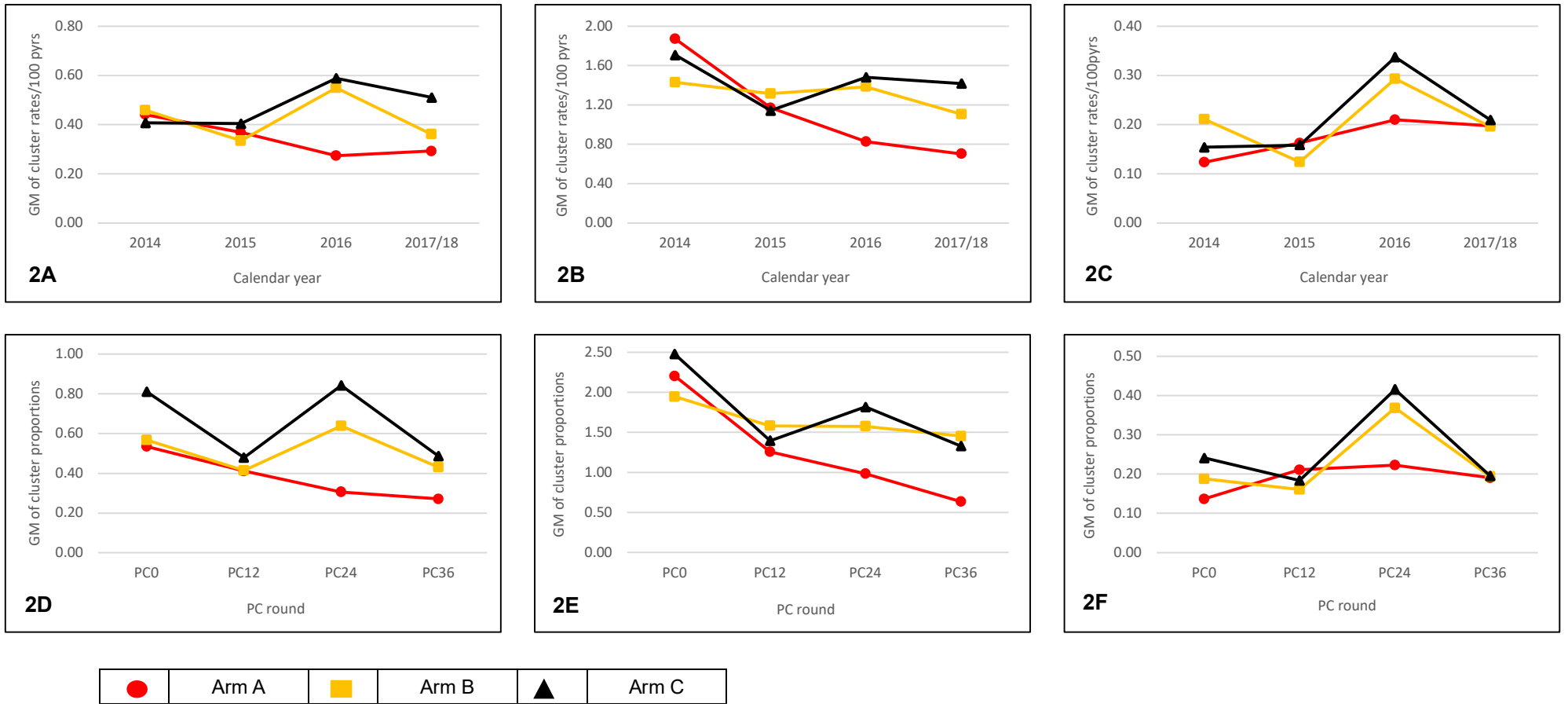


Figure-2: Geometric mean of the cluster rates (2A to 2C) of self-reported TB treatment by year and study arm in the cohort analysis, and, geometric mean of the cluster proportions (2D to 2F) of self-reported TB treatment by Population Cohort visit and study arm in the cross-sectional analysis, among Population Cohort participants from all 21 HPTN 071 (PopART) communities

GM=Geometric mean; pyrs=person years PC=Population cohort; 2A=total population; 2B=people living with HIV; 2C=people who were HIV negative; 2D=total population; 2E=People living with HIV; 2F=people who were HIV negative

The incidence of self-reported tuberculosis treatment with community-wide universal testing and treatment for HIV and tuberculosis screening in Zambia and South Africa: A planned analysis of the HPTN 071 (PopART) cluster-randomised trial

Supplementary Appendices

L. Telisinghe, S. Floyd, D. MacLeod, A. Schaap, R. Dunbar, J. Bwalya, N. Bell-Mandla, E. Piwowar-Manning, D. Donnell, K. Shaunaube, P. Bock, S. Fidler, R. J. Hayes and H M Ayles on behalf of the HPTN 071 (PopART) study team.

Supplementary Appendix-S1

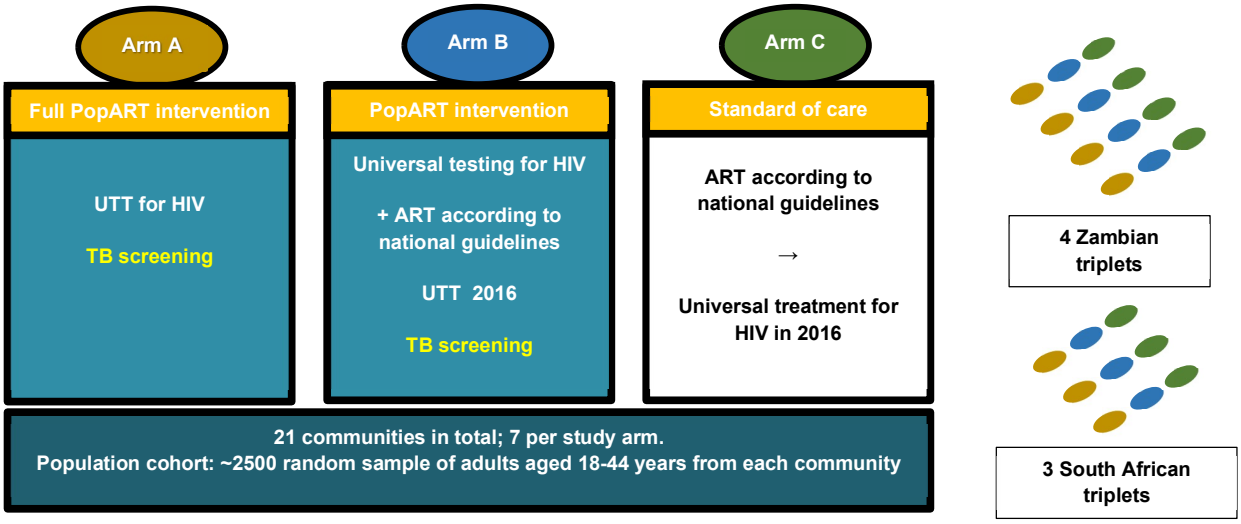


Figure: The three study arms
UTT=universal testing and treatment for HIV; ART=antiretroviral therapy.
There were 2 intervention arms – arm A (7 communities) and B (7 communities). Arm A received the full intervention package, which included universal testing for HIV, with universal treatment for HIV (irrespective of CD4 cell count) from 2013 and community-wide TB screening from 2013. In arm B there was universal testing for HIV, but ART start was according to national guidelines, which changed to universal treatment in April 2016 in Zambia and October 2016 in South Africa. There was community-wide TB screening in arm B from 2013. Therefore from April 2016 in Zambia and October 2016 in South Africa, the arm A and B communities were the same; giving a full intervention year – 2017 – in which there was no difference in the intervention package delivered in the 2 intervention arms. Arm C (7 communities), the control received the standard of care through routine services. ART initiation criteria followed national guidelines, changing to universal treatment in 2016. There was no universal testing for HIV or TB screening in arm C communities.

Supplementary Appendix-S2

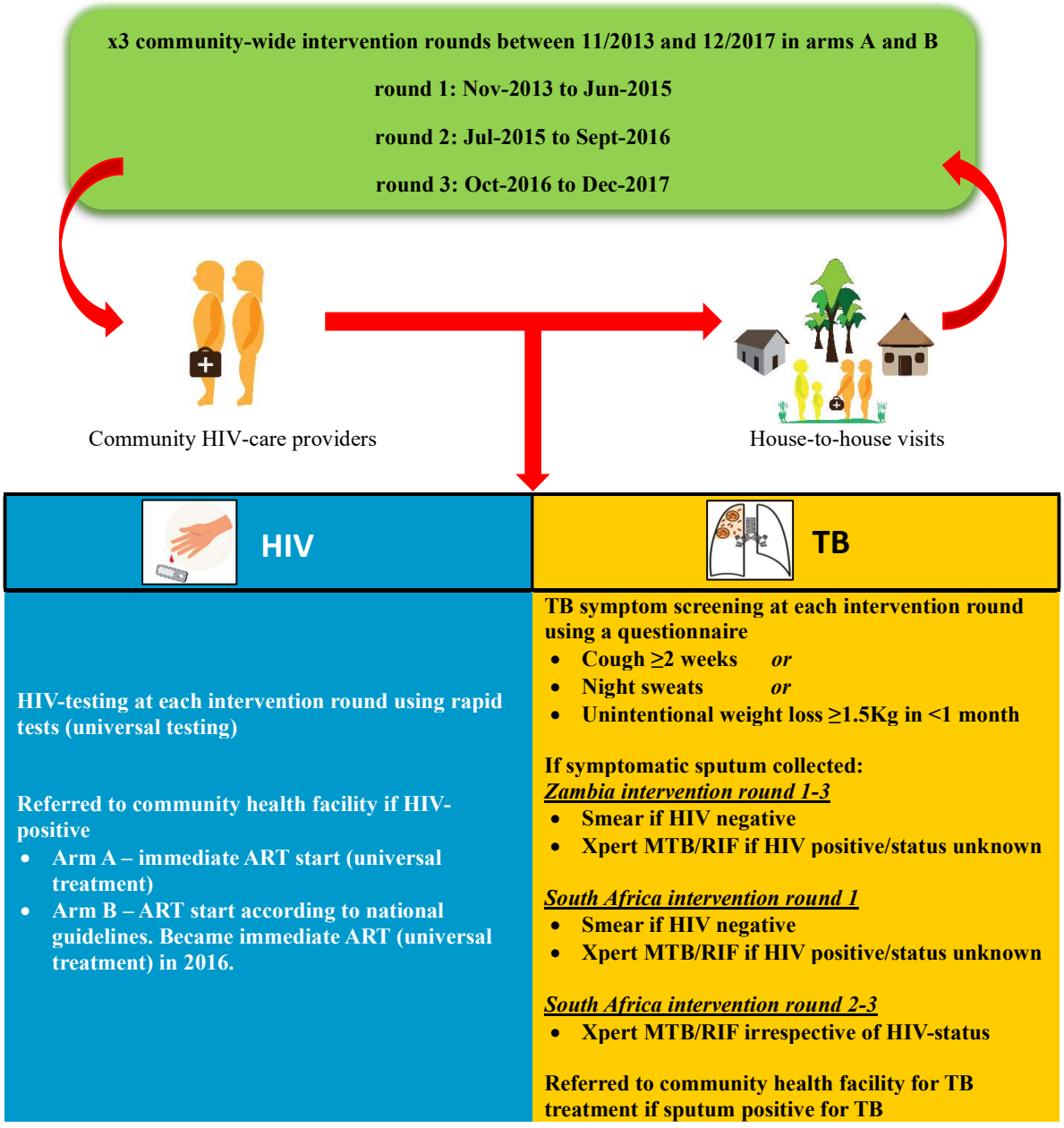


Figure: The PopART HIV/TB intervention delivered at each intervention round, over 3 rounds between November 2013 and December 2017 in study arms A and B
Trained community health workers called Community HIV-Care Providers delivered the house-to-house community-wide intervention. Each household in the community was visited at least 3 times over the intervention period. In addition to screening and referral activities, the Community HIV-Care Providers followed-up on all referrals and treatment adherence support was also provided.

Supplementary Appendix-S3

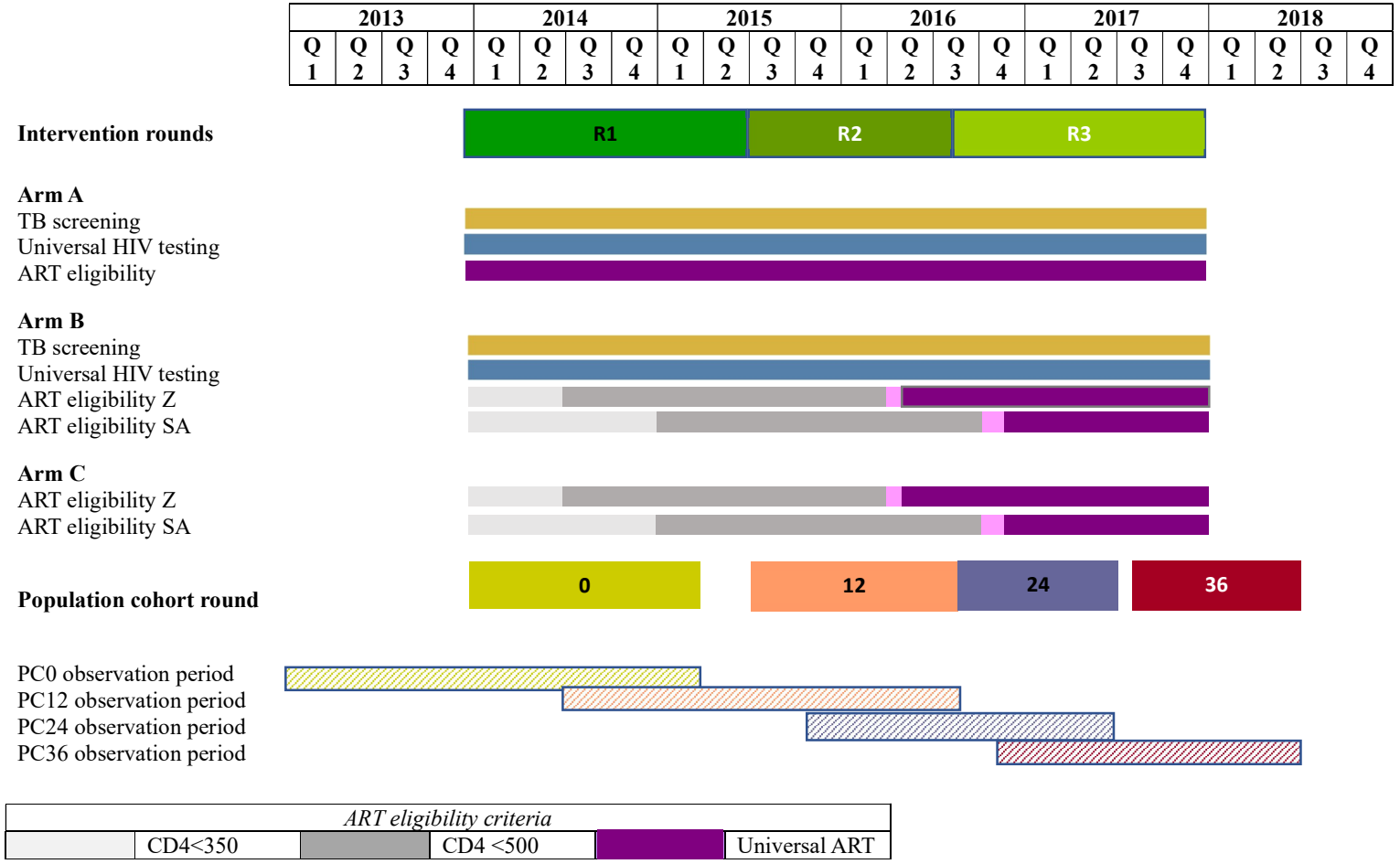


Figure: HPTN 071 (PopART) study timelines showing intervention rounds, intervention components, ART eligibility criteria, Population Cohort rounds (PC0-PC36) and the observation period for the analysis in this TB study for each Population Cohort visit (generated as 14 months before the date of the PC-visit).
Q=Quarter; Z=Zambia; SA=South Africa; ART=Antiretroviral therapy; PC=Population Cohort. Transition to universal ART in Zambia: 19th April to 9th May 2016 and in South Africa: 10th October – 21st November 2016

Supplementary Appendix-S4

Statistical considerations detailing the pre-defined proposed analyses, outcomes, power calculations, and analysis plan.

Rationale: self-reported TB treatment (self-reported TB) among population cohort (PC) participants should reflect TB notifications. Therefore, comparing self-reported TB in intervention arms compared to the control, should reflect the effect of the HPTN 071 (PopART) intervention on **all** TB notifications (bacteriologically confirmed and clinically diagnosed, pulmonary and extrapulmonary TB). Linkage of self-reported TB to routine TB notification data would have allowed treatment starts to be verified and the effect of the HPTN 071 (PopART) intervention on **bacteriologically confirmed** TB notifications to be explored.

TB outcomes among PC participants which were pre-defined and documented for this work:

1) Primary outcome: Notified bacteriologically confirmed (smear, Xpert and/or culture positive) pulmonary TB incidence. Bacteriologically confirmed TB was to be determined through linkage of PC data to routine TB notification data.

2) Secondary outcome: All (bacteriologically confirmed and clinically diagnosed, pulmonary and extrapulmonary) notified TB incidence. All TB was to be determined through self-reported TB and by using self-reported TB linked to TB notification data.

3) Time period for comparison: By year and overall. The overall analysis was restricted to the last 24 months of follow-up (2017-2018). This was done to exclude large initial rises in TB notifications expected with TB screening. Intervention effects were likely to accrue over time with repeated rounds of Universal Testing and Treatment for HIV (UTT) and TB screening and therefore the effect was likely to be maximal (as evidenced through preliminary mathematical modelling work undertaken for HPTN 071) in the last intervention years.

Mathematical modelling to inform study power calculations: The complexity of the multiple components of the intervention made it difficult to estimate its population impact on notified TB incidence. To determine the likely effect of the HPTN 071 (PopART) interventions on TB epidemiology, a deterministic, compartmental mathematical model was developed in R. Run over one-month time-steps, it captured the intervention and control arms and allowed comparisons across arms over time.

In the intervention arms, the model captured the effects of 3 rounds of UTT and TB screening over 4 years on TB epidemiology. Baseline data for the communities (e.g. TB disease prevalence and annual risk of TB infection) were available from the ZAMSTAR trial[1], conducted in the same study areas between 2006-2010. This allowed TB disease incidence at baseline to be estimated (incidence=prevalence/duration). From this equilibrium at baseline, the model was run, capturing the dynamic monthly and cumulative changes in notified bacteriologically confirmed pulmonary TB incidence in study arms and relative to one another.

The model predicted a ~40-55% decrease in notified bacteriologically confirmed pulmonary TB incidence in the intervention arms over the last 24 months if annual TB screening rounds identified 20-30% of previously undiagnosed TB cases and 40-60% of untreated people living with HIV (PLHIV) were identified and linked to care. An average notified bacteriologically confirmed pulmonary TB incidence rate of 0.87 per 100-person years in the control arm was also predicted.

The coefficient of between-community variation k was assumed to be in the range 0.20-0.25[1]. In the Zamstar trial, within each country (Zambia and South Africa) trial communities were grouped into 2 strata based on estimates of TB infection among schoolchildren at the start of the trial. Thus, there were 4 strata (2 countries, and 2 strata within each country). In the TB prevalence survey conducted in 2010 to measure the primary endpoint of the Zamstar trial, the coefficient of between-community variation in TB prevalence – among communities in the same strata - was estimated to be k=0.29. Taking account of key covariates, however, the data were consistent with a lower value of k in the range 0.20-0.25. In HPTN 071 (PopART), communities were pair-matched on geographical area and adult HIV prevalence (a stronger risk factor for TB incidence than TB prevalence). Further, the analysis planned to adjust for TB risk factors, further reducing between-community variation.

Study power was calculated using standard formulae for pair-matched cluster-randomised trials. The reduction in bacteriologically confirmed pulmonary TB incidence in the intervention arms was assumed to be in the range of 40-50%. The average notified bacteriologically confirmed pulmonary TB incidence rate was assumed to be 0.87 per 100-person years in the control arm. The average estimated person years of follow-up in each community of

the Population Cohort was estimated to be ~1964-person years (estimated for the parent HPTN071 [PopART] trial), over the last 24 months of follow-up. With k=0.2, this gave a power of 76-85% to detect a 45-50% decrease in notified bacteriologically confirmed pulmonary TB incidence in the intervention arm. The power was 68-78% when k=0.25.

Analytic approach: All data preparation and analysis were undertaken in Stata. To analyse TB data within PC, the start of the HPTN 071 (PopART) intervention was defined as January 1, 2014. The aim was to include all PC participants in the analysis (including those newly enrolled at PC12N and PC24N).

The data were to be analysed in 2 ways – cohort and cross sectional. The cohort analysis allowed full use of the data – in longitudinal format. Incidence rates of TB could be estimated. This was the primary analysis. The cross-sectional approach analysed each PC visit as an independent cross-sectional sample. The proportion with TB was estimated for each PC visit. This was the secondary analysis.

Statistical inference used the 2-stage approach recommended for cluster-randomized trials with <15 clusters/arm[2,3] – see further details on the 2-stage approach below. The aim was to include triplet, HIV status, age, and sex (with an interaction term between age and sex) as covariates at the first stage of the analysis. Formal cross arm comparisons would be Arm A versus C and Arm B versus C, separately. Data were to be analysed overall and by HIV status (for PLHIV and those who are HIV negative separately).

Changes to original research plans:

March 2022: There were challenges with linking PC data to TB notification data in South Africa and Zambia due to the quality of TB notification data available for use. In South Africa, there were shortfalls in TB notifications captured through the Electronic TB Registers, across multiple communities and multiple calendar years, during the study period. In Zambia all TB notification data were in paper form and had to be captured electronically. There were missing registers for parts of/whole calendar years for multiple communities. Therefore, in both South Africa and Zambia, PC data could not be linked to TB notification data, for large periods of PC follow-up. The analysis was therefore restricted to self-reported TB alone. Details of the analysis plan for self-reported TB are presented.

March 2022: Community HIV-care Providers' intervention data were summarised during the trial. This showed significant churn within the communities (representing ~1/3 of the total population in intervention communities in the 3rd intervention round, during which data on migration pattern were collection. These figures were likely to be generalisable to the previous intervention rounds and to control communities). Therefore, the TB analysis was restricted to PC participants enrolled at PC0 only. This was because TB incidence in PC participants enrolled at later visits (PC12N and PC24N) may not have been representative of study community incidence as:

1. In intervention communities, the migration pattern could have represented movement from areas not receiving the intervention, to intervention areas.
2. How long a PC participant had resided within the community was not an eligibility criterion for enrolment and data on migration was not captured in the PC questionnaire.
3. The questionnaire asked about TB treatment in the 12 months before a PC visit. As TB disease takes months/years to develop following infection, the reported TB treatment start could be for a transmission event that may not represent transmission occurring in the study communities.

August 2022: There were insufficient self-reported TB events among those who were HIV negative. There were no events among HIV negative individuals in six communities in 2014, eight communities in 2015, two communities in 2016 and five communities in 2017/18. Therefore, rates were summarised, but formal cross-arm comparisons were not conducted. Due to the small number of events during later calendar years (especially in 2017/18 in arm A), the total population analysis only included triplet and HIV status as covariates (without adjusting for age and sex). Analyses among PLHIV included triplet alone.

Outcome definition: To determine self-reported TB the variables (listed) in the TB screening section of the PC questionnaire were used. All these variables were linked through skip patterns.

TBTOLD	In the last 12 months, have you been told that you have TB?
TBTRT	PC0: Have you started TB treatment? PC12-36: Have you started TB treatment in the last 12 months?
TBTRTMM	When did you start TB treatment? Please give the month and year.
TBTRTYY	When did you start TB treatment? Please give the month and year.

Variables listed in the TB screening section of the PC questionnaire which were not used:

TBASK	During the past 12 months, has a health worker, at the clinic or in the community, asked you questions about TB such as whether you have a cough, fever, night sweats, weight loss? *About TB screening. Not linked to TB treatment related questions.*
TBTXT	Do you have your TB number? *TB patients would only have their TB number if: given a TB card, TB number was documented on the card (not always done), they were still on TB treatment (card usually taken back at the end of TB treatment) and the TB card was not lost. Therefore, not having a number did not mean individual were not on or had not been on TB treatment.*
TBNUM	Do you have your TB number? *As above*
TBIPT	Have you ever/are you currently taking isoniazid preventive treatment to prevent TB? *Not relevant for determining TB treatment start. Not linked to TB treatment related questions*

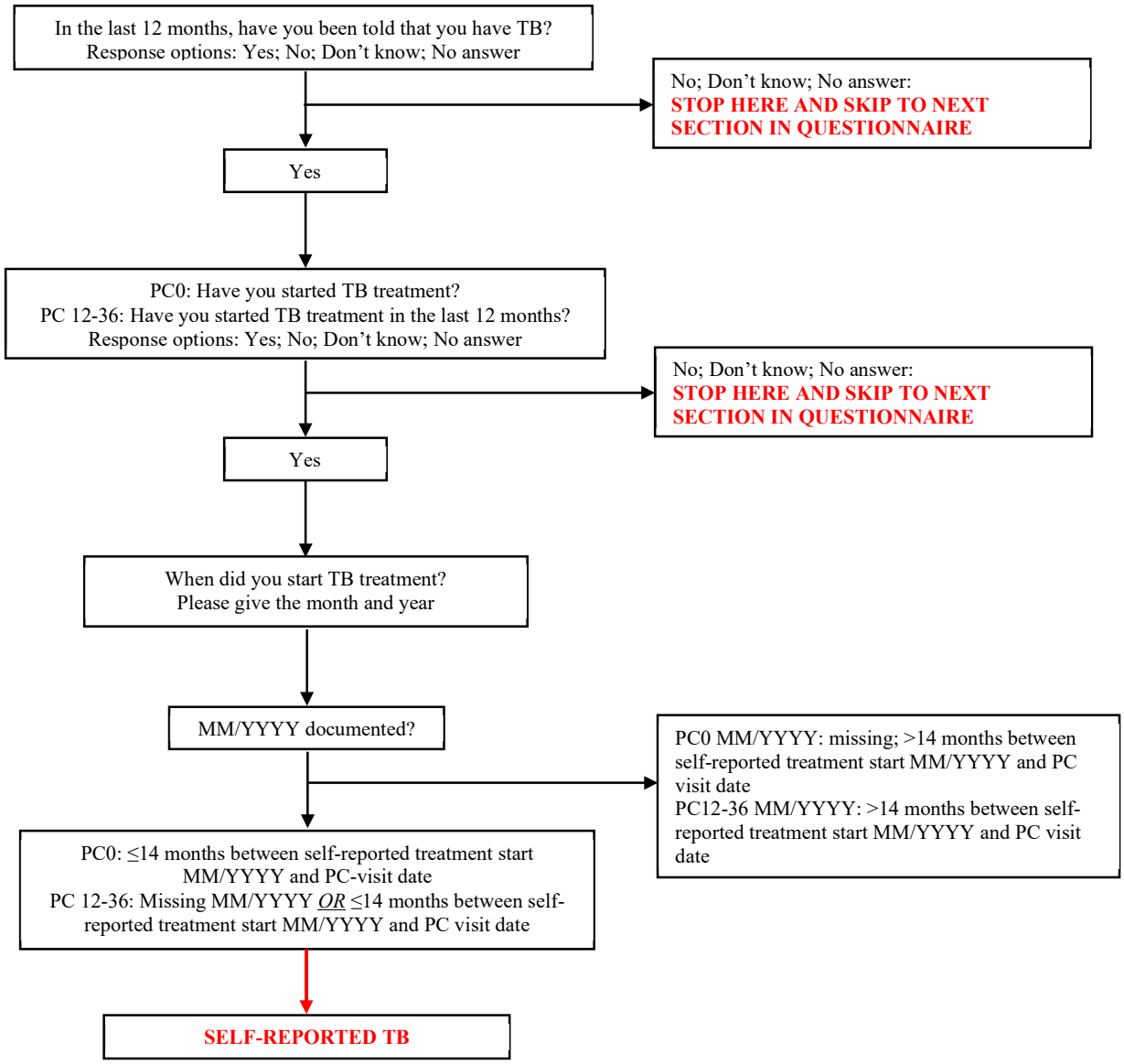
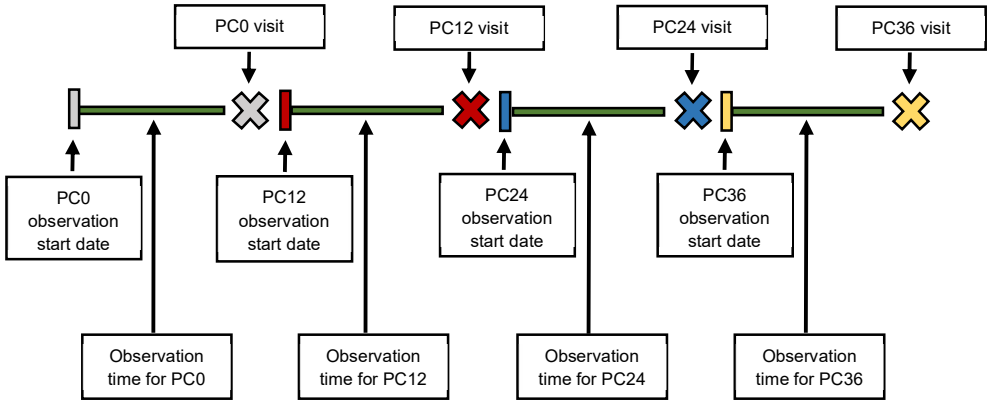


Figure 3: Flow of questions asked by research staff at each PC visit from each PC participant to determine if they had started TB treatment in the preceding 12 months AND criteria used to define self-reported TB. MM/YYYY=Month/Year

Strategy to prepare and analyse the cohort data

Step 1

Generating observation times for each PC visit that took place for each PC participant.
Because self-reported TB was determined over the 14 months before each PC visit, for each PC participant, an **observation start date**, 14 months before each PC visit was generated. The time between the observation start date for a PC visit, and the date of that PC visit was the observation time for that PC visit, during which the outcome (self-reported TB) was determined.



Step 2

Restricting the analysis to the first self-reported TB episode to determine self-reported TB incidence from a "new" TB transmission event.
Individuals reporting multiple episodes of self-reported TB were explored to understand if these were likely to be treatment starts for TB disease due to new transmission events.

The results of this exploration are shown below.
The total enrolled at PC0 was 38474. TB treatment was self-reported by 628 at any PC visit of whom 55/628 (9%) self-reported TB treatment at >1 PC visit.

Characteristics of 55 PC participants with >1 self-reported TB treatment episode

Characteristic		**>1 self-reported TB episode**	
		n/N	**%**
Study arm	A	7/55	13%
	B	26/55	47%
	C	22/55	40%
Country	Zambia	15/55	27%
	South Africa	40/55	73%

Among these 55 PC participants with >1 self-reported TB treatment episode, 45 (82%) had month and year of TB treatment starts.

If the interval between the two self-reported TB treatment start months/years was ≤14 months, these were considered as starting TB treatment for the same TB episode. This is because TB treatment takes 6-8 months. New TB events following MTB infection take months/years to develop. Therefore 2 self-reported TB treatment starts within 12 months were unlikely to represent TB disease due to new transmission events. They were more likely to represent treatment after lost to follow-up, re-treatment after failure etc. As month of TB treatment start may have been recalled incorrectly a 14-month period between two self-reported TB treatment starts was allowed.

Characteristic		**n/N**	**%**
Number of months between TB treatment starts among 34/45 (76%) where interval between self-reported TB treatment start months/years was ≤14 months. 33/34 (97%) reported starting TB treatment at consecutive PC visits.	same month/year	11/34	32%
	>0 to ≤2 months	9/34	26%
	>2 to ≤6 months	2/34	6%
	>6 to ≤9 months	5/34	15%
	>9 to ≤12 months	6/34	18%
	>12 to ≤14 months	1/34	3%
	>14 to ≤18 months	2/11	18%

	Number of months between TB treatment starts among 11/45 (24%) where interval between self-reported TB treatment start months/years was >14 months. 7/11 (64%) did **not** report starting TB treatment at consecutive PC visits	>18 to ≤24 months	4/11	36%
		>24 months	5/11	45%
	Arm of n=11 where interval between self-reported TB treatment start months/years was >14 months	A	1/11	9%
		B	4/11	36%
		C	6/11	55%
	Country of n=11 where duration between self-reported TB treatment start months/years was >14 months	Zambia	4/11	36%
		South Africa	7/11	64%

Among 10/55 (18%) month and year for at least 1 self-reported TB episode was missing. Therefore, interval between treatment starts could not be ascertained. All self-reported TB treatment episodes occurred at consecutive PC visits. For these 10 individuals, the median time between the PC visits at which they self-reported TB treatment was 11.8 months (range 9.5-13.6 months).

The frequency measure of interest is incidence. There were very few repeat self-reported TB events that were likely to represent treatment starts for unique TB episodes. The most plausible estimate of repeat treatment starts for unique TB episodes was 1.8% (11/628 who all had a duration between self-reported TB months/years of >14 months). The maximum value is likely to be 3.3% (21/628, which included the 10 PC participants for whom interval between self-reported TB could not be calculated, but who all reported TB treatment start at consecutive PC visits). As a higher proportion of repeat TB treatment starts were documented in arm C than A, using only the first self-reported TB episode will give a conservative estimate of the impact of the interventions in arms A vs C.

Step 3

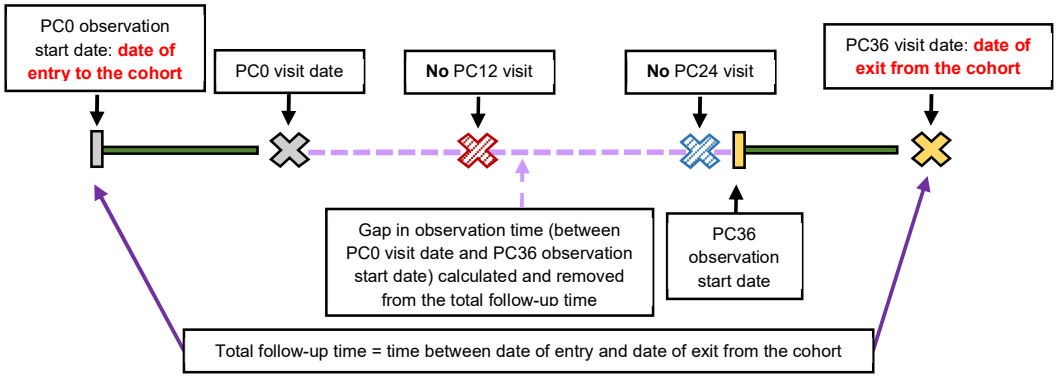
Defining the date of self-reported TB.
For n=628 individuals who self-reported TB. 587/628 (93%) provided a month and year of treatment start. The day of the month was imputed as 15 for these individuals. 41/628 (7%) did not provide a month and year of TB treatment start. For these individuals, the date of TB treatment start was imputed as the mid-point between two consecutive PC visits, or 7 months before the PC visit where treatment was reported if PC visits were not consecutive.

Step 4

Defining the date of entry and exit from the cohort.
The date of entry was the PC0 observation start date that was generated 14 months before the PC0 visit. The date of exit was the last PC visit date if NO self-reported TB. If TB treatment was reported, the date of exit was the date of self-reported TB.

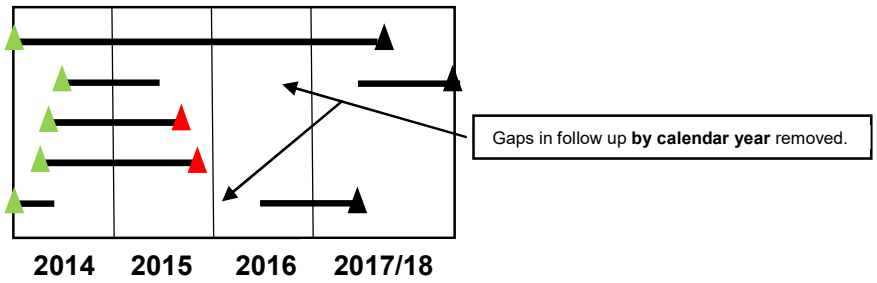
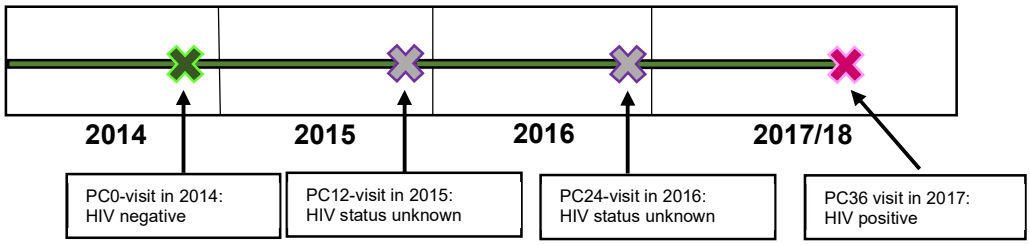
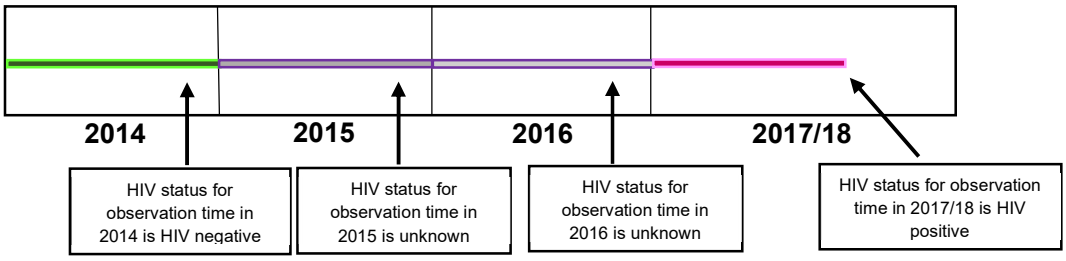
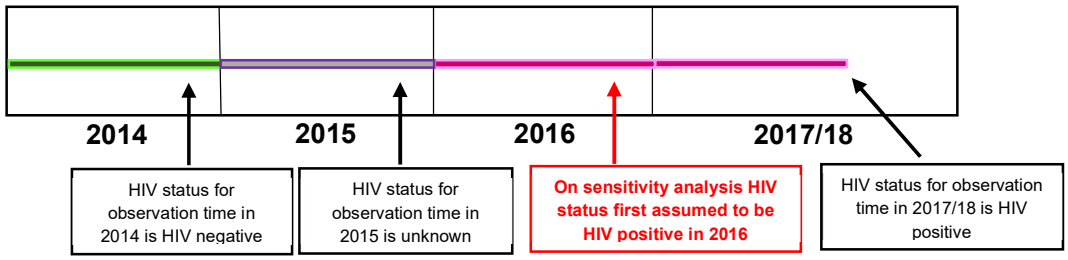
Step 5

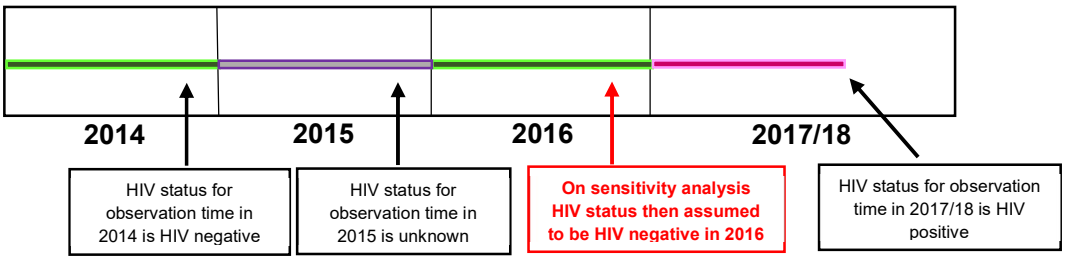
Generating gaps in observation time by calendar year.
The time between the date of entry and the date of exit from the cohort, was the total follow-up time. Where there were gaps in observation time (e.g. due to missed PC visits), the gap in observation time was determined as the difference between the PC visit date (after which there was a gap) and the observation start date for the subsequent PC visit that took place. All gaps in observation time for each PC participant was generated by the calendar year/s in which the gaps occurred.



Step 6

Splitting follow-up time into calendar years and removing the calculated gaps in observation time.
The total follow-up time generated for each PC participant (time between the date of entry and exit from the cohort) was split into calendar years from 2014 (the first full study year). The calendar periods analysed were 2014, 2015, 2016 and 2017/18 (as follow up in 2018 was only 6 months [PC ended in July 2018], 2017/18 was

	analysed as one calendar period). Gaps in observation time during which outcome status was unknown, were removed. Gaps were removed according to the calendar year/s in which they occurred. 
Step 7	**Assigning HIV status for each calendar year and running sensitivity analysis on HIV status.** **A:** The HIV status at each PC visit was determined using blood HIV testing done at the PC visit. This HIV blood test result was used to define the primary HIV endpoint of the trial.  **B:** The HIV status at the PC visit was assumed to be the HIV status for the whole calendar year in which the PC visit took place and therefore, for the observation time contributed by the PC participant for that calendar year. If HIV status in a calendar year to which the PC participant contributed observation time was HIV positive, all subsequent calendar years to which the PC participant contributed observation time where HIV status was unknown, was imputed as HIV positive. If HIV status in a calendar year in which the PC participant contributed observation time was HIV negative, all preceding calendar years to which the PC participant contributed observation time where HIV status was unknown, was imputed as HIV negative. Analyses stratified by calendar year and HIV status were conducted based on this HIV status assignment.  **C:** Where HIV status in the year preceding a HIV positive result was unknown (i.e. in 2016 in this example), a first sensitivity analysis was conducted assuming the missing HIV status was positive. 

	D: Where HIV status in the year preceding a HIV positive result was unknown (i.e. in 2016 in this example), a second sensitivity analysis was conducted assuming the missing HIV status was negative. 
Step 8	**Summary of the characteristics of PC participants contributing person time to the cohort analysis, by calendar year and study arm** For 2014, 2015, 2016 and 2017/18 separately. By study arm (A, B, C, and total) for each calendar year Variables summarised • Country – Zambia, South Africa (defined at PC0) • Sex – Male, Female (defined at PC0) • Age/years – in years (defined at PC0) stratified into ~5year age groups (18-24, 25-29, 30-34, 35-39, 40-44) • HIV-status – as defined for each calendar year (step 7B) Data showed losses to follow up over calendar years by study arm and characteristics of those who were included in the analysis over calendar years by study arm. Data were stratified by HIV status**,** for PLHIV and those HIV negative separately, by calendar year and study arm. For 2014, 2015, 2016 and 2017/18 separately By study arm (A, B, C, and total) for each calendar year Variables summarised • Country – Zambia, South Africa (defined at PC0) • Sex – Male, Female (defined at PC0) • Age/years – in years (defined at PC0) stratified into ~5year age groups (18-24, 25-29, 30-34, 35-39, 40-44)
Step 9	**The number of events, total person years and incidence rate (per 100 person years) of self-reported TB** For each community, data were summarised for each calendar year (2014, 2015, 2016 and 2017/18) separately. Within a calendar year, communities were stratified by triplet and arm. Where there are no self-reported TB events for a community – 0.5 was added to the numerator to compute a rate. This was needed to compute geometric means, for which rates were multiplied and the nth root of the multiplied value taken. The overall incidence rate by arm (A, B and C) was computed as the geometric mean of the estimated incidence rates for the 7 communities in each study arm. Geometric means were used to reduce skewness. Data were also be summarised by HIV status (for people who are HIV positive and HIV negative separately) for each calendar year. HIV status used the assignment generated in Step 7B. Sensitivity analysis explored assigning HIV status as described in Step 7 C-D.
Step 10	**Cross-arm comparison of incidence rate of self-reported TB** Arm A versus B and Arm B versus C separately. For each calendar year (2014, 2015, 2016 and 2017/18) separately. Overall and for PLHIV. Stage 1: Poisson regression was used to adjust for confounding variables at the individual level for each country separately. Covariates added: • Triplet – primary model for analysis among PLHIV • Triplet + HIV status – primary model for overall analysis

	• Triplet + age#sex – over-parameterised model for overall analysis and analysis among PLHIV (insufficient events in later calendar years for this model). This additional analysis was carried out to check the effect of adjusting for age and sex on the point estimate of the rate ratio. • Triplet + age#sex + HIV status - over-parameterised model for overall analysis (insufficient events in later calendar years for this model). This additional analysis was carried out to check the effect of adjusting for age, sex, and HIV status on the point estimate of the rate ratio. Study arm was NOT included in stage 1. For each PC participant a fitted value of the outcome (incident self-reported TB) was predicted from the model. These fitted values were summed for each community, to get E, the expected number with incident self-reported TB for each community, after adjusting for covariates, assuming null intervention effects. The ratio residual for each community was calculated as the Observed number of incident self-reported TB events (O, with 0.5 added if no events were observed), divided by the Expected number of incident self-reported TB events (E). Stage 2: A two-way analysis of variance was carried out on the log(O/E) (log ratio-residuals), with matched triplet and study arm as factors. The test statistic was the estimated difference in means of log(O/E) between study arms, with two-sided p-values and 95% confidence intervals computed using the t-distribution. The corresponding rate ratios and 95% confidence interval for the comparison of Arms A and C, and Arms B and C, was calculated with exponentiation. A log transformation is generally used for the analysis of ratio measures of effect (e.g. rate ratios, risk ratios, prevalence ratios) because they are often positively skewed. NB: models with age and sex added gave similar point estimates of the rate ratios, as models without age and sex.

Strategy to prepare and analyse the cross-sectional data

Step 1	**Generating the samples for analysis.** Each PC visit – PC0, PC12, PC24, and PC36 – was treated as an independent cross-sectional sample. The denominator included all PC participants seen at that PC visit
Step 2	**Self-reported TB.** Included all PC participants meeting the case definition of self-reported TB. All episodes of self-reported TB (n=686 which included repeat episodes) were analysed.
Step 3	**Assigning HIV status for each PC visits.** The HIV status at each PC visit was determined using blood HIV testing done at the PC visit. This HIV blood test result was used to define the primary HIV endpoint of the trial.
Step 4	**Summary of the number of PC participants meeting the self-reported TB case definition.** For each PC visit - PC0, PC12, PC24, and PC36 – separately Overall and stratified by country and HIV status, for each PC visit
Step 5	**Summary of the characteristics of PC participants seen at PC0, PC12, PC24 and PC36, by study arm.** For each PC visit - PC0, PC12, PC24, and PC36 – separately Variables to be summarised • Country – Zambia, South Africa (defined at PC0) • Sex – Male, Female (defined at PC0) • Age/years – in years stratified into ~5year age groups (18-24, 25-29, 30-34, 35-39, 40-max). Age determined at PC0. Age at each subsequent PC visits, was based on adding 1 to age. • HIV-status – as defined for each PC visit. Data showed losses to follow up at each PC visit by study arm and characteristics of those included in the analysis at each PC visit by study arm. Results were stratified by HIV status, for PLHIV and those HIV negative separately, for each PC visit and by study arm. Variables to be summarised: • Country – Zambia, South Africa (defined at PC0) • Sex – Male, Female (defined at PC0)

	• Age/years – in years stratified into ~5year age groups (18-24, 25-29, 30-34, 35-39, 40-max). Age determined at PC0. Age at each subsequent PC visits, was based on adding 1 to age.
Step 6	**The number of events, total number of PC participants and proportion with self-reported TB** For each community, data were summarised for each PC visit - PC0, PC12, PC24, and PC36 – separately. For each PC visit, communities were stratified by triplet and arm. Where there are no self-reported TB events for a community – 0.5 was added to the numerator to compute a proportion. This was needed to generate geometric means, for which proportions were multiplied and the nth root of the multiplied value taken. The overall proportion by arm (A, B and C) was computed as the geometric mean of the estimated proportions for the 7 communities in each study arm. Geometric means were used to reduce skewness. Data were summarised by HIV status (for people who are HIV positive and HIV negative separately) for each PC visit.
Step 7	**Cross-arm comparison of proportion self-reporting TB** Arm A versus B and Arm B versus C separately For each PC visit – PC0, PC12, PC24, and PC36 - separately. Overall and for PLHIV Stage 1: Logistic regression was used to adjust for confounding variables at the individual level for each country separately. Covariates to be added: • Triplet – primary model for analysis among PLHIV • Triplet + HIV status – primary model for overall analysis • Triplet + age#sex– over-parameterised model for overall analysis and analysis among PLHIV (insufficient events in later calendar years for this model). This additional analysis was carried out to check the effect of adjusting for age and sex on the point estimate of the prevalence ratio. • Triplet + age#sex + HIV status - over-parameterised model for overall analysis (insufficient events in later calendar years for this model). This additional analysis was carried out to check the effect of adjusting for age, sex, and HIV status on the point estimate of the prevalence ratio. Study arm was NOT included in stage 1. For each PC participant a fitted value of the outcome (self-reported TB) was predicted from the model. These fitted values were summed for each community, to get E, the expected number with self-reported TB for each community, after adjusting for covariates, assuming null intervention effects. The ratio residual for each community was calculated as the Observed number of self-reported TB events (O, with 0.5 added if no events were observed), divided by the Expected number of self-reported TB events (E). Stage 2: A two-way analysis of variance was carried out on the log(O/E) (log ratio-residuals), with matched triplet and study arm as factors. The test statistic was the estimated difference in means of log(O/E) between study arms, with two-sided p-values and 95% confidence intervals computed using the t-distribution. The corresponding prevalence ratios and 95% confidence interval for the comparison of Arms A and C, and Arms B and C, was calculated with exponentiation. A log transformation is generally used for the analysis of ratio measures of effect (e.g. rate ratios, risk ratios, prevalence ratios) because they are often positively skewed. NB: models with age and sex added gave similar point estimates of the prevalence ratios, as models without age and sex.

[1] Ayles H, Muyoyeta M, Du Toit E, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet 2013; 382(9899): 1183-94
[2] Eldridge S, Kerry S. A practical guide to cluster randomised trials in health services research. Chichester, United Kingdom: John Wiley, 2012.
[3] Hayes RJ, Moulton LH. Cluster randomised trials. 2nd ed. Boca Raton, FL:CRC Press, 2017

Supplementary Appendix-S5

		PC0				PC12				PC24				PC36			
		A	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**
Total seen		12,671*	13,404*	12,399*	38,474*	8234* (65%)¶	8572* (64%)¶	8484* (68%)¶	25290* (66%)¶	6938* (55%)¶	7873* (59%)¶	6867* (55%)¶	21678* (56%)¶	6623* (52%)¶	7416* (55%)¶	6383* (51%)¶	20422* (53%)¶
Country	Zambia	6,500 (51%)	6,433 (48%)	6,791 (55%)	19,724 (51%)	4067 (49%)	3893 (45%)	4371 (52%)	12331 (49%)	3530 (51%)	3760 (48%)	3637 (53%)	10927 (50%)	3539 (53%)	3720 (50%)	3686 (58%)	10945 (54%)
	SA	6,171 (49%)	6,971 (52%)	5,608 (45%)	18,750 (49%)	4167 (51%)	4679 (55%)	4113 (48%)	12959 (51%)	3408 (49%)	4113 (52%)	3230 (47%)	10751 (50%)	3084 (47%)	3696 (50%)	2697 (42%)	9477 (46%)
Sex	Male	3595 (28%)	3906 (29%)	3701 (30%)	11202 (29%)	2150 (26%)	2289 (27%)	2381 (28%)	6820 (27%)	1753 (25%)	2122 (27%)	1930 (28%)	5805 (27%)	1654 (25%)	1967 (27%)	1775 (28%)	5396 (26%)
	Female	9042 (71%)	9458 (71%)	8639 (70%)	27139 (71%)	6084 (74%)	6281 (73%)	6103 (72%)	18468 (73%)	5185 (75%)	5751 (73%)	4937 (72%)	15873 (73%)	4969 (75%)	5449 (73%)	4607 (72%)	15025 (74%)
	Missing	34 (<1%)	40 (<1%)	59 (<1%)	133 (<1%)	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
Age (years)†	18-24	5065 (40%)	5179 (39%)	4981 (40%)	15225 (40%)	2791 (34%)	2801 (33%)	2811 (33%)	8403 (33%)	1959 (28%)	2176 (28%)	1889 (28%)	6024 (28%)	1517 (23%)	1671 (22%)	1400 (22%)	4588 (22%)
	25-29	2781 (22%)	2881 (21%)	2608 (21%)	8270 (22%)	1825 (22%)	1777 (21%)	1830 (21%)	5432 (21%)	1517 (22%)	1661 (21%)	1450 (21%)	4628 (21%)	1499 (23%)	1640 (22%)	1406 (22%)	4545 (22%)
	30-34	2147 (17%)	2289 (17%)	2080 (17%)	6516 (17%)	1456 (18%)	1600 (19%)	1499 (18%)	4555 (18%)	1343 (19%)	1538 (19%)	1314 (19%)	4195 (19%)	1346 (20%)	1449 (20%)	1250 (19%)	4045 (20%)
	35-39	1464 (12%)	1713 (13%)	1558 (13%)	4735 (12%)	1119 (13%)	1236 (14%)	1253 (15%)	3608 (14%)	1015 (15%)	1166 (15%)	1083 (16%)	3264 (15%)	1034 (16%)	1150 (16%)	1064 (17%)	3248 (16%)
	40/max†	1179 (9%)	1302 (10%)	1109 (9%)	3590 (9%)	1043 (13%)	1156 (13%)	1091 (13%)	3290 (13%)	1104 (16%)	1332 (17%)	1129 (16%)	3565 (16%)	1226 (18%)	1506 (20%)	1261 (20%)	3993 (20%)
	Missing	35 (<1%)	40 (<1%)	63 (<1%)	138 (<1%)	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	2 (<1%)	2 (<1%)	1 (<1%)	0 (0%)	2 (<1%)	3 (<1%)
HIV status‡	Positive	2583 (20%)	2734 (20%)	2687 (22%)	8004 (21%)	1661 (20%)	1660 (19%)	1765 (21%)	5086 (20%)	1459 (21%)	1608 (21%)	1512 (22%)	4579 (21%)	1549 (23%)	1637 (22%)	1572 (25%)	4758 (23%)
	Negative	9594 (76%)	10235 (77%)	9301 (75%)	29130 (76%)	5781 (70%)	6210 (73%)	5678 (67%)	17669 (70%)	4931 (71%)	5691 (72%)	4672 (68%)	15294 (71%)	4873 (74%)	5587 (75%)	4651 (73%)	15111 (74%)
	ND	494 (4%)	435 (3%)	411 (3%)	1340 (3%)	792 (10%)	702 (8%)	1041 (12%)	2535 (10%)	548 (8%)	574 (7%)	683 (10%)	1805 (8%)	201 (3%)	192 (3%)	160 (2%)	553 (3%)

Table: Characteristics of Population Cohort participants enrolled at PC0 and follow-up at PC12, PC24 and PC36 respectively from all 21 HPTN 071 (PopART) communities: overall and by study arm

PC=population cohort; SA=South Africa; ND=not determined. *Denominator for all column percentages shown in the column (unless otherwise indicated); ¶Denominator for this proportion was the number seen at PC0 in each study arm and in total; †Age determined at PC0. Age at each subsequent PC-visit, based on adding 1 to the age the PC-participant would have been at the preceding PC-visit, starting at PC0. Upper limits of age are PC0=44 years PC12=45 years, PC24=46 years, and PC36=47years; ‡based on laboratory HIV-testing

Supplementary Appendix-S6

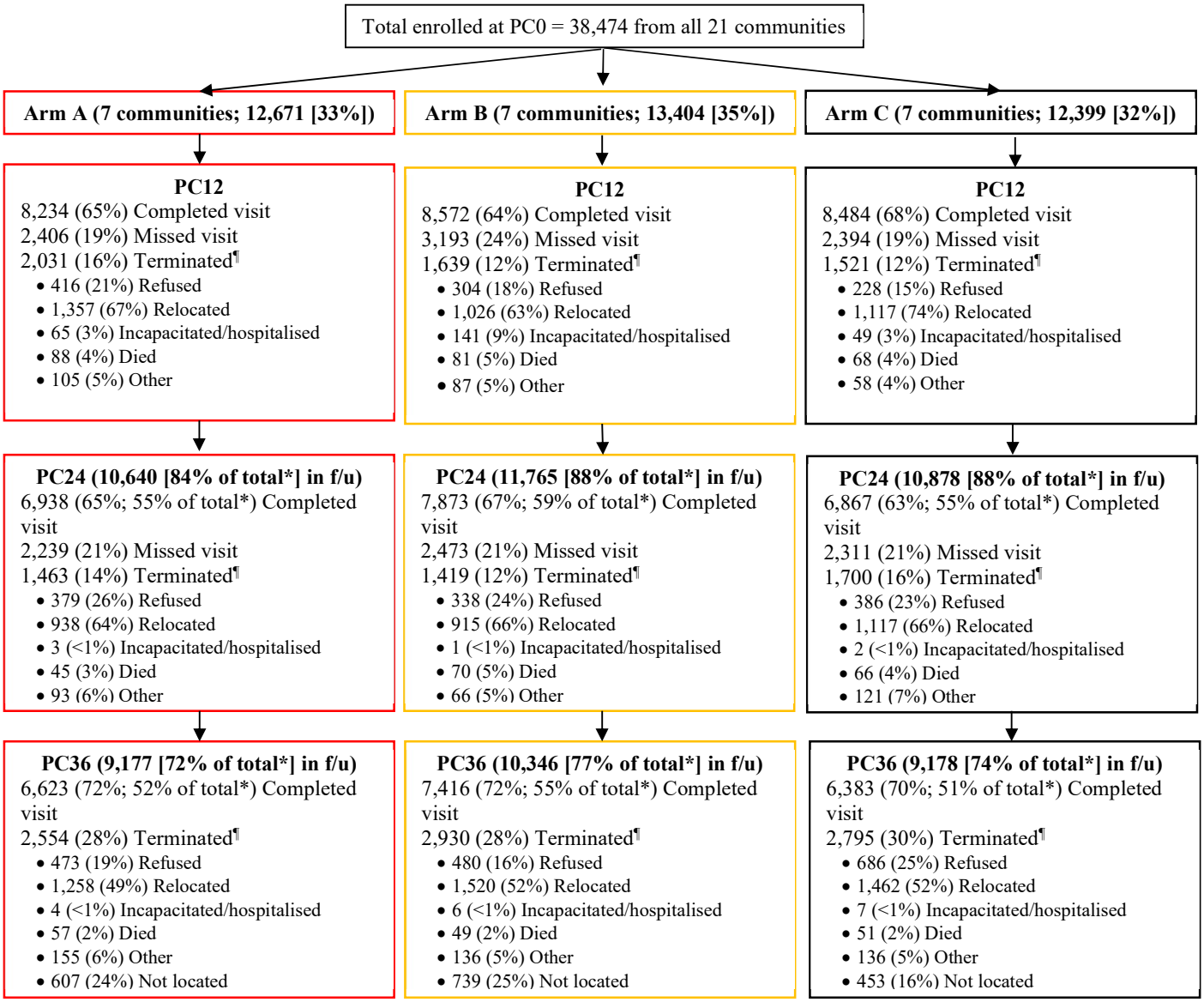


Figure: Consort flow diagram showing the Population Cohort participants from all 21 HPTN 071 (PopART) communities that contributed to the cross-sectional analysis

PC=Population Cohort; f/u=follow-up; ¶1 person with unknown termination reason at PC12; 42 people with unknown termination reason at PC24 (5 [<1% in arm A; 29 [2%] in arm B; and 8 [<1%] in arm C); *denominator was the total enrolled in that arm at PC0

Supplementary Appendix-S7

		All follow-up visits (PC12-36)		PC12 visit		PC24 visit		PC36 visit	
		Not seen	Seen at least once	Not seen	Seen	Not seen	Seen	Not seen	Seen
Total		10,526 (27%)¶	27,948 (73%)¶	13,184 (34%)¶	25,290 (66%)¶	16,796 (44%)¶	21,678 (56%)¶	18,052 (47%)¶	20,422 (53%)¶
Country	Zambia	5,670 (54%)	14,054 (50%)	7,393 (56%)	12,331 (49%)	8,797 (52%)	10,927 (50%)	4,096 (49%)	10,945 (54%)
	SA	4,856 (46%)	13,894 (50%)	5,791 (44%)	12,959 (51%)	7,999 (48%)	10,751 (50%)	9,273 (51%)	9,477 (46%)
Sex	Male	3,460 (33%)	7,742 (28%)	4,382 (34%)	6,820 (27%)	5,397 (32%)	5,805 (27%)	5,806 (32%)	5,396 (26%)
	Female	6,936 (67%)	20,203 (72%)	8,671 (66%)	18,468 (73%)	11,266 (68%)	15,873 (73%)	12,114 (68%)	15,025 (74%)
Age (years)†	18-24	4,582 (44%)	10,643 (38%)	5,693 (44%)	9,532 (38%)	7,244 (43%)	7,981 (37%)	7,748 (43%)	7,477 (37%)
	25-29	2,465 (24%)	5,805 (21%)	3,012 (23%)	5,258 (21%)	3,894 (23%)	4,376 (20%)	4,133 (23%)	4,137 (20%)
	30-34	1,618 (16%)	4,898 (18%)	2,091 (16%)	4,425 (18%)	2,590 (16%)	3,926 (18%)	2,857 (16%)	3,659 (18%)
	35-39	1,000 (10%)	3,735 (13%)	1,304 (10%)	3,431 (14%)	1,709 (10%)	3,026 (14%)	1,847 (10%)	2,888 (14%)
	40/max	729 (7%)	2,861 (10%)	948 (7%)	3,431 (10%)	1,223 (7%)	2,367 (11%)	1,332 (7%)	2,258 (11%)
HIV status‡	Negative	7,630 (76%)	21,500 (79%)	9,642 (77%)	19,488 (79%)	12,390 (77%)	16,740 (79%)	13,355 (77%)	15,775 (79%)
	Positive	2,377 (24%)	5,627 (21%)	2,906 (23%)	5,098 (21%)	3,667 (23%)	4,337 (21%)	3,908 (23%)	4,096 (21%)

Table: Characteristics of individuals not seen and seen (at least once during follow up and at each follow up PC visit [PC12, PC24 AND PC36, respectively]).

PC=population cohort; SA=South Africa; †age at PC0; ‡HIV-status at PC0; ¶column percentages shown

Supplementary Appendix-S8

Characteristics, by PC round, of people who were HIV-positive at each PC round

		PC0				PC12				PC24				PC36			
		A	B	C	Total	A	B	C	Total	A	B	C	Total	A	B	C	Total
Total seen		2,583* (32%)¶	2,734* (34%)¶	2,687* (34%)¶	8,004* (100%)¶	1,661* (33%)¶	1,660* (33%)¶	1,765* (34%)¶	5,086* (100%)¶	1,459* (32%)¶	1,608* (35%)¶	1,512* (33%)¶	4,579* (100%)¶	1,549* (33%)¶	1,637* (34%)¶	1,572* (33%)¶	4,758* (100%)¶
Country	Zambia	1254 (49%)	1396 (51%)	1395 (52%)	4045 (51%)	860 (52%)	882 (53%)	949 (54%)	2691 (53%)	788 (54%)	917 (57%)	838 (55%)	2543 (56%)	862 (56%)	950 (58%)	920 (59%)	2732 (57%)
	SA	1329 (51%)	1338 (49%)	1292 (48%)	3959 (49%)	801 (48%)	778 (47%)	816 (46%)	2395 (47%)	671 (46%)	691 (43%)	674 (45%)	2036 (44%)	687 (44%)	687 (42%)	652 (41%)	2026 (43%)
Sex	Male	414 (16%)	406 (15%)	430 (16%)	1250 (16%)	239 (14%)	202 (12%)	265 (15%)	706 (14%)	205 (14%)	207 (13%)	221 (15%)	633 (14%)	216 (14%)	217 (13%)	235 (15%)	668 (14%)
	Female	2160 (84%)	2324 (85%)	2241 (83%)	6725 (84%)	1422 (86%)	1458 (88%)	1500 (85%)	4380 (86%)	1254 (86%)	1401 (87%)	1291 (85%)	3946 (86%)	1333 (86%)	1420 (87%)	1337 (85%)	4090 (86%)
	Missing	9 (<1%)	4 (<1%)	16 (<1%)	29 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age (years) †	18-24	457 (18%)	522 (19%)	501 (19%)	1480 (18%)	225 (13%)	232 (14%)	274 (16%)	731 (14%)	167 (11%)	180 (11%)	186 (12%)	533 (12%)	157 (10%)	164 (10%)	157 (10%)	478 (10%)
	25-29	606 (23%)	600 (22%)	600 (22%)	1806 (23%)	351 (21%)	315 (19%)	341 (19%)	1007 (20%)	252 (17%)	296 (18%)	247 (16%)	795 (17%)	262 (17%)	293 (18%)	260 (17%)	815 (17%)
	30-34	623 (24%)	674 (25%)	625 (23%)	1922 (24%)	398 (24%)	412 (25%)	381 (21%)	1191 (23%)	361 (25%)	406 (25%)	326 (21%)	1093 (24%)	366 (24%)	352 (21%)	326 (21%)	1044 (22%)
	35-39	506 (20%)	568 (21%)	555 (21%)	1629 (20%)	361 (22%)	377 (23%)	419 (24%)	1157 (23%)	311 (21%)	348 (22%)	389 (26%)	1048 (23%)	331 (21%)	358 (22%)	377 (24%)	1066 (22%)
	40/max†	382 (15%)	366 (13%)	389 (14%)	1137 (14%)	326 (20%)	324 (20%)	350 (20%)	1000 (20%)	368 (25%)	378 (23%)	364 (24%)	1110 (24%)	432 (28%)	470 (29%)	452 (29%)	1354 (28%)
	missing	9 (<1%)	4 (<1%)	17 (<1%)	30 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)

Characteristics, by calendar year, of people who were HIV-positive at each calendar year, who contributed person time to the cohort analysis during that specific calendar year

		2014				2015				2016				2017/18			
		A	B	C	Total	A	B	C	Total	A	B	C	Total	A	B	C	Total
Total seen		2071* (32%)¶	2215 * (35%)¶	2099* (33%)¶	6,385* (100%)¶	1884* (32%)¶	1943* (33%)¶	2047* (35%)¶	5874* (100%)¶	1707* (32%)¶	1775* (33%)¶	1854* (35%)¶	5336* (100%)¶	1620* (32%)¶	1728* (35%)¶	1649* (33%)¶	4997* (100%)¶
Country	Zambia	980 (47%)	1147 (52%)	1094 (52%)	3221 (50%)	924 (49%)	1026 (53%)	1063 (52%)	3013 (51%)	889 (52%)	962 (54%)	989 (53%)	2840 (53%)	878 (54%)	975 (56%)	956 (58%)	2809 (56%)
	SA	1091 (53%)	1068 (48%)	1005 (48%)	3164 (50%)	960 (51%)	917 (47%)	984 (48%)	2861 (49%)	818 (48%)	813 (46%)	865 (47%)	2496 (47%)	742 (46%)	753 (44%)	693 (42%)	2188 (44%)

Sex	Male	305 (15%)	321 (14%)	320 (15%)	946 (15%)	278 (15%)	252 (13%)	314 (15%)	844 (14%)	239 (14%)	233 (13%)	275 (15%)	747 (14%)	232 (14%)	221 (13%)	240 (15%)	693 (14%)
	Female	1757 (85%)	1890 (85%)	1763 (84%)	5410 (85%)	1606 (85%)	1691 (87%)	1,733 (85%)	5030 (86%)	1468 (86%)	1542 (87%)	1579 (85%)	4589 (86%)	1388 (86%)	1507 (87%)	1,409 (85%)	4,304 (86%)
	Missing	9 (<1%)	4 (<1%)	16 (<1%)	29 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age/years[ϕ]	18-24	352 (17%)	410 (19%)	381 (18%)	1143 (18%)	310 (17%)	349 (18%)	390 (19%)	1049 (18%)	310 (18%)	338 (19%)	357 (19%)	1005 (19%)	321 (20%)	371 (21%)	339 (21%)	1031 (21%)
	25-29	487 (24%)	484 (22%)	464 (22%)	1435 (23%)	416 (22%)	396 (20%)	425 (21%)	1237 (21%)	367 (21%)	338 (19%)	383 (21%)	1088 (21%)	343 (21%)	337 (20%)	327 (20%)	1007 (20%)
	30-34	505 (24%)	548 (25%)	495 (24%)	1548 (24%)	461 (24%)	506 (26%)	477 (23%)	1444 (25%)	407 (24%)	451 (26%)	436 (24%)	1294 (24%)	381 (24%)	412 (24%)	369 (22%)	1162 (23%)
	35-39	417 (20%)	469 (21%)	430 (20%)	1316 (21%)	400 (21%)	414 (21%)	448 (22%)	1262 (21%)	355 (21%)	380 (21%)	397 (21%)	1132 (21%)	328 (20%)	353 (20%)	362 (22%)	1043 (21%)
	40/max	301 (15%)	300 (13%)	312 (15%)	913 (14%)	297 (16%)	278 (15%)	307 (15%)	882 (15%)	268 (16%)	268 (15%)	281 (15%)	817 (15%)	246 (15%)	255 (15%)	252 (15%)	753 (15%)
	Missing	9 (<1%)	4 (<1%)	17 (<1%)	30 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)

Table: Characteristics of Population Cohort participants from all 21 HPTN 071 (PopART) communities, who were HIV-positive (based on laboratory HIV-testing) and contributed to the cross-sectional and cohort analysis: overall and by study arm

PC=population cohort; SA=South Africa; All percentages rounded to the nearest whole number; *Denominator for all column percentages shown in the column (unless otherwise indicated); ¶Denominator for this proportion was the total number seen (row percentage); †Age determined at PC0. Age at each subsequent PC-visit, based on adding 1 to the age the PC-participant would have been at the preceding PC-visit, starting at PC0. Upper limits of age are PC0=44 years PC12=45 years, PC24=46 years, and PC36=47years; ϕAge at PC0

Supplementary Appendix-S9

		PC0 N=38,474	PC12 N=25,290	PC24 N=21,678	PC36 N=20,422
Self-reported being told they had TB AND starting TB treatment‡	Yes	361/38474 (0.94%)	164/25290 (0.65%)	177/21678 (0.82%)	110/20422 (0.54%)
Duration between visit date and MM/YYYY of TB treatment startᒧ₮	missing	67/361 (18.56%)	21/164 (12.80%)	17/177 (9.6%)	12/110 (10.91%)
	≤14 months*	279/361 (77.29%)	121/164 (73.78%)	143/177 (80.8%)	93/110 (84.55%)
	>14 months*	15/361 (4.16%)	22/164 (13.41%)	17/177 (9.6%)	5/110 (4.54%)
Self-reported being told they had TB AND starting TB treatment AND duration between visit date and MM/YYYY of TB treatment start ≤14 months: overall and by country	Yes (both countries)	279/38474 (0.73%)	121/25290 (0.48%)	143/21678 (0.66%)	93/20422 (0.46%)
	Zambia	114/19724 (0.58%)	30/12331 (0.24%)	39/10927 (0.36%)	29/10945 (0.26%)
	SA	165/18750 (0.88%)	91/12959 (0.70%)	104/10751 (0.97%)	64/9477 (0.68%)
Self-reported being told they had TB AND starting TB treatment AND duration between visit date and MM/YYYY of TB treatment start ≤14 months: by HIV-status$	Negative	79/29130 (0.27%)	37/17669 (0.21%)	62/15294 (0.41%)	38/15111 (0.25%)
	Positive	192/8004 (2.40%)	69/5086 (1.36%)	65/4579 (1.42%)	53/4758 (1.11%)
	Not determined	8/1340 (0.60%)	15/2535 (0.59%)	16/1805 (0.89%)	2/553 (0.36%)

Table: Number and proportion self-reporting being told they had TB and starting TB treatment with duration between visit date and MM/YYYY of TB treatment start ≤14 months, by Population Cohort visit, in the cohort enrolled at PC0 (N=38474) from all 21 HPTN 071 (PopART) communities

TB=tuberculosis; PC=Population Cohort; MM/YYYY=month and year of TB treatment start ‡**Question asked:** "in the last 12 months, have you been told that you have TB" with response options of yes, no and don't know. If response was yes, **Question asked:** at PC0 "have you started TB treatment" and at PC12-36 "have you started TB treatment in the last 12 months" with response options of yes, no and don't know; ᒧIf response was yes to "in the last 12 months, have you been told that you have TB" AND yes to "have you started TB treatment/ have you started TB treatment in the last 12 months", **Question asked:** "When did you start TB treatment? Please give the month and year?"; ₮Denominator is number of people self-reporting being told they have TB in the last 12 months and starting TB treatment; ¶unable to calculate duration due to missing month and year of TB treatment start; *number of months between self-reported TB treatment start month and year, and, visit date; $HIV-status based on laboratory testing.

Supplementary Appendix-S10

		2014				2015				2016				2017/18			
		A	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**	**A**	**B**	**C**	**Total**
Total N		12616¶ (33%)*	13347¶ (35%)*	12297¶ (32%)*	38,260¶ (100%)*	9406¶ (33%)*	9720¶ (34%)*	9442¶ (33%)*	28,568¶ (100%)*	8046¶ (32%)*	8715¶ (35%)*	8144¶ (33%)*	24,905¶ (100%)*	7042¶ (32%)*	7889¶ (36%)*	6866¶ (32%)*	21,797¶ (100%)
Country	Zambia	6465 (51%)	6389 (48%)	6736 (55%)	19590 (51%)	4734 (50%)	4670 (48%)	5040 (53%)	14444 (51%)	4094 (51%)	4170 (48%)	4388 (54%)	12652 (51%)	3689 (52%)	3903 (49%)	3931 (57%)	11523 (53%)
	SA	6151 (49%)	6958 (52%)	5561 (45%)	18670 (49%)	4672 (50%)	5050 (52%)	4402 (47%)	14124 (49%)	3952 (49%)	4545 (52%)	3756 (46%)	12253 (49%)	3353 (48%)	3986 (51%)	2935 (43%)	10274 (47%)
Sex	Male	3578 (28%)	3890 (29%)	3655 (30%)	11123 (29%)	2572 (27%)	2666 (27%)	2715 (29%)	7953 (28%)	2112 (26%)	2385 (27%)	2315 (28%)	6812 (27%)	1799 (26%)	2126 (27%)	1901 (28%)	5826 (27%)
	Female	9004 (72%)	9417 (71%)	8583 (70%)	27004 (71%)	6831 (73%)	7050 (73%)	6727 (71%)	20608 (72%)	5934 (74%)	6328 (73%)	5829 (72%)	18091 (73%)	5243 (74%)	5763 (73%)	4964 (72%)	15970 (73%)
	Missing	34 (<1%)	40 (<1%)	59 (<1%)	133 (<1%)	3 (<1%)	4 (<1%)	0 (0%)	7 (<1%)	0 (0%)	2 (<1%)	0 (<1%)	2 (<1%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
Age/years‡	18-24	5045 (40%)	5162 (39%)	4960 (40%)	15167 (40%)	3673 (39%)	3692 (38%)	3687 (39%)	11052 (39%)	3097 (39%)	3279 (37%)	3105 (38%)	9481 (38%)	2655 (38%)	2922 (37%)	2556 (37%)	8133 (37%)
	25-29	2771 (22%)	2867 (21%)	2585 (21%)	8223 (22%)	2023 (22%)	2014 (21%)	1983 (21%)	6020 (21%)	1697 (21%)	1739 (20%)	1659 (20%)	5095 (20%)	1486 (21%)	1578 (20%)	1380 (20%)	4444 (20%)
	30-34	2137 (17%)	2278 (17%)	2058 (17%)	6473 (17%)	1624 (17%)	1713 (18%)	1604 (17%)	4941 (17%)	1403 (17%)	1563 (18%)	1428 (18%)	4394 (18%)	1247 (18%)	1414 (18%)	1216 (18%)	3877 (18%)
	35-39	1453 (12%)	1705 (13%)	1535 (13%)	4693 (12%)	1161 (12%)	1299 (13%)	1258 (13%)	3718 (13%)	1026 (13%)	1196 (14%)	1130 (14%)	3352 (14%)	916 (13%)	1101 (14%)	995 (15%)	3012 (14%)
	40-44	1175 (9%)	1295 (10%)	1096 (9%)	3566 (9%)	922 (10%)	998 (10%)	910 (10%)	2830 (10%)	823 (10%)	936 (11%)	820 (10%)	2579 (10%)	737 (10%)	874 (11%)	716 (10%)	2327 (11%)
	missing	35 (<1%)	40 (<1%)	63 (<1%)	138 (<1%)	3 (<1%)	4 (<1%)	0 (0%)	7 (<1%)	0 (0%)	2 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	0 (0%)	3 (<1%)	4 (<1%)
HIV-status†	Positive	2071 (17%)	2215 (17%)	2099 (17%)	6385 (17%)	1884 (20%)	1943 (20%)	2047 (22%)	5874 (21%)	1707 (21%)	1775 (20%)	1854 (23%)	5336 (21%)	1620 (23%)	1728 (22%)	1649 (24%)	4997 (23%)
	Negative	9745 (77%)	10320 (77%)	9372 (76%)	29437 (77%)	7047 (75%)	7361 (76%)	6864 (73%)	21272 (74%)	5908 (74%)	6541 (75%)	5761 (71%)	18210 (73%)	5163 (73%)	5919 (75%)	4977 (72%)	16059 (74%)
	ND	800 (6%)	812 (6%)	826 (7%)	2438 (6%)	475 (5%)	416 (4%)	531 (5%)	1422 (5%)	431 (5%)	399 (5%)	529 (6%)	1359 (6%)	259 (4%)	242 (3%)	240 (4%)	741 (3%)

Table: Characteristics of Population Cohort participants contributing person time to the cohort analysis from all 21 HPTN 071 (PopART) communities, by calendar year and study arm

PC=Population Cohort; SA=South Africa; ND=not determined; All percentages rounded to the nearest whole number, where possible; ¶denominator for all column percentages shown in the column (unless otherwise indicated); *denominator is the total number contributing person time each year (row percentage); ‡age in years at PC0; †HIV-status based on laboratory HIV-testing

Supplementary Appendix-S11

	2014						2015						2016						2017/18					
	A		B		C		A		B		C		A		B		C		A		B		C	
	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate	n/pyrs	rate
Total population																								
triplet 1	4/909	0.44	6/840	0.71	4/1473	0.27	3/710	0.42	3/690	0.43	2/1223	0.16	0.5/632	0.08	3/610	0.49	2/1049	0.19	2/598	0.33	0.5/616	0.08	4/1147	0.35
triplet 2	8/1594	0.50	2/1931	0.10	1/1395	0.07	3/1314	0.23	1/1563	0.06	4/1168	0.34	4/1098	0.36	5/1495	0.33	7/939	0.75	3/1130	0.27	2/1560	0.13	5/971	0.51
triplet 3	3/1254	0.24	7/1039	0.67	12/1636	0.73	4/835	0.48	2/729	0.27	4/1108	0.36	1/752	0.13	3/685	0.44	5/950	0.53	1/730	0.14	2/670	0.30	3/972	0.31
triplet 4	4/1334	0.30	4/ 1166	0.34	6/868	0.69	0.5/1082	0.05	5/806	0.62	3/772	0.39	1/1017	0.10	3/903	0.33	1/651	0.15	2/888	0.23	6/755	0.80	2/644	0.31
triplet 5	7/1583	0.44	19/1894	1.00	19/1349	1.41	12/1325	0.91	8/1630	0.49	12/1216	0.99	12/1121	1.07	16/1393	1.15	12/949	1.26	2/919	0.22	6/1181	0.51	5/699	0.71
triplet 6	10/1538	0.65	13/1619	0.80	8/1502	0.53	10/1354	0.74	10/1147	0.87	4/1388	0.29	9/1136	0.79	10/1114	0.90	17/1086	1.57	3/1071	0.28	10/1016	0.98	5/852	0.59
triplet 7	9/1261	0.71	5/1496	0.33	3/1166	0.26	8/1245	0.64	4/1597	0.25	10/1248	0.80	4/1073	0.37	9/1444	0.62	12/1098	1.09	10/969	1.03	8/1266	0.63	11/890	1.24
Overall*	45/9473	**0.44**	56/9985	**0.46**	53/9389	**0.41**	40/7865	**0.37**	33/8161	**0.33**	39/8124	**0.40**	31/6827	**0.27**	49/7643	**0.55**	56/6722	**0.59**	23/6305	**0.29**	34/7064	**0.36**	35/6175	**0.51**
People living with HIV																								
triplet 1	3/86	3.48	2/89	2.24	3/236	1.27	1/117	0.85	2/124	1.61	2/268	0.75	0.5/110	0.45	2/113	1.76	1/241	0.41	1/121	0.82	0.5/124	0.40	1/284	0.35
triplet 2	3/196	1.53	2/386	0.52	1/195	0.51	2/236	0.85	1/366	0.27	2/218	0.92	2/212	0.94	2/356	0.56	3/183	1.64	1/245	0.41	2/405	0.49	4/204	1.96
triplet 3	2/164	1.22	4/170	2.36	8/206	3.88	4/157	2.55	2/167	1.20	3/211	1.42	0.5/154	0.32	2/166	1.21	2/192	1.04	1/166	0.60	1/171	0.58	2/211	0.95
triplet 4	3/262	1.14	1/189	0.53	5/180	2.77	0.5/289	0.17	2/187	1.07	1/222	0.45	1/293	0.34	1/230	0.44	0.5/205	0.24	1/259	0.39	2/207	0.97	2/211	0.95
triplet 5	2/340	0.59	4/337	1.19	8/273	2.93	10/381	2.63	7/457	1.53	9/336	2.68	7/335	2.09	12/404	2.97	9/275	3.28	1/289	0.35	4/373	1.07	4/212	1.89
triplet 6	6/261	2.30	6/255	2.35	4/343	1.16	4/ 297	1.35	5/188	2.65	4/470	0.85	6/262	2.29	6/175	3.42	14/387	3.62	2/285	0.70	6/167	3.59	5/330	1.52
triplet 7	7/88	7.99	3/100	3.00	0.5/28	1.79	3/113	2.66	4/134	2.99	1/39	2.55	1/87	1.16	2/109	1.83	3/39	7.74	4/91	4.39	5/106	4.72	2/31	6.42
Overall*	26/1397	**1.87**	22/1526	**1.43**	29/1463	**1.71**	24/1590	**1.17**	23/1624	**1.31**	22/1764	**1.14**	17/1453	**0.83**	27/1554	**1.38**	32/1521	**1.48**	11/1458	**0.70**	20/1552	**1.11**	20/1483	**1.42**
People who were HIV-negative																								
triplet 1	0.5/741	0.07	3/689	0.44	0.5/1148	0.04	2/567	0.35	1/542	0.18	0.5/925	0.05	0.5/497	0.10	1/476	0.21	1/794	0.13	1/462	0.22	0.5/474	0.11	3/854	0.35
triplet 2	3/1292	0.23	0.5/1461	0.03	0.5/1131	0.04	0.5/995	0.05	0.5/1170	0.04	1/898	0.11	2/826	0.24	3/1109	0.27	4/714	0.56	2/850	0.24	0.5/1145	0.04	1/730	0.14
triplet 3	0.5/1022	0.05	2/816	0.25	2/1281	0.16	0.5/649	0.08	0.5/549	0.09	1/828	0.12	1/572	0.17	1/509	0.20	3/709	0.42	0.5/547	0.09	1/492	0.20	1/754	0.13
triplet 4	0.5/993	0.05	2/886	0.23	1/613	0.16	0.5/771	0.06	2/606	0.33	1/520	0.19	0.5/713	0.07	2/660	0.30	1/435	0.23	1/626	0.16	4/542	0.74	0.5/419	0.12
triplet 5	4/1099	0.36	8/1263	0.63	7/958	0.73	1/856	0.12	1/1042	0.10	3/795	0.38	4/722	0.55	2/877	0.23	1/606	0.17	1/588	0.17	1/741	0.13	1/457	0.22
triplet 6	4/1129	0.35	3/1305	0.23	2/961	0.21	6/974	0.62	5/926	0.54	0.5/814	0.06	3/810	0.37	4/900	0.44	3/598	0.50	1/746	0.13	4/837	0.48	0.5/502	0.10
triplet 7	1/1115	0.09	2/1336	0.15	3/1111	0.27	5/1083	0.46	0.5/1374	0.04	9/1140	0.79	3/955	0.31	7/1288	0.54	9/1023	0.88	6/866	0.69	3/1140	0.26	9/851	1.06

Overall*	12/7392	**0.12**	20/7755	**0.21**	15/7202	**0.15**	14/5894	**0.16**	9/6208	**0.12**	15/5921	**0.16**	13/5093	**0.21**	20/5820	**0.29**	22/4878	**0.34**	12/4684	**0.20**	13/5371	**0.20**	15/4567	**0.21**
Sensitivity analysis (1) - People living with HIV																								
triplet 1	4/144	2.78	2/138	1.45	4/310	1.29	1/121	0.83	2/125	1.60	2/276	0.72	0.5/115	0.43	2/118	1.69	1/245	0.41	1/121	0.82	0.5/124	0.40	1/284	0.35
triplet 2	4/268	1.49	2/450	0.44	1/240	0.42	2/253	0.79	1/374	0.27	2/230	0.87	2/221	0.90	2/366	0.55	3/187	1.61	1/245	0.41	2/405	0.49	4/204	1.96
triplet 3	3/219	1.37	5/208	2.41	10/306	3.27	4/161	2.49	2/169	1.18	3/219	1.37	0.5/156	0.32	2/171	1.17	2/200	1.00	1/166	0.60	1/171	0.58	2/211	0.95
triplet 4	4/335	1.19	2/273	0.73	5/236	2.12	0.5/300	0.17	3/193	1.56	1/236	0.42	1/299	0.33	1/232	0.43	0.5/207	0.24	1/259	0.39	2/207	0.97	2/211	0.95
triplet 5	3/458	0.65	10/526	1.90	12/361	3.32	10/398	2.51	7/472	1.48	9/351	2.57	7/341	2.06	13/419	3.10	10/283	3.53	1/289	0.35	4/373	1.07	4/212	1.89
triplet 6	6/344	1.74	10/302	3.31	6/508	1.18	4/310	1.29	5/195	2.56	4/485	0.83	6/273	2.20	6/188	3.19	14/396	3.53	2/285	0.70	6/167	3.59	5/330	1.52
triplet 7	8/112	7.11	3/132	2.27	0.5/31	1.61	3/115	2.61	4/141	2.85	1/42	2.36	1/91	1.10	2/111	1.80	3/41	7.40	4/91	4.39	5/106	4.72	2/31	6.42
Overall*	32/1881	**1.77**	34/2028	**1.49**	38/1992	**1.57**	24/1656	**1.13**	24/1668	**1.36**	22/1840	**1.09**	17/1495	**0.80**	28/1606	**1.35**	33/1559	**1.47**	11/1458	**0.70**	20/1553	**1.11**	20/1483	**1.42**
Sensitivity analysis (2) - HIV negative individuals																								
triplet 1	0.5/741	0.07	3/689	0.44	0.5/1148	0.04	2/570	0.35	1/543	0.18	0.5/934	0.05	0.5/502	0.10	1/481	0.21	1/798	0.13	1/462	0.22	0.5/474	0.11	3/854	0.35
triplet 2	3/1292	0.23	0.5/1461	0.03	0.5/1131	0.04	0.5/1012	0.05	0.5/1178	0.04	1/910	0.11	2/836	0.24	3/1119	0.27	4/718	0.56	2/850	0.24	0.5/1145	0.04	1/730	0.14
triplet 3	0.5/1022	0.05	2/816	0.25	2/1281	0.16	0.5/653	0.08	0.5/551	0.09	1/836	0.12	1/573	0.17	1/514	0.19	3/717	0.42	0.5/547	0.09	1/492	0.20	1/754	0.13
triplet 4	0.5/993	0.05	2/886	0.23	1/613	0.16	0.5/782	0.06	3/611	0.49	1/535	0.19	0.5/719	0.07	2/663	0.30	1/437	0.23	1/626	0.16	4/542	0.74	0.5/419	0.12
triplet 5	4/1099	0.36	8/1263	0.63	7/958	0.73	1/872	0.11	1/1057	0.09	3/810	0.37	4/728	0.55	3/892	0.34	2/615	0.33	1/588	0.17	1/741	0.13	1/457	0.22
triplet 6	4/1129	0.35	3/1305	0.23	2/961	0.21	6/987	0.61	5/932	0.54	0.5/829	0.06	3/821	0.37	4/913	0.44	3/606	0.49	1/746	0.13	4/837	0.48	0.5/502	0.10
triplet 7	1/1115	0.09	2/1336	0.15	3/1111	0.27	5/1085	0.46	0.5/1380	0.04	9/1143	0.79	3/959	0.31	7/1290	0.54	9/1024	0.88	6/866	0.69	3/1140	0.26	9/851	1.06
Overall*	12/7392	**0.12**	20/7755	**0.21**	15/7202	**0.15**	14/5961	**0.16**	10/6253	**0.13**	15/5997	**0.16**	13/5136	**0.21**	21/5871	**0.31**	23/4916	**0.37**	12/4684	**0.20**	13/5371	**0.20**	15/4567	**0.21**

Table: Incidence rate of self-reported TB treatment, by community, triplet, study arm and calendar year (2014 to 2017/18) among Population Cohort participants from all 21 HPTN 071 (PopART) communities

n/pyrs=number self-reporting TB treatment/total person years; rate=per 100 person years; *rate calculated as the geometric mean of the cluster rates; Sensitivity analysis (1): If HIV-positive for a calendar year and HIV-status was not determined in the preceding year, HIV-status in the preceding year assumed to be positive and rates among people living with HIV determined; Sensitivity analysis (2): If HIV-positive for a calendar year and HIV-status was not determined in the preceding year, HIV-status in the preceding year assumed to be negative and rates among HIV negative individuals determined. NB: this excluded N=1560 who had a missing HIV-status in 2014 and a positive HIV-status in 2015, mainly due to having their enrolment visit in 2015 (1530/1560; 98%), where the HIV-status in 2014 was kept as missing.

Supplementary Appendix-S12

	PC0						PC12						PC24						PC36					
	A		B		C		A		B		C		A		B		C		A		B		C	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Total population																								
triplet 1	3/1067	0.28	8/1006	0.80	6/1795	0.33	4/715	0.56	3/738	0.41	2/1262	0.16	0.5/651	0.08	3/634	0.47	4/1067	0.37	2/647	0.31	1/661	0.15	2/1073	0.19
triplet 2	17/2019	0.84	5/2437	0.21	8/1724	0.46	4/1375	0.29	3/1633	0.18	5/1202	0.42	4/1116	0.36	5/1509	0.33	7/955	0.73	3/1178	0.25	3/1500	0.20	6/1013	0.59
triplet 3	6/1647	0.36	13/1417	0.92	19/2194	0.87	4/842	0.48	2/742	0.27	4/1111	0.36	1/760	0.13	4/701	0.57	8/959	0.83	1/729	0.14	1/704	0.14	2/926	0.22
triplet 4	8/1767	0.45	9/1573	0.57	12/1078	1.11	0.5/1135	0.04	2/780	0.26	4/796	0.5	1/1003	0.10	6/916	0.66	3/656	0.46	2/985	0.2	8/855	0.94	3/674	0.45
triplet 5	14/2226	0.63	25/2533	0.99	40/1907	2.10	14/1389	1.01	11/1719	0.64	16/1329	1.2	14/1131	1.24	13/1454	0.89	16/958	1.67	2/994	0.2	10/1249	0.80	5/801	0.62
triplet 6	18/2208	0.82	15/2352	0.64	25/2120	1.18	10/1453	0.69	15/1264	1.19	7/1477	0.47	10/1152	0.87	11/1158	0.95	14/1130	1.24	3/1100	0.27	13/1148	1.13	7/909	0.77
triplet 7	11/1737	0.63	7/2086	0.34	10/1581	0.63	12/1325	0.91	9/1696	0.53	11/1307	0.84	7/1125	0.62	13/1501	0.87	16/1142	1.40	9/990	0.91	10/1299	0.77	12/987	1.22
Overall*	77/12671	**0.53**	82/13404	**0.57**	120/12399	**0.81**	48/8234	**0.41**	45/8572	**0.41**	49/8484	**0.48**	37/6938	**0.31**	55/7873	**0.64**	68/6867	**0.84**	22/6623	**0.27**	46/7416	**0.43**	37/6383	**0.49**
People living with HIV																								
triplet 1	3/166	1.81	3/165	1.82	6/387	1.55	2/124	1.61	2/129	1.55	2/282	0.71	0.5/114	0.44	2/123	1.63	2/256	0.78	1/133	0.75	1/135	0.74	0.5/270	0.19
triplet 2	10/338	2.96	4/559	0.72	7/304	2.30	1/257	0.39	3/385	0.78	2/225	0.89	3/217	1.38	2/371	0.54	3/169	1.78	1/265	0.38	3/387	0.78	4/217	1.84
triplet 3	6/296	2.03	10/297	3.37	14/412	3.40	4/159	2.52	2/179	1.12	2/200	1.00	0.5/158	0.32	2/182	1.10	3/197	1.52	1/171	0.58	1/191	0.52	2/211	0.95
triplet 4	8/454	1.76	6/375	1.60	10/292	3.42	0.5/320	0.16	1/189	0.53	2/242	0.83	1/299	0.33	3/241	1.24	2/216	0.93	1/293	0.34	3/237	1.27	3/222	1.35
triplet 5	10/648	1.54	17/678	2.51	24/516	4.65	10/384	2.60	8/440	1.82	10/325	3.08	9/320	2.81	7/389	1.80	8/271	2.95	1/312	0.32	7/381	1.84	5/256	1.95
triplet 6	11/501	2.20	11/460	2.39	20/730	2.74	5/313	1.60	10/216	4.63	6/449	1.34	6/257	2.33	6/188	3.19	8/364	2.20	2/284	0.70	7/197	3.55	6/357	1.68
triplet 7	7/180	3.89	5/200	2.50	0.5/46	1.09	5/104	4.81	5/122	4.10	2/42	4.76	2/94	2.13	4/114	3.51	2/39	5.13	3/91	3.30	6/109	5.50	2/39	5.13
Overall*	55/2583	**2.20**	56/2734	**1.95**	81/2687	**2.48**	27/1661	**1.26**	31/1660	**1.58**	26/1765	**1.40**	21/1459	**0.98**	26/1608	**1.58**	28/1512	**1.82**	10/1549	**0.63**	28/1637	**1.45**	22/1572	**1.33**
People who were HIV-negative																								
triplet 1	0.5/845	0.06	3/811	0.37	0.5/1382	0.04	2/540	0.37	1/549	0.18	0.5/926	0.05	0.5/510	0.10	1/487	0.21	2/790	0.25	1/497	0.20	0.5/503	0.10	2/793	0.25
triplet 2	5/1603	0.31	1/1833	0.05	1/1373	0.07	2/962	0.21	0.5/1200	0.04	2/876	0.23	1/776	0.13	3/1087	0.28	3/653	0.46	2/874	0.23	0.5/1101	0.05	2/751	0.27
triplet 3	0.5/1323	0.04	2/1088	0.18	5/1687	0.30	0.5/626	0.08	0.5/544	0.09	1/737	0.14	1/559	0.18	2/512	0.39	4/666	0.60	0.5/540	0.09	0.5/504	0.10	0.5/710	0.07
triplet 4	0.5/1299	0.04	3/1177	0.25	2/747	0.27	0.5/794	0.06	1/569	0.18	1/519	0.19	0.5/698	0.07	3/658	0.46	0.5/428	0.12	1/689	0.15	5/613	0.82	0.5/433	0.12
triplet 5	4/1520	0.26	7/1642	0.43	15/1330	1.13	2/841	0.24	2/970	0.21	3/754	0.40	4/690	0.58	2/819	0.24	3/553	0.54	1/629	0.16	1/765	0.13	0.5/504	0.10
triplet 6	7/1512	0.46	4/1864	0.21	4/1318	0.30	4/932	0.43	5/975	0.51	0.5/752	0.07	4/746	0.54	5/883	0.57	2/558	0.36	1/760	0.13	6/933	0.64	1/519	0.19
triplet 7	4/1492	0.27	2/1820	0.11	10/1464	0.68	5/1086	0.46	3/1403	0.21	9/1114	0.81	5/952	0.53	8/1245	0.64	14/1024	1.37	6/884	0.68	4/1168	0.34	10/941	1.06
Overall*	20/9594	**0.14**	22/10235	**0.19**	37/9301	**0.24**	15/5781	**0.21**	12/6210	**0.16**	16/5678	**0.18**	15/4931	**0.22**	24/5691	**0.37**	28/4672	**0.42**	12/4873	**0.19**	16/5587	**0.19**	15/4651	**0.20**

Table: Proportion self-reporting TB treatment, by community, triplet, study arm and Population Cohort visit among Population Cohort participants from all 21 HPTN 071 (PopART) communities

PC=Population Cohort; n/N=number self-reporting TB treatment/total number seen at each PC-visit; %=proportion; *proportion calculated as the geometric mean of the cluster proportion

Supplementary Appendix-S13

PC visit	accounting for between-trial-arm variation	accounting for between-trial-arm variation and between-triplet variation
PC0	0.48	0.42
PC12	0.50	0.22
PC24	0.44	0.00
PC36	0.52	0.18

Table: The estimated coefficient of between-community variation k at each Population Cohort visit (PC0, PC12, PC24 and PC36, respectively).

PC=population cohort;

CONSORT 2010 checklist of information to include when reporting a randomised trial, with extension to cluster randomized trials checklist items (*shown in italics*) taken from BMJ 2012;345:e5661

Section/Topic	Item No	Checklist item	Reported on*
Title and abstract			
	1a	Identification as a *cluster* randomised trial in the title	Included in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Structured abstract included
Introduction			
Background and objectives	2a	Scientific background, explanation of rationale and *rationale for using a cluster design*	Background paragraph 1-5
	2b	Specific objectives or hypotheses and *whether objectives pertain to the cluster level, the individual participant level of both*	Background paragraph 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio; *definition of cluster and description of how the design features apply to the clusters*	Methods paragraph 2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants; *eligibility criteria for clusters*	Methods paragraph 2
	4b	Settings and locations where the data were collected	Methods paragraph 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered; *whether the intervention pertain to the cluster level, the individual participant level, or both*	Methods paragraph 3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed; *whether outcome measures pertain to the cluster level, the individual participant level, or both*	Methods paragraph 4-5 Appendix-S4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Appendix-S4
Sample size	7a	How sample size was determined; *method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty*	*

	7b	When applicable, explanation of any interim analyses and stopping guidelines	*
Randomisation: Sequence generation	8a	Method used to generate the random allocation sequence	*
	8b	Type of randomisation; details of any restrictions (such as blocking and block size); *details of stratification or matching if used*	Methods paragraph 2 and *
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned; *specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level, or both*	*
Implementation	10a	Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	*
	10b	Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Methods paragraph 3
	10c	From whom consent was sought (representatives of the cluster, or individual cluster members, or both) and whether consent was sought before or after randomisation	*
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes; *how clustering was into account*	Methods paragraph 6-12 Appendix-S4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Methods paragraph 12 Appendix-S4
Results			
Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome; *for each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome*	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons; *for each group, losses and exclusions for both clusters and individual cluster members*	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Defined in the methods (paragraph 3 and 4)
	14b	Why the trial ended or was stopped	Defined in the

			methods (paragraph 3 and 4)
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group; *baseline characteristics for the individual and cluster levels as applicable for each group*	Results Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups; *for each group, number of clusters included in each analysis*	Results paragraph 1-2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval); *results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome*	Results paragraph 3-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Results paragraph 3-6
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Results paragraph 4 and 6
Harms	19	All important harms or unintended effects in each group	n/a
Discussion Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussion paragraph 4 and 8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings; *generalisability to clusters and/or individual participants (as relevant)*	Discussion paragraph 1, 5 and 6
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion paragraph 1-3, 6-7
Other information Registration	23	Registration number and name of trial registry	*
Protocol	24	Where the full trial protocol can be accessed, if available	*
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Funding statement provided

*Please note that some items have been marked as see additional information because the information has been reported elsewhere. The current manuscript is not the main results of the HPTN 071 trial (which has been published, is referred to and referenced throughout the manuscript). The following provides additional information about the parent trial.

HPTN 071 study overview and trial protocol versions: https://www.hptn.org/research/studies/hptn071#block-views-block-study-related-publications-block-1

HPTN 071 trial protocol: doi: 10.1186/1745-6215-15-57

HPTN 071 trial primary outcome paper: DOI: 10.1056/NEJMoa1814556

TB reduction through ART and TB screening (TREATS) project – which aimed to measure TB outcomes of HPTN 071, study overview: clinicaltrials.gov ID NCT03739736

Chapter 6: Does tuberculosis screening improve individual outcomes? A systematic review

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	159168	**Title**	Dr
First Name(s)	Lilanganee		
Surname/Family Name	Telisinghe		
Thesis Title	Can universal testing and treatment for HIV and community-wide active case finding for tuberculosis control the African TB epidemic?		
Primary Supervisor	Professor Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	eClinicalMedicine		
When was the work published?	2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This systematic review was undertaken to inform the 2021 WHO TB screening guideline development. The review questions and eligibility criteria were developed by the Guideline Development Group convened by the WHO. I led the clinical outcomes review. I developed the review protocol, study selection process, and SOPs. I trained the team, who undertook the clinical outcomes review, on the study procedures and undertook as a reviewer the abstract and full text screens and the risk of bias assessment. I synthesised the evidence. I drafted and edited the manuscript.

SECTION E

Student Signature	L. Telisinghe
Date	28/02/2024

Supervisor Signature	Helen Ayles
Date	18/03/2024

Does tuberculosis screening improve individual outcomes? A systematic review

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Abstract

Background

To determine if tuberculosis (TB) screening improves patient outcomes, we conducted two systematic reviews to investigate the effect of TB screening on diagnosis, treatment outcomes, deaths (clinical review assessing 23 outcome indicators); and patient costs (economic review).

Methods

Pubmed, EMBASE, Scopus and the Cochrane Library were searched between 1/1/1980-13/4/2020 (clinical review) and 1/1/2010-14/8/2020 (economic review). As studies were heterogeneous, data synthesis was narrative.

Findings

Clinical review: of 27,270 articles, 18 (n=3 trials) were eligible. Nine involved general populations. Compared to passive case finding (PCF), studies showed lower smear grade (n=2/3) and time to diagnosis (n=2/3); higher pre-treatment losses to follow-up (screened 23% and 29% vs PCF 15% and 14%; n=2/2); and similar treatment success (range 68-81%; n=4) and case fatality (range 3-11%; n=5) in the screened group. Nine reported on risk groups. Compared to PCF, studies showed lower smear positivity among those culture-confirmed (n=3/4) and time to diagnosis (n=2/2); and similar (range 80-90%; n=2/2) treatment success in the screened group. Case fatality was lower in n=2/3 observational studies; both reported on established screening programmes. A neonatal trial and post-hoc analysis of a household contacts trial found screening was associated with lower all-cause mortality. Economic review: From 2841 articles, six observational studies were eligible. Total costs (n=6) and catastrophic cost prevalence (n=4; range screened 9-45% vs PCF 12-61%) was lower among those screened.

Interpretation

We found very limited patient outcome data. Collecting and reporting this data must be prioritised to inform policy and practice.

Funding

WHO and EDCTP.

Research in Context

Evidence before this study

Tuberculosis (TB) remains a leading infectious cause of death worldwide, and therefore improving access to diagnosis and treatment, closing the case-detection gap and improving patient outcomes is a priority. In 2019, a MEDLINE and EMBASE search for English language articles on TB screening identified a systematic review. Synthesising data published between 1/1/1980-13/10/2010, it found little evidence that TB screening benefited individuals screened; patient costs were not assessed.

Added value of this study

Synthesising evidence between 1980-2020, our systematic review investigating the effects of TB screening on patient outcomes, found 24 articles (including three trials) from 12 countries. The limited available data suggests that compared to passive case finding, TB screening may be associated with less severe disease; decreased time to diagnosis/first contact with health services; decreased deaths (among risk groups alone); decreased patient costs; and higher pre-treatment losses to follow-up. There was no difference in treatment success between screened and passive case finding groups.

Implications of all available evidence

With World Health Organization targets to END-TB calling for decreases in TB deaths, incidence and catastrophic costs, countries have renewed their interest in TB screening, to find, test and treat “the missing millions”. We found very limited data on the individual effects of TB screening. Routine/research programme implementation must be combined with rigorous data collection and analysis of critical patient outcomes that allows the benefits and harms of TB screening to be characterised.

Introduction

Despite effective, curative treatment, tuberculosis (TB) is a leading infectious cause of death worldwide.[1] In most TB-endemic settings, standard case-detection through routine services (passive case-finding [PCF]), is the mainstay of access to TB diagnosis and treatment.[2, 3] This may be augmented by facility-based TB screening in specific high-risk populations, such as people living with HIV/AIDS. But these measures alone do not identify the substantial burden of undiagnosed TB in these settings, or effectively reach the poor and vulnerable who face barriers to seeking health care.[3-5] In 2019, ~3 million TB patients were either not diagnosed or not notified.[1] If untreated, TB is associated with high mortality and morbidity.[6] Therefore, closing the case-detection gap by improving access to TB diagnosis and treatment is a priority.

One strategy to address this is TB screening, which encompasses a wide range of activities aimed at detecting and treating TB patients earlier in their clinical course.[4, 5] This should improve the individual's clinical outcomes,[4, 5] a requirement for traditional screening programmes.[7] While infectious diseases screening can have both individual and population effects,[4] understanding whether screening benefits the individual is critical when considering if to screen. The costs borne by people seeking TB services and their households (patient costs) can be high, hindering diagnosis and treatment.[8] Such costs can exacerbate poverty, increasing the vulnerability of individuals, with further social and health consequences.[9, 10] TB screening, by helping individuals navigate the TB care pathway, may also potentially decrease patient costs.

But evidence that TB screening improves clinical outcomes and reduces patient costs is lacking.[4, 11] Therefore, we undertook two systematic reviews to determine if TB screening 1) identifies TB patients earlier in their clinical course; improves linkage-to-care; improves treatment outcomes; and decreases deaths (clinical review) and 2) decreases patient costs (economic review).

Methods

We undertook two systematic reviews to identify studies reporting the effect of TB screening on clinical outcomes and patient costs. These were conducted to inform World Health Organization (WHO) TB screening guideline development. The Population, Intervention, Comparison(s) and Outcomes were determined in collaboration with the guideline development group (GDG), consisting of a panel of experts in the field of TB. The methods followed standard procedures for undertaking systematic reviews[12] and grading evidence quality.[13]

Study populations, interventions, outcomes and definitions

Studies conducted in any population group were considered. Screening was defined as any provider-initiated intervention including 1) using health information/education to encourage appropriate health-seeking behaviours, with or without increasing access to diagnostic services (enhanced case-finding [ECF]); and 2) systematic screening using any test/procedure (active case-finding in communities [ACF] and case-finding in health facilities). PCF, the comparator, was defined as the routine diagnosis of symptomatic TB patients self-presenting to health services.

We included 23 clinical outcome indicators (Table 1) for earlier diagnosis (e.g. smear grade, body mass index), linkage-to-care (e.g. pre-treatment loss to follow-up [LTFU]), treatment outcome (e.g. success) and death (e.g. case fatality, mortality). These outcomes were all rated as critical or very important by the GDG. Clinical outcomes were assessed among bacteriologically-confirmed TB patients (culture, Xpert MTB/RIF or smear positive). Treatment success was defined as cured and treatment completed (without microbiological evidence of cure).[14] Pre-treatment LTFU was defined as LTFU between diagnosis and treatment start. Patient cost input data (Table 1) were broadly categorised as direct medical (e.g. hospitalisation costs), direct non-medical (e.g. transportation) and indirect (e.g. lost productivity). Patient costs were assessed among all TB patients (bacteriologically-confirmed

and clinically diagnosed). Catastrophic cost was defined as total costs for seeking TB care >20% of the annual household income.[1]

Search strategy

Clinical review: we updated the systematic review conducted by Kranzer 2013,[11] which covered the period 1/1/1980-13/10/2010 (Figure 1). Articles addressing the research questions from the Kranzer 2013 review were also included in our review. Our update used the same methods as Kranzer 2013; the search was nested within a systematic review to determine the number needed to screen to detect a TB patient in any population.[15] 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 the concepts of TB and screening (Appendix 1). The title and abstract screens were broad; articles needed to be original research on TB screening. Full text screens determined eligibility. Articles from the number needed to screen review reporting on screening for all forms of TB were assessed for eligibility for our review.

Economic review: Medline, EMBASE, Scopus and the Cochrane Library were searched from 1/1/2010-14/8/2020. Subject headings and key words covered the concepts of 1) TB; 2) screening; and 3) economic evaluations or economic/financial analysis (Appendix 1). The Global Health Cost Consortium Unit Cost Study Repository was also searched for additional articles.[16]

For both reviews, bibliographies of identified studies were searched, and authors contacted for additional data if needed.

Eligibility criteria

Only articles in English, French and Spanish were included. Both (quasi-)randomised controlled trials (RCTs) and observational studies with screened and PCF groups were eligible. Studies comparing two different screening strategies or where screening and PCF

occurred in different populations (e.g. screened miners and PCF in the general population) were excluded. Observational studies not disaggregating data by screened and PCF groups were excluded. RCTs (individual and cluster [CRTs]) comparing treatment, death and cost outcomes by randomised arm were eligible, as this design can mitigate biases inherent in observational screening studies. For the clinical review, household contact screening studies where index cases formed the PCF group and household contacts the screened group were excluded as individuals from the same households are clustered.

Study selection, data extraction and risk of bias assessment

Study selection, data extraction and risk of bias assessments were undertaken by two independent reviewers (LT, MR, MAS, MH and CD conducted the clinical review and LM, and EK conducted the economic review). Disagreements were resolved through discussion or, if required, consultation with a third reviewer.

For the clinical review, abstracts of articles were searched to shortlist studies with a control population (parallel or before-after design). For the economic review, articles were initially shortlisted based on the title and abstract. For both reviews, inclusion was based on full text review of shortlisted articles.

Data were extracted into case report forms. Variables extracted included study design, population, calendar period, screening strategy, PCF algorithm, TB case definition, participant numbers and outcome data. Methodological quality of cross-sectional studies was assessed across four domains; valid participant selection, valid exposure ascertainment, valid outcome ascertainment, and adequate control for confounders.[13] Quality assessment of CRTs was undertaken using the Cochrane Risk of Bias tool.[17, 18] For economic studies the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used.[19]

Data synthesis and analysis

Due to the heterogeneity of included studies (populations, screening tools, effect estimates, etc), data synthesis for both reviews was narrative. For treatment success and on-treatment case fatality calculations, we only included cured, treatment completed, death, treatment failure, LTFU, and not evaluated (including transferred out) in the denominator; other outcomes reported, such as still on treatment, were excluded. Smear grade was recategorized, with grades scanty/1+/2+ combined to reflect lower grades (and less extensive disease) and 3+ reflecting higher grades (and more extensive disease). A sensitivity analysis was conducted recategorizing smear grades scanty/1+ as lower grade and 2+/3+ as higher grade. Where proportions were reported, 95% confidence intervals (95%CI) were calculated using Stata version 15 (StataCorp).

Role of the funding source

The WHO commissioned this work to inform TB screening guideline development. The WHO had no role in the conduct of the study or writing the report. The corresponding and last author had access to all data and final responsibility for the decision to submit for publication.

Results

Clinical review

From 27,270 articles, 18 were eligible[20-37] (Figure 1 and Table 2); seven were not reported in the previous review.[20, 29-32, 36, 37] We only identified n=12/23 (52%) of the outcome indicators sought (Table 1); no studies reported on the remainder. All studies reported on smear and/or culture positive TB (Table 2); no studies reported on Xpert MTB/RIF positive TB.

Fifteen were observational studies. The characteristics of TB patients identified through screening and PCF varied across these studies (Tables 3-5). All had a high risk of bias for the outcomes identified (Appendix 2); most (n=11/15) did not adjust for potential confounders.

General populations

Eight observational studies were conducted in rural and/or urban populations; all were from South Asia and sub-Saharan Africa.[20-27] Most (n=7/8) involved one-off house-to-house ACF strategies (n=5/7 were prevalence surveys).[20-25, 27] Four (50%) used symptom screening,[20, 22, 26, 27] three (38%) chest radiographs (CXRs) and symptoms,[23-25] and one (12%) prevalence survey conducted sputum smear and culture on all individuals.[21]

Three studies[(20, 21, 25)] reported on smear grade (Table 3 showing proportions and prevalence ratios and Appendix 3). All showed screened TB patients were less likely to have higher smear grades, but the small sample size of the screened group gave wide CIs in one.[21] Two studies conducted in the same south Indian population over consecutive calendar periods reported on pre-treatment LTFU (Table 4).[23, 24] In both, the proportion LTFU among those screened was higher (screened 23% and 29% versus PCF 15% and 14%). Among individuals LTFU, none died in the screened group, while nearly 20% had died in the PCF group for whom outcomes were available.[23] Symptom duration was longer in the PCF group in one study (cough <3 weeks 13% in PCF versus 28% in screened group)[25] but shorter in another (mean cough duration 6.8 weeks in PCF versus 10.3 weeks in screened group).[20] One study found no difference in time to treatment start between screened and PCF groups.[22]

Four studies involving different screening strategies (symptom; CXR; and smear/culture screening) reported on treatment outcomes (Table 5 showing proportions and prevalence ratios). In three the proportions with treatment success among screened and PCF groups was similar, ranging from 68-80%.[21, 25, 26] Two studies also reported on pre-treatment LTFU; both only provided data for the screened group (26-32%).[21, 25] There was no difference in the proportion who died between screened (range 6-8%) and PCF (range 4-11%) groups in four studies.[21, 25-27] There was no difference in the proportion LTFU during TB treatment between screened (range 6-20%) and PCF (range 8-19%) groups.[25, 26]

One CRT, conducted in 32 contiguous rural Ethiopian communities with difficult access to health care, used monthly ECF with outreach clinics to initiate diagnosis (continued at health facilities through routine services) over 1 year in 12 intervention communities (Table 2, Table 5 and Appendix 2).[28] There was no difference in TB patient characteristics, treatment success, on-treatment case fatality or on-treatment LTFU by study arm. Data on pre-treatment LTFU was not provided. But pre-treatment symptom duration was significantly lower in the intervention group (median difference between intervention and control group -47 days; 95%CI -76 to -19; 55-60% reduction in duration in the last three quarters compared to the first quarter in intervention communities, with corresponding 3-20% fall in control communities). Because of insufficient information to assess one bias domain, the risk of bias assessment raised some concerns.

Risk groups

Seven observational studies reported on risk groups, including prisoners,[29-32] migrants,[33] miners,[34] and homeless people.[32, 35] Four involved established European and South African CXR screening programmes.[32-35] Three studies from India and Brazil reported on one-off/limited ACF using symptoms.[29-31]

One Indian study found no difference in smear grade among screened and PCF groups (Table 3 showing proportions and prevalence ratios).[29] Three European and one Brazilian study reported on smear positivity among culture-confirmed TB patients.[31-33, 35] The proportion with positive smears was lower in those screened in three.[31-33] One study showed no association but small sample sizes gave wide CIs in both study groups.[35] No studies reported on pre-treatment LTFU (Table 4). Symptom duration was shorter in the screened group in two studies (prevalence of diagnosis delay ≥50 days was 23% lower in the screened group in an Indian study,[30] and the median symptom duration was 7.5 weeks in the PCF versus 0.0 weeks in the screened group in a study from the Netherlands[33]). Time to

treatment start in one Indian study[30] found no difference between the screened and PCF groups.

Three studies (including two established CXR screening programmes) reported on treatment outcomes (Table 5 showing proportions and prevalence ratios). The proportions with treatment success among screened and PCF groups was similar, ranging from 80-90% in two.[29, 33] In one Indian study reporting on one-off symptom screening, there was no difference in case fatality among screened and PCF groups.[29] Two studies reporting on ~4-5 years of data from established CXR screening programmes among migrants to the Netherlands and South African miners showed higher case fatality among the PCF group (PCF versus screened odds ratio [OR] 15.3; 95%CI 2.0-118.0; adjusted OR 5.6; 95%CI 2.6-12.2 respectively).[33, 34] There was no difference in the proportion LTFU during TB treatment between screened (range 6-10%) and PCF (range 7-10%) groups.[29, 33]

Two CRTs were identified (Table 2, Table 5 and Appendix 2).[36, 37] One among Indian neonates compared fortnightly ACF over 2 years, in 297 intervention communities to PCF in 295 control communities.[36] Screening was associated with lower all-cause mortality compared to PCF (adjusted OR 0.68 [95%CI 0.47-0.98]), which was attributed to decreases in pneumonia/respiratory infections. The risk of bias was high which could work to underestimate the effect of screening on mortality. A CRT among Vietnamese household contacts of TB patients, compared CXR and symptom screening at 0, 6, 12 and 24 months in 36 intervention communities to PCF in 34 control communities.[37] Screening was associated with lower all-cause mortality compared to PCF (risk ratio 0.60 [95%CI 0.50-0.80]). The risk of bias assessment raised some concerns as the data represented a post-hoc analysis.

Economic review

From 2841 articles, six observational studies were eligible[38-43] (Figure 2 and Table 2); none were included in the previous review. Most were from South Asia (n=4; 67%),[38-41] with one

from South East Asia,[42] and one from sub-Saharan Africa.[43] Most studies included general populations (n=4; 67%);[38-40, 43] three involved house-to-house screening.[38, 39, 43] Risk groups were those with structural risk factors (n=1),[41] household and neighbourhood contacts (n=1),[42] and social contacts (n=1)[39] of TB patients, and health facility attendees (n=2).[39, 40] Four studies (67%) used symptom screening alone,[39-41, 43] whereas two (33%) used CXR and symptoms.[38, 42] The analyses undertaken varied; four performed cost analysis[38, 39, 41, 42] and two conducted cost-effectiveness analysis.[40, 43] All studies reported findings transparently; three[38-40] met all CHEERS checklist criteria (Appendix 4).

Data were summarised using different measures (means, medians). The illness periods for which costs were reported varied; two studies reported diagnosis costs alone,[41, 43] two pre-treatment and treatment costs,[39, 42] one diagnosis and treatment costs,[38] and one pre-diagnosis, diagnosis and treatment costs[40] (Table 2 and 6; Appendix 5). While cost inputs and granularity of reporting varied across studies, all calculated aggregated costs for the reported illness period (Table 6 and Appendix 5). In all studies, higher total costs were incurred in the PCF compared to screened group. Four studies assessed catastrophic cost prevalence, which was higher in the PCF (range 12-61%) compared to screened (range 9-45%) group.[38, 39, 41, 42] In two Indian studies, using house-to-house screening among general populations[38] and those with structural risk factors,[41] total costs and catastrophic costs (on multivariable analysis) were significantly lower in the screened compared to PCF groups. In two studies with small sample sizes, among Cambodian household and neighbourhood contacts of TB patients[42] and among mainly outpatient attendees and social contacts of TB patients in Nepal,[39] there was no statistically significant difference in total costs and catastrophic costs on univariable analysis between screened and PCF groups. Two studies did not assess differences in mean total costs or report catastrophic costs.[40, 43]

Discussion

We synthesised literature published between 1980-2020, to generate up-to-date evidence for the individual effects of TB screening. We found very few studies addressing the review questions. The WHO END-TB strategy sets out ambitious targets to reduce TB death, incidence and catastrophic costs by 2035.[44] At the 2018 United Nations General Assembly high-level meeting, world leaders reaffirmed their commitment to ending TB.[45, 46] At a time of unprecedented political commitment to find, test and treat TB patients, evidence for strategies such as TB screening to inform in-country decision making globally, is vital. Further, the reversal in TB control efforts and case-detection due to the COVID-19 pandemic[47, 48] may going forward, make TB screening even more important.

A general challenge with interpreting the findings is the observational design of most studies. This is compounded by differences in reported outcome measures, insufficient data on the care cascade, unadjusted analyses, small sample sizes, and length-time bias (where screening may detect individuals with less severe indolent disease who may have different characteristics, longer disease course and better outcomes including survival, than those who are identified through PCF). These limitations must be kept in mind when interpreting results. Definitive evidence for the effects of TB screening requires well-conducted RCTs. However, these require large sample sizes, long term follow-up and are resource intensive. We only identified three RCTs, conducted over relatively short time-periods (1-2 years).[28, 36, 37] Therefore, insights from routine programme implementation are essential. While overall screening approaches will depend on the context and available resources, general principles dictate that screening is not one-off, is integrated into health systems, with quality-assured diagnosis and treatment services.[4, 7] We only identified four studies (all in risk groups) reporting on established screening programmes.[32-35] But there was general consistency in most findings, irrespective of the screening strategy used.

TB screening, by engaging individuals earlier into care, should result in earlier diagnosis when disease is less severe.[4] Smear grade and proportion smear positive among culture-confirmed TB patients was lower in the screened group in most studies with larger sample

sizes, suggesting screening does identify individuals with less severe disease. Length-time bias may explain this. But the reported reduction in pre-diagnosis symptom duration among those screened, while subject to recall bias, suggests earlier diagnosis plays a role. If individuals are identified earlier, when disease is less severe, and linked to care, this should translate to better outcomes for the individual.[4]

Studies consistently showed no difference in treatment success between screened and PCF groups. This could be a true finding (screening does not improve treatment success). Or it may be due to potential confounders or the inherent limitations of routine data, where identifying TB patients screened from those self-presenting can be challenging and successful outcomes may be over-ascertained, potentially biasing the effect towards the null. Data on pre-treatment LTFU, while limited and not generalisable, suggests pre-treatment LTFU is high among screened TB patients; in one study, no deaths were reported in the screened group.[23] In the PCF group, there was high pre-treatment case fatality,[23] similar to other reports.[49] Therefore, on-treatment outcomes, which ignore deaths pre-treatment, may underestimate the effects of screening.

Two studies (Churchyard 2000 and Verver 2001) found screening was associated with lower case fatality,[33, 34] but due to their observational nature we cannot exclude length-time bias and uncontrolled confounders. Both report on established CXR screening programmes, with large sample sizes, access to good health systems and better reporting of deaths. While neither study report on pre-treatment LTFU, individuals treated could be more representative of those diagnosed. Churchyard 2000, among miners did not report treatment success by screened and PCF groups.[34] Verver 2001, showed no difference in treatment success,[33] but this study among migrants, had few deaths overall which may reflect a healthy migrant effect, giving better overall outcomes across study groups. Two CRTs (Jenum 2018 in neonates and Fox 2018 in household contacts of TB patients) found screening was associated with lower all-cause mortality,[36, 37] with Fox 2018, showing no difference in on-treatment outcomes (among all TB patients) between study groups.[37] The limitations of

these CRTs (generalisability, post-hoc analysis) need to be borne in mind when interpreting findings. But, in line with these are RCTs comparing different screening strategies in risk groups, showing lower mortality/case fatality among individuals, especially with severe disease, receiving more intensive screening.[50, 51] As all data represent risk groups, findings cannot be extrapolated to general populations.

Pre-treatment LTFU, while likely to be setting-specific, can be frequent with interventions targeting "well" individuals. Programmes should ensure that all individuals diagnosed are linked to treatment, with context-specific barriers to engaging with care identified and mitigated. A CRT in rural Ethiopia where health care access is difficult, compared ECF to ECF plus community-based care (sputum collection, providing treatment and supporting adherence) by community health workers over one year.[52] Treatment success was significantly higher in the latter group, highlighting how combining screening with strategies that minimise pre-treatment LTFU can increase treatment success. Further, if all individuals diagnosed at an earlier stage are not started on treatment, reducing transmission, population-level benefits[4] shown in trials[53, 54] may not be realised.

Due to the limitations of the identified economic studies (e.g. differences in the cost inputs and illness periods; small sample sizes; recall bias; and unadjusted analyses) we cannot directly compare findings between studies. Further, the data are mostly from South Asia, limiting generalisability. Nevertheless, all studies consistently showed lower total costs and catastrophic cost prevalence among those screened. While we did not assess screening costs/cost-effectiveness from a health system perspective, this can be high. When viewed from a societal perspective, there may be potential offsets to these costs. But, given the limitations of the included studies, only cautious conclusions can be drawn. Patient costs are often reported as barriers to accessing TB care.[8, 55-57] Therefore, standardising the collection and reporting of patient cost inputs as part of routine programme monitoring could help identify how interventions affect this patient important outcome, guiding policy making.

These reviews have several limitations. We only searched four databases; the grey literature was not searched. Only English, French and Spanish articles were included. The economic review only included articles from 2010. Therefore, some relevant articles may have been missed. As studies were heterogeneous, we could not meta-analyse the data. We did not assess publication bias.

An important finding was the limited data on individual outcomes, despite many publications on TB screening studies/programmes[58]. Going forward, studies/programmes must prioritise reporting this data, along with the screening cascade. Evaluations should be carefully designed, to identify appropriate control groups and adjust for potential confounders, allowing valid comparisons across diagnosed TB patients in screened and unscreened populations.

In conclusion, we found very limited data on the effect of TB screening on individual outcomes. Routine/research programmes must prioritise collecting and reporting this data.

Contributors

Study design: LT, MR, MAS, LM, TM, RK, AES, JEG, ELC, PM, VB, EK, HMA

Study selection, data extraction and risk of bias assessment: LT, MR, MAS, LM, MH, CD, EK

Drafted manuscript: LT wrote the first draft, with input from HMA

Edited manuscript: LT, MR, MAS, LM, TM, RK, MH, LHC, FN, AES, JEG, CM, ELC, RMB, PM, RJH, VB, CD, EK, HMA

Approved final draft: LT, MR, MAS, LM, TM, RK, MH, LHC, FN, AES, JEG, CM, ELC, RMB, PM, RJH, VB, CD, EK, HMA

Declaration of interests

LT reports WHO consultancy work for the guideline development process and a Clinical Research Training Fellowship from the MRC (Grant Ref: MR/N020618/1).

LHC reports a contract from WHO TB Programme to Jonathan Golub for systematic review of ACF for TB and sub-contract/consulting for JHU for systematic review of ACF for TB.

JEG received a contract provided to Johns Hopkins University to conduct systematic reviews for the WHO's TB screening guidelines; received an NIH grant to conduct TB case finding in India, a second to test for and treat latent TB infection in Brazil; received UNITAID grants to conduct implementation research around latent TB infection in several African countries; and sat on the Scientific Advisory Board for the Aurum Institute in November 2019.

CM is a salaried staff of the WHO and is involved in policy development on TB. CM alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.

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The designations used and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area, or of its authorities, nor concerning the delimitation of its frontiers or boundaries.

Data sharing statement

All data are included within the article and supplementary material.

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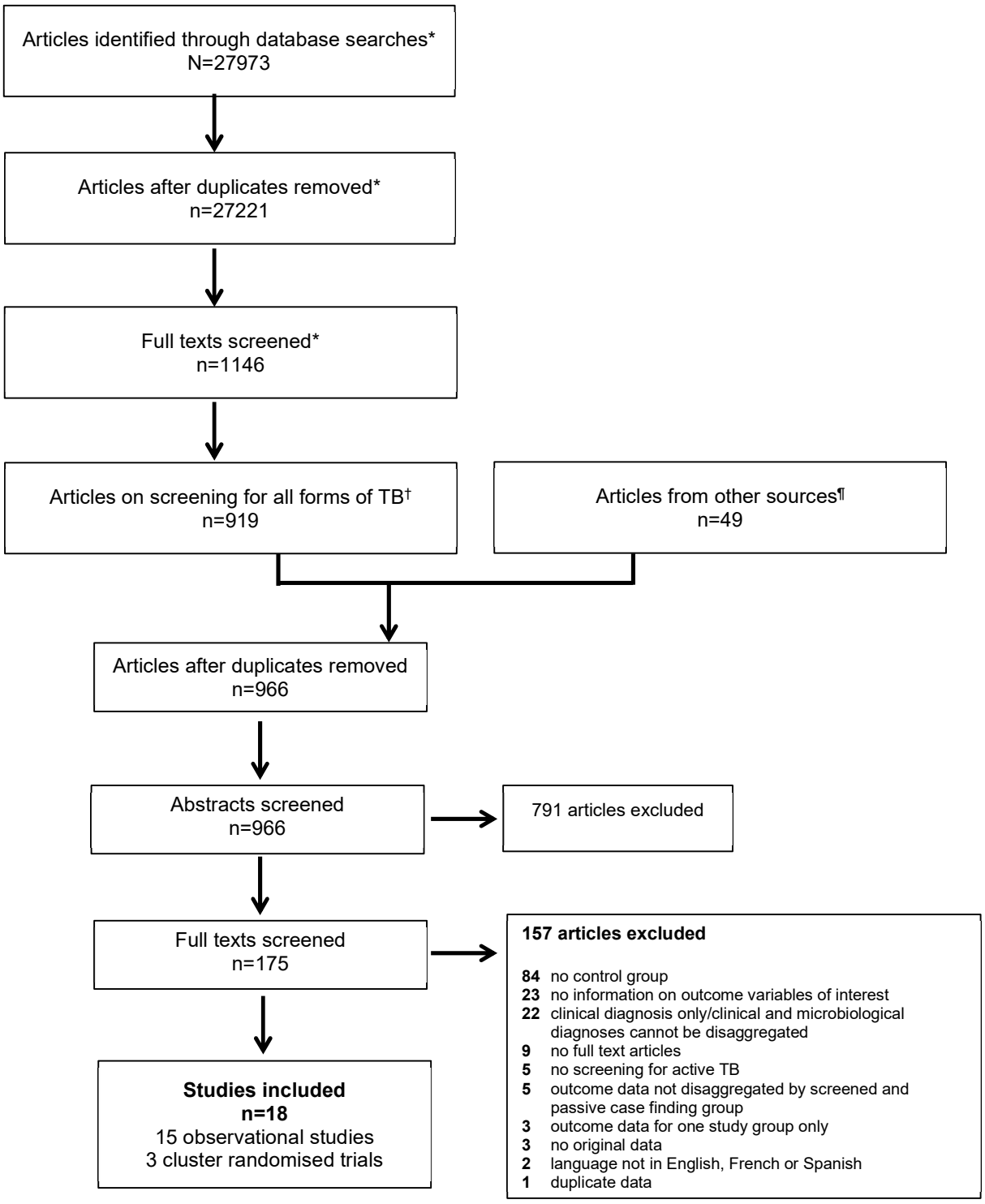
Figure 1: Study selection process - flow diagram of number of original research articles considered for the clinical review



The clinical review was nested within a systematic review to determine the number needed to screen to detect a TB patient in any population. *represents the study selection process for the number needed to screen review.

†The starting point of the clinical review, which is reported in this manuscript

¶previous systematic review by Kranzer et al 2013, authors and bibliography searches

Figure 2: Study selection process - flow diagram of number of original research articles considered for the economic review

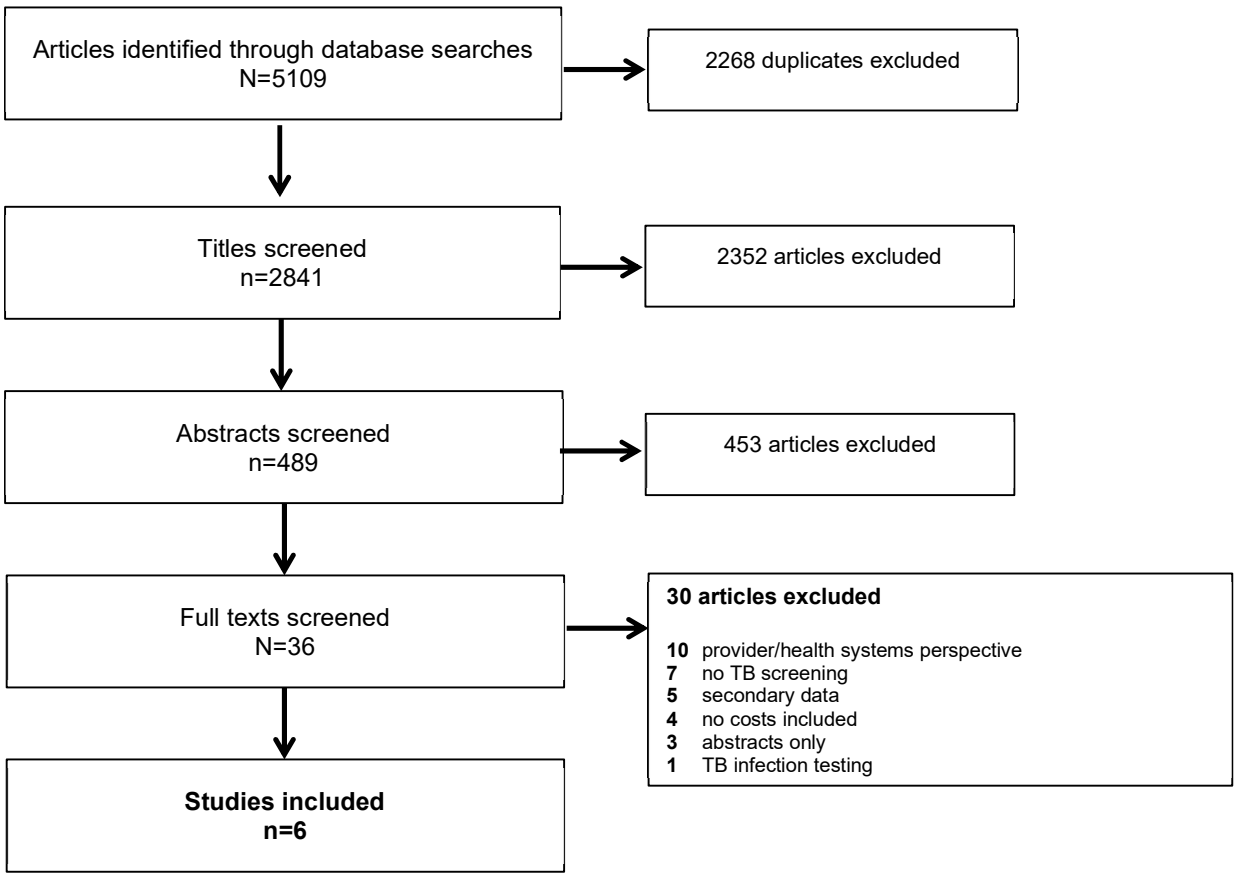


Table 1: Clinical outcomes and patient costs* for the clinical and economic review

Clinical outcomes for clinical review			
Outcome category		**Outcome indicator**	
		Sought	**Identified**
Earlier diagnosis	Disease severity at diagnosis - microbiology	smear positivity among bacteriologically-confirmed TB patients; smear grade; Xpert cycle threshold values; culture grade/colonies; time to culture positivity	smear positivity among bacteriologically-confirmed TB patients; smear grade
	Disease severity at diagnosis - radiology	CXR severity score/grading	-
	Disease severity at diagnosis - anthropometric	body mass index	-
Earlier diagnosis and linkage to care	Time to first contact with health services	duration from start of symptoms to first contact with health services	duration from start of symptoms to first contact with health services
	Time to diagnosis	duration from start of symptoms to diagnosis	duration from start of symptoms to diagnosis
	Time to treatment start	duration from start of symptoms to treatment start; time between diagnosis and treatment start	duration from start of symptoms to treatment start; time between diagnosis and treatment start
	Pre-treatment loss to follow-up	lost to follow-up between diagnosis and treatment start	lost to follow-up between diagnosis and treatment start
Treatment	Treatment outcomes at treatment end	treatment success (cure and completion); lost to follow-up	treatment success (cure and completion); lost to follow-up
	Disease outcome at treatment end - morbidity	body mass index; lung function test results; TB recurrence	-
Deaths	Mortality among screened and unscreened groups	all-cause mortality; TB-specific mortality	all-cause mortality
	Case fatality among diagnosed TB patients	all-cause case fatality; TB-specific case fatality	-
	Case fatality among treated TB patients	all-cause case fatality; TB-specific case fatality	all-cause case fatality; TB-specific case fatality
Patient costs* for economic review			
Outcome category		**Outcome – cost input**	
Pre-diagnosis	Costs before TB diagnosis	Direct medical - consultation/administration fees; drugs (TB, other); hospitalisation; laboratory investigations, radiology investigations, other investigations Direct non-medical costs - transport, food, accommodation, nutritional supplements, childcare Indirect - productivity loss	
Diagnosis	Costs during TB diagnosis		
Pre-treatment	Costs before TB treatment May include pre-diagnosis and diagnosis costs		
Treatment	Costs during TB treatment		
Entire illness period	Costs during the illness period reported in the study		
Catastrophic cost	Prevalence	proportion of total cost for TB care >20% of annual household income	

*costs incurred by TB patients and their households

Table 2: Characteristics of studies included in the clinical review (N=18) and economic review (N=6)

First author and Location	Population	Study years	Screening: strategy and tools	TB case definition	Sample/cohort*		Outcomes *OR* Details of costing studies and costs collected
					Screen	PCF	
Clinical review – general population observational studies							
Abdurrahman 2016 Abuja, Nigeria	Urban including slums	2010-2014	ACF: One off community health worker house-to-house symptom screen. Sputum collected for smear if symptoms.	Smear + Adult ≥18 years	485	209	Smear grade Symptom duration at diagnosis
den Boon 2008 Cape Town, South Africa	2 suburbs	2002-2005	Prevalence survey: sputum smear and culture for all collected at health centres.	Smear or culture + Adult ≥15 years	27	473	Smear grade Treatment outcomes
Shargie 2006 Hadiya zone, Southern Ethiopia	Rural 1 district	2003	Prevalence survey: symptoms and/or on TB treatment. Sputum collected for smear if +.	Smear + Adult ≥15 years	13	24	Symptom duration at treatment start
Gopi 2005 Tiiruvallur South India	Rural and urban 1 sub-district	2001-2003	Prevalence survey: CXR and symptoms. Sputum collected for smear and culture if symptoms or abnormal CXR.	Smear + Adult ≥15 years	243	1049	Pre-treatment loss to follow-up
Balasubramanian 2004; Tiiruvallur South India	Rural and urban 1 sub-district	1998-2001	Prevalence survey: CXR and symptoms. Sputum collected for smear and culture if symptoms or abnormal CXR.	Smear + Adult ≥15 years	231	833	Pre-treatment loss to follow-up
Santha 2003 Tiiruvallur South India	Rural and urban 1 sub-district	1999-2000	Prevalence survey: CXR and symptoms. Sputum collected for smear and culture if symptoms or abnormal CXR.	Smear +	96	330	Smear grade Symptom duration at first contact with health services Treatment outcomes
Harper 1996 East Nepal	Rural 8 districts	1990-1993	Likely ECF (unclear): outreach TB camps (diagnostic services) lasting 2-4 days with pre-camp publicity in areas away from health posts, with high TB burden or where community requested services. If symptomatic sputum collected at camps. 45 camps over 3 years.	Smear + New TB	68	1306	Treatment outcomes
Cassels1982 East Nepal	Rural 1 district	1978-1980	ACF: one-off house-to-house symptom screen by vaccinators. Pots left for sputum collection if symptoms, with drop-off at designated centres within 20 minutes walking distance.	Smear +	111	159	Treatment outcomes
Clinical review – general population cluster randomised trials							
Shargie 2006 Hadiya Zone Southern Ethiopia	Rural 2 districts	2003-2004	ECF: x1/month for 12 months IEC activities by community promoters¶ encouraging those with symptoms to attend monthly diagnostic outreach clinic where sputum collected for smear.	Smear +	159	221	Treatment outcomes
Clinical review – risk groups observational studies							
Shewade 2019ʃ 18 districts in 7 states across India	Marginalised/ vulnerable populations‡	2016-2017	ACF: one-off community volunteer house-to-house symptom screen. Referral for sputum smear if symptoms.	Smear + Adult ≥15 years	275	297	Smear grade Treatment outcomes
Shewade 2019ʃ	Marginalised/	2016-2017	ACF: one-off community volunteer house-to-house symptom screen. Referral for sputum smear if symptoms.	Smear + Adult ≥15 years	234	231	Duration of symptoms to 1) first contact with health services; 2) diagnosis

First author and Location	Population	Study years	Screening: strategy and tools	TB case definition	Sample/cohort*		Outcomes *OR* Details of costing studies and costs collected
					Screen	PCF	
18 districts in 7 states across India	vulnerable populations[Ŧ]						Time between diagnosis and treatment start Time between symptoms and treatment start
Paiao 2016 Mato Grosso do Sul state, Brazil	Prisoners in 12 prisons	2013-2014	ACF: x2 symptom screen (at baseline and 1 year later). Sputum collected if symptoms.	Culture + Adult ≥18 years	40	53	Smear positivity of culture confirmed TB patients
Story 2012 London, UK	Homeless people, drug users, asylum seekers, prisoners	2005-2010	ACF: mobile CXR screening programme. Screening in community settings where hard to reach people can be accessed (e.g. hostels, day centres, drug treatment services, prisons).	Culture + Age >15 years	23	146	Smear positivity of culture confirmed TB patients
Verver 2001 Netherlands	Migrants	1993-1998	ACF: entry and every 6 months for 2 years CXR screening programme. Sputum for smear and culture if abnormal CXR.	Smear or culture + Stay <30 months	454	368	Smear positivity of culture confirmed TB patients Symptom duration at diagnosis Treatment outcomes
Churchyard 2000 Free State, South Africa	Miners in 1 company	1993-1997	ACF: annual miniature CXR screening programme. Standard CXR and sputum for smear and culture if abnormal.	Culture + Known HIV status and treatment outcome	1225	1011	Treatment outcomes
Capewell 1986 Edinburgh, UK	Hostel dwellers	1976-1982	ACF: x2/year miniature CXR screening programme, with monetary incentive. Referred to clinic if abnormal CXR.	Culture +	42	26	Smear positivity of culture confirmed TB patients
Clinical review – risk groups cluster randomised trials							
Jenum 2018 Palamaner in Andhra Pradesh, South India	Neonates receiving BCG by 72 hours of birth	2006-2010	ACF: x2/month for 2 years, home visits with screens for symptoms, TB exposure and failure to thrive. Referral with reminders to study medical ward for work up if +.	n/a	2215[†]	2167[†]	Mortality – all cause
Fox 2018, 70 districts in 8 provinces of Vietnam	Household contacts in rural and urban areas	2010-2015	ACF: CXR and symptom screen at 0, 6, 12 and 24 months by National TB programme staff at district clinics. Sputum for smear and culture if symptoms or abnormal CXR	n/a	10069[†]	15638[†]	Mortality – all cause
Economic review							
Muniyandi 2020 India	General population (rural)	2016-2018	Prevalence survey: house-to house screening with symptoms and CXR. Sputum for smear and culture if symptoms or abnormal CXR.	Adult ≥15 years with TB	110	226	Empirical; CA from patient perspective; Primary costing data; 2018 cost reference year Diagnosis costs - *Direct (medical and non-medical); Indirect* – no input information Treatment costs - *Direct (medical and non-medical); indirect* – no input information
Gurung 2019 Nepal	OPD attendees; social contacts of TB patients; general	2018	ACF: Symptom screen in OPD; symptom screen social contacts; general population TB camp with community health worker house-to-house symptom screen 1-2 days before. Sputum for Xpert if symptoms.	Adult ≥15 years with PTB between 2-12 weeks of treatment	50	49	Empirical; CA from patient perspective; Primary costing data; 2018 cost reference year Pre-treatment costs: *Direct medical* – consultation, x-ray, lab tests, drugs, other; *Direct non-medical* – transport, food; *Indirect* – time loss, income loss

First author and Location	Population	Study years	Screening: strategy and tools	TB case definition	Sample/cohort*		Outcomes *OR* Details of costing studies and costs collected
					Screen	PCF	
	population (rural);						intensive phase treatment costs: *Direct medical* – consultation, x-ray, drugs; *Direct non-medical* – transport, food; *Indirect* – time loss, income loss
Hussain 2019 Pakistan	Private clinic attendees; general population (urban)	2011-2012	ACF: HCW incentives; symptom screen clinic attendees; ECF: TB IEC to general population. Sputum for smear/Xpert and CXR if symptoms.	TB patients on treatment for at least 2 months	84	45	Decision modelling; CEA from provider and patient perspective; Primary and secondary costing data; 2012 cost reference year Pre-diagnosis costs: *Direct medical* – consultation, tests, drugs; *Direct non-medical* – food and transport Diagnosis costs: *Direct medical* – consultation, tests, drugs; *Direct non-medical* – food and transport Treatment costs: *Direct medical* – consultation, tests, drugs; *Direct non-medical* – food and transport Indirect costs – lost earnings
Shewade 2018 India	Marginalised and vulnerable populations[ŦŦ]	2016-2017	ACF: one-off community volunteer house-to house symptom screen. Referral for sputum smear if symptoms.	Smear + Adult ≥15 years newly registered for treatment	234	231	Empirical; CA from patient perspective; Primary costing data; 2018 cost reference year Diagnosis costs: *Direct medical* – consultation, drugs, tests; *Direct non-medical* – travel; *Indirect* – wages/income lost
Morishita 2016 Cambodia	Household and neighbourhood contacts of smear + TB patients	2014	ACF: all household and symptomatic neighbourhood contacts invited for CXR screening on a specific date. Sputum for Xpert if abnormal CXR or symptoms.	New PTB with cured or completed treatment outcome	108	100	Empirical; CA from patient perspective; Primary costing data; 2014 cost reference year Pre-treatment costs: *Direct medical* – administration, tests, x-ray, drugs, hospitalisation; *Direct non-medical* – transport, food, guardian, insurance reimbursement; *Indirect* – lost income from health seeking and sick leave Treatment costs: *Direct medical* –hospitalisation; *Direct non-medical* – transport (DOTS, drug pick-up, follow-up visits), supplemental food, guardian/care giver, interest for borrowed money, insurance re-imbursement; *Indirect* – lost income (patient, guardian/care giver), reduced household activity, value lost from sold property
Sekandi 2015 Uganda	General population (urban)	2012	Prevalence survey: house-to-house symptom screen. Sputum collection if symptoms for smear/culture.	Adult ≥15 years on at least 2 weeks of TB treatment	103		Decision modelling; CEA from societal perspective; Primary and secondary costing data; 2013 cost reference year Diagnosis costs: *Direct non-medical* - transportation, food, care giver, child care/hired help; *Indirect* – patient and care giver time lost

*number of people with TB unless otherwise indicated; PCF=passive case-finding; ACF=active case-finding; + = positive; CXR=chest radiograph; ECF=enhanced case finding; IEC=information, education and communication; ¶community-promoters - individuals with previous experience in community outreach activities who are provided training about TB); [Ŧ]includes 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; [J]Papers report different outcomes on the same study participants; BCG=Bacillus Calmette–Guérin; n/a=not applicable; [†]total number in screened and passive case-finding group; CA=cost analysis; OPD=outpatient department; PTB=pulmonary TB; x-ray=radiography; HCW=health care worker; CEA=cost effectiveness analysis; DOTS=Directly Observed Treatment, Short-course

Table 3: Smear grade 3+ and smear positivity among culture confirmed TB patients reported in n=8 observational studies

First author, country and population, screening tool	Group	Smear grade 3+ / all smear positives		Smear + / culture confirmed		Prevalence ratio (screen/PCF)	Comments
		n/N*	% (95%CI)	n/N**	% (95%CI)		
General population							
Abdurrahman 2016 Nigeria Symptoms	Screen	101/480	21% (17-25%)	-	-	0.46	Diagnosed TB patients Screened vs PCF - screened group more likely to be older, married and less likely to be HIV infected.
	PCF	96/208	46% (39-53%)	-	-		
den Boon 2008 South Africa Smear & culture	Screen	6/18	33% (13-59%)	-	-	0.63	Denominator for smear grade - screened group includes those lost to follow-up pre-treatment; PCF those starting treatment only Diagnosed in screened and on treatment in PCF groups - no difference in age and gender.
	PCF	234/446	52% (48-57%)	-	-		
Santha 2003 India CXR and symptoms	Screen	3/96	3% (1-9%)	-	-	0.07	Denominator for smear grade - screened group includes those lost to follow-up pre-treatment; PCF those starting treatment only All (smear +ve and -ve) diagnosed in screened and on treatment in PCF groups - screened group more likely to be older, male, illiterate, sole earner, have poor quality house and a 1 room house
	PCF	139/330	42% (37-48%)	-	-		
Risk groups							
Shewade 2019 India: Marginalised/vulnerable† Symptoms	Screen	39/233	17% (12-22%)	-	-	0.84	On treatment TB patients Screened vs PCF- screened group more likely to be older, from rural areas and live further from microscopy units.
	PCF	53/265	20% (15-25%)	-	-		
Paiao 2016 Brazil: Prisoners Symptoms	Screen	-	-	4/40	10% (3-24%)	0.20	Diagnosed TB patients
	PCF	-	-	27/53	51% (37-65%)		
Story 2012 UK: Homeless people, drug users, prisoners, asylum seekers CXR	Screen	-	-	11/23	48% (27-69%)	0.67	On treatment TB patients Association between screening and smear positivity maintained after adjusting for age and gender
	PCF	-	-	104/146	71% (63-78%)		
Verver 2001 Netherlands: Migrants CXR	Screen	-	-	60/159	38% (30-46%)	0.68	On treatment TB patients Screened vs PCF - screen detection varied by country of origin, decreased with increasing length of stay and was less likely among illegal migrants.
	PCF	-	-	59/107	55% (45-65%)		
	Screen			11/16	69% (41-89%)	0.87	On treatment TB patients

Capewell 1986 UK: Hostel dwellers CXR	PCF			15/19	79% (54-94%)		

*n/N=number with smear grade 3+/total number with smear grade scanty, 1+, 2+ and 3+; **n/N=number smear positive/total number culture positive; 95%CI = 95% confidence interval; PCF=passive case-finding; †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; CXR=chest radiograph;

Table 4. Pre-treatment LTFU, time from symptoms to first contact with health services, diagnosis and treatment start reported in n=7 observational studies

First author, Population	Screening tools TB case definition	Outcomes						Comments
General population								
Pre-treatment LTFU				N	n	%	95%CI	
Gopi 2005 India	CXR and symptoms Smear +ve	-	Screened	243	57	23	18-29	Screened group – no deaths. Reasons for defaulting included not interested in initiating treatment, symptoms too mild, too sick/old and work-related problems. PCF group – 19% died from among those for whom a default reason was known.
			PCF	1049	156	15	13-17	
Balasubramanian 2004 India	CXR and symptoms Smear +ve	-	Screened	231	68	29	24-36	
			PCF	833	120	14	12-17	
Time to first contact with health services				N	n	%	p-value	
Santha, 2003 India	CXR and symptoms Smear +ve	Cough <3 weeks	Screened	96	27	28	<0.001	Baseline characteristics of all (smear +ve and -ve) diagnosed in screened and on treatment in PCF groups - screened group more likely to be older, male, illiterate, sole earner, have poor quality house, 1 room house, lower smear grade and new smear -ve disease.
			PCF	272	35	13		
Time to diagnosis				N	Mean	SD	p-value	
Abdurrahman 2016[Δ] Nigeria	Symptoms Smear +ve	Cough duration in weeks	Screened	485	10.3	2.4	<0.001	Baseline characteristics of diagnosed TB patients (screened vs PCF) - screened group more likely to be older, married and less likely to be HIV infected.
			PCF	209	6.8	2.6		
Time to treatment				N	n	%	p-value	
Shargie, 2006 Ethiopia	Symptoms or on TB treatment Smear +ve	Symptom ≤90 days	Screened	13	6	46	1	Baseline characteristics of on treatment TB patients (screened vs PCF) - screened group younger and a higher proportion were women
			PCF	24	10	42		
Risk groups								
Time to diagnosis				N	Median	IQR	p-value	
Shewade, 2019 India	Symptoms Smear +ve	Patient-level diagnosis delay from sputum eligible[†] (days)	Screened	225	12	3-31	0.999	Baseline characteristics of on treatment TB patients (screened vs PCF)- screened group more likely to be older, from rural areas, less educated and live further from microscopy units.
			PCF	230	10	3-43		

Marginalised/ vulnerable populations*		Health system diagnosis delay[ŦŦ] (days)	Screened	229	5	0-61	0.008	Adjusted analysis showed no association between patient-level delay and case-finding, but showed reduction in total diagnosis delay among those screened (screened versus PCF linear regression of log transformed delay in days after adjusting for confounders and clustering beta coefficient -0.31; 95%CI -0.62 to 0.00; p=0.052; screened versus PCF adjusted prevalence ratio for delay ≥50 days 0.77; 95%CI 0.63-0.94; p=0.009)
			PCF	229	19	1-76		
		Total diagnosis delay[¶] (days)	Screened	229	45	18-106	0.131	
			PCF	230	61	20-121		
Verver, 2001 Netherlands Migrants	CXR Smear or culture +ve	Symptom duration in weeks among those reporting symptoms	Screened	142	0.0	-	<0.001[ʃ]	Baseline characteristics of on treatment TB patients (screened vs PCF) - screen detection varied by country of origin, decreased with increasing length of stay and was less likely among illegal migrants.
			PCF	332	7.5	-		
Time to treatment				N	Median	IQR	p-value	
Shewade, 2019 India Marginalised/ vulnerable populations*	Symptoms Smear +ve	Total treatment delay from sputum eligible[ï] (days)	Screened	227	52	22-112	0.37	Baseline characteristics of on treatment TB patients (screened vs PCF)- screened group more likely to be older, from rural areas, less educated and live further from microscopy units. Adjusted analysis showed no association with case-finding (screened versus PCF linear regression of log transformed delay in days after adjusting for confounders and clustering beta coefficient -0.20; 95%CI -0.50 to 0.10; p=0.181).
			PCF	229	62	23-128		

LTFU=loss to follow-up; pre-treatment LTFU=default between diagnosis and treatment start; N=total number of people with TB; n=number with outcomes; %=proportion; 95%CI=95% confidence interval; CXR=chest radiograph; +ve=positive; PCF=passive case-finding; -ve=negative; IQR=interquartile range; SD=standard deviation; ∆Other symptom (fever, weight loss, chest pain and anorexia) durations to diagnosis were assessed, only weight loss was significantly higher in the screened population compared to passively found TB patients;*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; †patient diagnosis delay=from sputum eligible (15th day of continuous cough/fever or day of the first episode of haemoptysis) to first visit to health care provider; ŦŦhealth system diagnosis delay=from first visit to health care provider to date of diagnosis; ¶total diagnosis delay=from eligible for sputum examination to diagnosis; ʃsimilar difference observed when results were restricted to n=99 with smear positive disease; ïtotal treatment delay= from sputum eligible (15th day of continuous cough/fever or day of the first episode of haemoptysis) to treatment start;

Table 5: On-treatment outcomes (treatment success, case fatality and default on-treatment) among smear, Xpert and/or culture positive TB patients reported in n=7 observational studies and n=1 CRT, and, all-cause mortality reported in n=2 CRT

Observational studies												
First author, country and population, screening tool	**Group**	**Treatment success**		**PR**	**Case fatality**		**PR**	**LTFU on treatment**		**Pre-treatment LTFU***		**Comments**
		n/N	**% (95%CI)**		**n/N**	**% (95%CI)**		**n/N**	**% (95%CI)**	**n/N[ʃ]**	**(%)**	
General population												
den Boon 2008 South Africa smear & culture	Screen	16/20	80% (56-94%)	1.00	2/27	7% (1-24%)	1.95	-	-	7/27	26%	Denominator for case fatality - screened group includes those LTFU pre-treatment; PCF those starting treatment only. Baseline characteristics of diagnosed in screened and on treatment in PCF groups - no difference in age, gender, smear grade between groups.
	PCF	379/473	80% (76-84%)		18/473	4% (2-6%)		-	-	-	-	
Santha 2003 India CXR and symptoms	Screen	45/65	69% (57-80%)	1.01	4/65	6% (2-15%)	0.88	13/65	20% (11-32%)	31/96	32%	Baseline characteristics of all (smear +ve and -ve) diagnosed in screened and on treatment in PCF groups - screened group more likely to be older, male, illiterate, sole earner, have poor quality house, 1 room house, lower smear grade and new smear -ve disease.
	PCF	225/330	68% (63-73%)		23/330	7% (4-10%)		63/330	19% (15-24%)	-	-	
Harper 1996 Nepal Symptoms	Screen	50/64	78% (66-87%)	1.00	5/64	8% (3-17%)	0.96	4/64	6% (2-15%)	-	-	Baseline characteristics of diagnosed TB patients (screened vs PCF) – screened more likely to be female (and age among women tended to be older).
	PCF	997/1272	78% (76-81%)		104/1272	8% (7-10%)		96/1272	8% (6-9%)	-	-	
Cassel 1982 Nepal Symptoms	Screen	-	-		9/111	8% (4-15%)	0.76	-	-	11/111	10%	Denominator for case fatality - screened group includes those LTFU pre-treatment; PCF group are those starting treatment. Baseline characteristics of diagnosed TB patients (screened vs PCF) – screened group were older and the male to female ratio was lower.
	PCF	-	-		17/159	11% (6-17%)		-	-	-	-	
Risk groups												
Shewade 2019 India; Marginalised and vulnerable[†] Symptoms	Screen	247/274	90% (86-93%)	1.03	7/274	3% (1-5%)	0.69	16/274	6% (3-9%)	-	-	Baseline characteristics of on treatment TB patients (screened vs PCF)- screened group more likely to be older, from rural areas and live further from microscopy units. No association between screening and treatment success after adjusting for age, gender and distance from microscopy unit.
	PCF	260/296	88% (83-91%)		11/296	4% (2-7%)		22/296	7% (5-11%)	-	-	
Verver 2001 Netherlands: Migrants CXR	Screen	384/454	85% (81-88%)	1.06	1/454	0.2% (0-1%)	0.07	47/454	10% (8-14%)	-	-	Baseline characteristics of on treatment TB patients (screened vs PCF) - screen detection varied by country of origin, decreased with increasing length of stay and was less likely among illegal migrants.
	PCF	293/368	80% (75-84%)		12/368	3% (2-6%)		36/368	10% (7-13%)	-	-	

Churchyard 2000 South Africa: Miners CXR	Screen	-	-		12/1225	1% (0.5-2%)	0.14	-	-	-	-	Baseline characteristics of on treatment TB patients (screened vs PCF) - screened less likely to be HIV infected. After adjusting for HIV status, sputum status, treatment category, age, disease extent on CXR, silicosis and drug resistance, association between PCF and case fatality maintained (PCF versus screened aOR 5.6; 95%CI 2.6-12.2)
	PCF	-	-		69/1011	7% (5-9%)		-	-	-	-	

Cluster randomised controlled trials			
First author, country and population, screening tool	**Community, number and baseline data**	**Results**	
General population			
Shargie 2006[Δ] Ethiopia: Symptoms	87 contiguous administrative units clustered into 32 communities 32 communities randomised – 12 to screening and 20 to PCF N[Ŧ] smear +ve TB patients - screen=159; PCF=221 Follow-up during treatment Communities and TB patients - similar baseline characteristics between groups	Treatment success: screen vs PCF	n=128 (81%) vs n=165 (75%); difference (95%CI) 6 (-4 to 15); p=0.12
		Death: screen vs PCF	n=5 (3.1%) vs n=7 (3.2%); difference (95%CI) -0.1 (-4 to 4); p=0.49
		LTFU on treatment: screen vs PCF	n=26 (16%) vs n=48 (22%); difference (95%CI) -6 (-14 to 3); p=0.11
Risk groups			
Jenum 2018 India: neonates Symptoms	Cluster – villages or subsection of towns 592 clusters randomised (8 strata) – 297 to screening and 295 to PCF N[Ŧ] in each group - screen=2215; PCF=2167 Follow-up 2 years Study groups – PCF group had more Hindus, lower paternal literacy and higher use of wood/agricultural residues for fuel. No difference in other characteristics	All-cause mortality: screen vs PCF	n=49 (2.2%) vs n=71 (3.3%); aOR[¶] (95%CI) 0.68 (0.47-0.98)
		Cause of death: screen vs PCF	Reduction in deaths due to pneumonia/respiratory infections (aOR[ɣ] 0.34; 95%CI 0.14-0.80).
		LTFU: screen vs PCF	n=38 (1.7%) vs n=60 (2.8%); aOR[¶] (95%CI) 0.62 (0.41-0.94)
Fox 2018 Vietnam: household contacts CXR and symptoms	70 of 112 districts in 8 Vietnamese provinces selected with probability proportional to population. 70 districts randomised – 36 to screened and 34 to PCF N[Ŧ] in each group - screen=10,069; PCF=15,638 Follow-up 2 years Study groups – PCF group household size higher and lower proportion reported prior history of TB.	All-cause mortality: screen vs PCF	n=60 (0.6%) vs 265 (1.7%); RR (95%CI) 0.60 (0.50-0.80)

CRT=cluster randomised controlled trial; PR=prevalence ratio (screened/passive case finding population); LTFU=loss to follow-up; *pre-treatment LTFU =lost to follow-up between diagnosis and treatment start; n/N=number with outcome/total number *started on TB treatment* (unless otherwise indicated); 95%CI = 95% confidence interval; [ƒ]n/N=number lost to follow-up pre-treatment/total number diagnosed with TB; [†]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; PCF=passive case-finding; CXR=chest radiographs; +ve=positive; -ve=negative; aOR=adjusted odds ratio; ŦDenominator in each study group; ¶adjusted for clustering, gender, religion, father's education and fuel type used; [ɣ]adjusted for clustering, gender, religion and father's education; RR=relative risk; ΔData not shown in table - weighted mean of median pre-treatment symptom duration 89 days in screened vs 136 days in control group (difference [95%CI] -47 [-76 to -19]; p=0.001)

Table 6: Costs for the entirety of the illness period and the prevalence of catastrophic costs from n=6 studies reporting on patient costs*

First author, population and screening method, illness period and costs reported		Combined cost for the illness period (US$)			Catastrophic cost prevalence			Comments
		Screen	PCF	p-value	Screen	PCF	p-value	
Muniyandi (2020); India General population; symptoms and CXR screen Diagnosis and treatment Direct (medical and non-medical) and indirect costs	Mean (SEM)	69 (18)	227 (20)	0.001	9%	29%	-	Screened group more likely to be older, illiterate, smoke and report no symptoms. No data on bacteriological status. On adjusted analysis catastrophic costs were significantly higher among the PCF group (aOR 3.68; 95%CI 1.62-8.33)
Gurung (2019); Nepal OPD attendees, social contacts of people with TB, general population TB camps; symptom screen Pre-treatment (from symptom start) and intensive treatment phase Direct (medical and non-medical) and indirect costs	Median (IQR)	253 (81–453)	315 (126–544)	0.16	45%	61%	0.14	60% OPD; 34% social contacts; 6% camps No difference in socio-demographic, disease and health seeking characteristics between groups. PCF group interviewed >1 month after treatment start (~70%) reported lower costs than those interviewed within 1 month. No difference seen with screened group.
Shewade (2018); India Marginalised/vulnerable populations**; symptom screen From sputum eligible¶ to diagnosis Direct (medical and non-medical) and indirect costs	Median (IQR)	5 (0-40)	20 (4-69)	<0.001	10%	12%	-	Screened group more likely to be older, from rural residence, have no formal education, have lower median monthly income and not report weight loss. No significant difference in smear grade, weight in Kg, haemoptysis or fever between screened and PCF group On adjusted analysis catastrophic costs were significantly lower among the screened group (aPR 0.68; 95%CI 0.69-0.97)
Morishita (2016); Cambodia HH and neighbourhood contacts; CXR screen Pre-treatment and during 6 months of treatment Direct (medical and non-medical) and indirect costs	Median (IQR)	241 (66–595)	290 (114–813)	0.10	36%	45%	0.24	No difference in socio-demographic characteristics. PCF group more likely to be smear/Xpert positive and live near health centres. No other clinical data provided
Hussain (2019); Pakistan HCW - incentives; clinic attendees – symptom screen; general population – TB IEC Pre-diagnosis, diagnosis and treatment phase Direct (medical, non-medical) and indirect costs	Mean†	59	71	NR	NR			52% smear negative in screened group and 42% smear negative in PCF group

Sekandi (2015); Uganda General population; symptom screen Diagnosis Direct (non-medical) and indirect costs	Mean (range)	5 (2–7)	29 (14–43)	NR	NR	

*All values (costs and proportions) rounded to the nearest whole number; PCF=passive case-finding; CXR=chest radiograph; SEM=standard error of the mean; aOR=adjusted odds ratio; 95%CI=95% confidence interval; OPD=outpatient department; IQR=interquartile range; **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; ¶from 15th day of continuous cough, fever or the day of the 1st episode of haemoptysis; aPR=adjusted prevalence ratio; HH=household; HCWs=health care workers; IEC=information, education and communication; †no measure of spread reported; NR=not reported

Appendix 1 Search terms

Search terms in EMBASE for each review are shown below. These were adapted for Pubmed/Medline, Scopus and the Cochrane Library

Clinical review

1	'tuberculosis'/exp OR 'lung tuberculosis'/exp
2	('tuberculosis' OR 'Pulmonary Consumption' OR 'Consumption, Pulmonary' OR Phthisis OR 'Tuberculoses' OR "MDR-TB" OR "XDR-TB" OR "MDR TB" OR "XDR TB"):ab,ti,kw
3	1 OR 2
4	'tuberculosis control'/exp OR 'case finding'/exp OR 'mass radiography'/exp OR 'mass screening'/exp OR 'contact examination'/exp OR 'screening'/exp
5	('Mass Chest X Ray' OR 'Mass Chest X-Rays' OR 'Screenings' OR 'screening' OR 'Cross-Sectional Studies' OR 'Case-detection' OR 'case finding' OR 'contact tracing' OR 'mass radiography' OR 'contact examination' OR 'health survey' OR 'cross-sectional' OR 'prevalence survey' OR 'prevalence studies'):ab,ti,kw
6	4 OR 5
7	3 AND 6
8	'animal'/exp NOT ('animal'/exp AND 'human'/exp)
9	7 NOT 8
10	[1-11-2010]/sd
11	9 AND 10

Economic review

1	exp screening/
2	exp case finding/
3	exp mass radiography/
4	exp tuberculosis control/
5	exp contact examination/
6	(screen* or case-find* or case-detect* or (active* adj3 case*) or (enhance* adj3 case*) or (intensi* adj3 case*) or (active* adj3 find*) or (enhance* adj3 find*) or (intensi* adj3 find*) or ACF or ECF or ICF).mp
7	or/1-6
8	exp tuberculosis/ or exp lung tuberculosis/
9	(tb or tuberculo*).mp
10	8 or 9
11	health economics/
12	medical fee/
13	exp economic evaluation/
14	exp "health care cost"/
15	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
16	(expenditure$ not energy).ti,ab.
17	(value adj2 money).ti,ab.
18	budget$.ti,ab.
19	financ*.ti,ab.
20	(expense or expensive).ti,ab.
21	(pay or payment or payments or paid or paying).ti,ab.
22	(attention adj3 (pay or paid or paying)).ab.
23	21 not 22
24	((spend or spending or spent) not ((spend or spending or spent) adj3 (time or hours))).ti,ab.
25	exp employment status/
26	job security/
27	unemploy*.ti,ab.
28	((employ* or job or work*) adj1 (loss or lost or lose)).ti,ab.
29	((employ* or job or work*) adj1 security).ti,ab.
30	redundan*.ti,ab.
31	((productivity or productive) adj2 (loss or lost or lose)).ti,ab.
32	quality adjusted life year/
33	life years.ti,ab.
34	or/11-20,23-33
35	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
36	Animal experiment/ not (human experiment/ or human/)
37	35 or 36
38	7 and 10 and 34
39	38 not 37
40	limit 39 to yr="2010-2020"
41	limit 40 to (english or french or spanish)
42	remove duplicates from 41

Appendix 2: Risk of bias assessment for studies identified in the clinical review

Section I. Risk of bias of observational studies reporting on smear grade or smear positivity among culture confirmed people with TB

Study	Shewade 2019	Abdurrahman 2016	den Boon 2008	Santha 2003	Paiao 2016	Story 2012	Verver 2001	Capewell 1986
Outcome	**Smear grade**				**Smear positivity among culture confirmed people with TB**			
Study Design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional data from cohort study	Cross-sectional	Cross-sectional	Cross-sectional
Participant selection: sample taking part similar to those not taking part / appropriate eligibility criteria	Unclear	Probably No	Probably No	Unclear	Probably Yes	Probably Yes	No	Unclear
Exposure ascertainment: objective data source	Yes	Yes	Yes	Probably Yes	Probably Yes	Probably No	Probably Yes	Unclear
Outcome data source	Treatment registers	Laboratory data from research	PCF: treatment register; screened: unclear	Treatment cards	Research records and clinical records/National notification data	National notification data	Anonymous database held by KNCV	Notification data
Outcome ascertainment: objective data source	Probably Yes	Yes	Unclear	Probably Yes	Probably Yes	Probably Yes	Probably Yes	Probably Yes
Analysis: adequate control for confounders	No	No	No	No	No	Probably No*	No	No

PCF=passive case-finding; KNCV=Dutch tuberculosis foundation; *undertook and adjusted analysis but residual confounding is possible

Section II. Observational studies reporting on treatment outcomes and case fatality

Study	Shewade 2019	den Boon 2008	Santha 2003	Verver 2001	Churchyard 2000	Harper 1996	Cassels 1982
Study Design	Cross-sectional	Cross- sectional	Cross -sectional	Cross -sectional	Cross-sectional data from cohort study	Cross-sectional	Cross-sectional
Participant selection: sample taking part similar to those not taking part / appropriate eligibility criteria	Unclear	Probably No	Unclear	No	Unclear	Unclear	Probably Yes
Exposure ascertainment: objective data source	Yes	Yes	Probably Yes	Probably Yes	Unclear	Unclear	Unclear
Outcome data source	Treatment registers	PCF: treatment register; screened: not specified	Treatment cards	Anonymous database held by KNCV	Limited autopsy and clinical records	Clinical records	Likely mix of clinical records and follow-up but not specified
Outcome ascertainment: objective data source	Probably Yes	Unclear	Probably Yes	Probably Yes	Probably Yes	Probably Yes	Unclear
Analysis: adequate control for confounders	Probable No*	No	No	No	Probably No*	No	No

PCF=passive case-finding; KNCV=Dutch tuberculosis foundation; *undertook an adjusted analysis but residual confounding is possible

Section III. Observational studies reporting on pre-treatment loss to follow-up and time to first contact with health services, diagnosis and treatment start

Item	Gopi 2005	Balasumbramanian 2004	Santha 2003	Shewade 2019	Abdurrahman 2016	Verver 2001	Shargie 2006
Study Design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Participant selection: sample taking part similar to those not taking part / appropriate eligibility criteria	Probably Yes	Unclear	Unclear	Probably No	Probably No	No	Probably No
Exposure ascertainment: objective data source	Unclear	Unclear	Probably Yes	Yes	Yes	Probably Yes	Yes
Outcome data source	Insufficient information	Insufficient information	Self-report	Self-report and clinical records	Self-report	Self-report	Self-report
Outcome ascertainment: objective data source	Unclear	Unclear	No	Probably No	No	No	No
Analysis: adequate control for confounders	No	No	No	Probably No*	No	No	No

*undertook an adjusted analysis but residual confounding is possible

Section IV: Cluster randomised controlled trials reporting on treatment outcomes and mortality (risk of bias assessed using the Cochrane Risk of Bias assessment tool 2.0)

	Study		
	Shargie 2006	**Jenum 2018**	**Fox 2018**
Outcome assessed	Treatment success Case fatality	All-cause mortality	All-cause mortality
Risk of bias domains			
Bias arising from the randomisation process	Some concerns	Low	Low
Bias arising from the timing of identification and recruitment of individual participants in relation to the timing of randomisation	Low	Low	Low
Bias due to deviation from the intended interventions	Low	Low	Low
Bias due to missing outcome data	Low	High	Low
Bias in measurement of the outcome	Low	Low	Low
Bias in the selection of the reported results	Low	Low	Some concerns
Risk of bias judgement	**Some concern**	**High**	**Some concern**
Comments	Insufficient information to assess one bias domain	Bias due to missing outcome data may have underestimated deaths, with proportionally less deaths reported among the passive case-finding group. Therefore the effect of screening on mortality could be a minimum estimate	All-cause mortality was a post-hoc analysis

Appendix 3: Smear grade 3+ and 2+ among all smear positive TB patients in n=3 general-population observational studies

First author, country, screening tool	Group	Smear grade (3+ and 2+) / all smear positives		Comments
		n/N*	% (95%CI)	
Abdurrahman 2016 Nigeria Symptoms	Screen	268/480	56% (51-60%)	Diagnosed TB patients Screened vs PCF - screened group more likely to be older, married and less likely to be HIV infected.
	PCF	151/208	73% (66-79%)	
den Boon 2008 South Africa Smear & culture	Screen	10/18	56% (31-78%)	Denominator for smear grade - screened group includes those lost to follow-up pre-treatment; PCF those starting treatment only Diagnosed in screened and on treatment in PCF groups - no difference in age and gender.
	PCF	314/446	70% (66-75%)	
Santha 2003 India CXR and symptoms	Screen	39/96	41% (31-51%)	Denominator for smear grade - screened group includes those lost to follow-up pre-treatment; PCF those starting treatment only All (smear +ve and -ve) diagnosed in screened and on treatment in PCF groups - screened group more likely to be older, male, illiterate, sole earner, have poor quality house and a 1 room house
	PCF	228/330	69% (64-74%)	

*n/N=number with smear grade (3+ and 2+)/total number with smear grade scanty, 1+, 2+ and 3+; 95%CI = 95% confidence interval; PCF=passive case-finding; CXR=chest radiograph;

Data from *Shewade HD et al. Active versus passive case finding for tuberculosis in marginalised and vulnerable populations in India: comparison of treatment outcomes. Global health action. 2019;12(1):1656451* not included as smear data only provided as scanty/1+/2+ and 3+, and therefore could not be recategorized.

Appendix 4: Risk of bias assessment for studies identified in the economics review using the CHEERS checklist

Questions	Responses					
	Muniyandi 2020	Gurung 2019	Hussain 2019	Shewade 2018	Morishita 2016	Sekandi 2015
Does the title include economic evaluation terms as ‘‘cost" or "cost-effectiveness’’ and describe the interventions compared?	Yes	Yes	Yes	Yes	Yes	Yes
Does the abstract provide a structured summary of objectives, perspective, setting, methods, results and conclusions?	Yes	Yes	Yes	Yes	Yes	Yes
Does the introduction include an explicit statement of the broader context for the study and present the study question and its relevance for health policy or practice decisions?	Yes	Yes	Yes	Yes	Yes	Yes
Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes
Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Yes	Yes	Yes
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	N/A	N/A	Yes	N/A	N/A	Yes
Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant costs for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes
Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes	Yes	Yes
Are costs valued appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant outcomes for each alternative identified?	N/A	N/A	Yes	N/A	N/A	Yes
Are all outcomes measured appropriately in physical units?	N/A	N/A	Yes	N/A	N/A	Yes
Are outcomes valued appropriately?	N/A	N/A	Yes	N/A	N/A	Yes
Is an incremental analysis of costs and outcomes of alternatives performed?	N/A	N/A	Yes	N/A	N/A	Yes
Are all future costs and outcomes discounted appropriately?	N/A	N/A	Yes	N/A	N/A	Yes
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N/A	N/A	Yes	N/A	N/A	Yes
Does the study discuss the generalizability of the results to other settings and patient/client groups?	Yes	Yes	Yes	No	Yes	Yes
Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes	Yes
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	Yes	Yes	No*	No*

**Sometimes not indicated in the manuscript but submitted through the online submission system*

Appendix 5: Pre-treatment and treatment costs for n=3 studies separating costs

First author, population and screening method, illness period and costs reported		Total diagnosis/pre-treatment costs			Total treatment costs			Comments
		Screened	PCF	p-value	Screened	PCF	p-value	
Muniyandi (2020); India General population; symptoms and CXR screen Diagnosis and treatment Direct (medical and non-medical) and indirect costs N=110 in screened and N=226 in PCF group	Mean (SEM)	30 (10)	130 (13)	0.001	39 (14)	97 (12)	0.004	Mean diagnosis costs – screened vs PCF Direct: 16 vs 75; p=0.001 Indirect: 14 vs 55; p=0.001 Mean treatment costs – screened vs PCF Direct: 2 vs 4; p=0.027 Indirect: 37 vs 93; p=0.001
Gurung (2019); Nepal OPD attendees, social contacts of people with TB, general population TB camps; symptom screen Pre-treatment (from symptom start) and intensive treatment phase Direct (medical and non-medical) and indirect costs N=50 in screened and N=49 in PCF group	Median (IQR)	132 (23–258)	172 (60–405)	0.103	85 (56-144)	104 (45-193)	0.557	Median (IQR) pre-treatment costs – screened vs PCF Direct medical: 14 (4-28) vs 32 (11-79); p=0.001 Direct non-medical: 3 (2-10) vs 10 (3-38); p=0.004 Indirect: 63 (5-255) vs 43 (14-248); p=0.430 Median (IQR) treatment costs – screened vs PCF Direct medical: p=0.070* Direct non-medical: 0 (0-14) vs 1.3 (0-45); p=0.034 Indirect: 55 (30-96) vs 60 (35-83)' p=0.817
Morishita (2016); Cambodia HH and neighbourhood contacts; CXR screen Pre-treatment and during 6 months of treatment Direct (medical and non-medical) and indirect costs N=108 in screened and N=100 in PCF group	Median (IQR)	5 (1-26)	22 (4-71)	<0.001	233 (52-568)	235 (88-636)	0.367	Median (IQR) pre-treatment costs – screened vs PCF Direct: 2 (1-11) vs 15 (2-47); p<0.001 Indirect: 0 (0-4) vs 1 (0-4); p=0.073 Median (IQR) treatment costs – screened vs PCF Direct: 67 (22-123) vs 90 (45-202); p=0.014 Indirect: 85 (0-450) vs 60 (0-382); p=0.553

All values (costs and proportions) rounded to the nearest whole number; PCF=passive case-finding; CXR=chest radiograph; SEM=standard error of the mean; OPD=outpatient department; IQR=interquartile range; HH=household; *comparing no costs incurred in screened group vs costs incurred in PCF group (for medicines)

PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE: Does tuberculosis screening improve individual outcomes? A systematic review			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Table 1

			pg 7-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	17
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 & 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Chapter 7: The association between TB screening and TB treatment outcomes: results from the Zambian HPTN 071 (PopART) trial communities

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	159168	**Title**	Dr
First Name(s)	Lilanganee		
Surname/Family Name	Telisinghe		
Thesis Title	Can universal testing and treatment for HIV and community-wide active case finding for tuberculosis control the African TB epidemic?		
Primary Supervisor	Professor Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLOS Global Public Health
Please list the paper's authors in the intended authorship order:	L. Telisinghe, S. Floyd, K. Shaunaube, M. Lithunga, O. Shibwela, B. Kangololo, M. Phiri, A. Schaap, P. Bock, S. Fidler, R. J. Hayes and H. M. Ayles
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the research question. I developed the data dictionary for the study database and trained the study data manager and data capturers on the data dictionary. I developed all study related SOPs. The study data manager and I photographed all registers. I worked up the matching algorithm, undertook all matching, and undertook all analyses. I drafted and edited the manuscript.

SECTION E

Student Signature	L. Telisinghe
Date	28/02/2024

Supervisor Signature	Helen Ayles
Date	18/03/2024

Full title: The association between TB screening and TB treatment outcomes: results from the Zambian HPTN 071 (PopART) trial communities

Short title: TB screening and TB treatment outcomes

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Abstract:

Earlier tuberculosis (TB) diagnosis with linkage-to-care should decrease the risk of TB disease progression, death, and onward transmission. Data on the effect of systematic TB screening on TB treatment outcomes are limited. We sought to identify if TB screening can improve the clinical outcomes of people with TB. In the eight Zambian HPTN 071 (PopART) intervention communities, a community-wide combination HIV/TB prevention intervention was delivered over three intervention rounds spanning 11/2013-12/2017. Between 2016-2017, the calendar period for this study, community-wide TB symptom screening and universal testing and treatment for HIV (UTT) was delivered in all eight communities. Presumptive-TB and TB-treatment registers for the communities were used to categorise all adults (≥15 years) with new, bacteriologically-confirmed (smear/Xpert positive) TB, started on TB treatment between 2016-2017 as identified through community TB screening (screen-identified) or diagnosed with TB through routine care at the clinic (clinic-identified). Outcomes were treatment success (cured and treatment completed combined) and case-fatality (deaths from all causes while on TB treatment). Using logistic regression, the association between the mode of diagnosis (screen-identified vs clinic-identified) and treatment success and case-fatality was investigated. Among 1,374 starting TB treatment, median age was 33 years (interquartile range 27-40), 69% (949/1,374) were male, 54% (731/1,354) were HIV-coinfected, and 15% (205/1,374) were screen-identified. Mode of diagnosis was not associated with treatment success (screen-identified vs clinic-identified adjusted odds ratio [aOR] 1.26 [95% confidence interval (95%CI) 0.83-1.91], p=0.28), or case-fatality (aOR 0.79 [95%CI 0.32-1.92], p=0.59). Treatment success was lower and case-fatality higher among people living with HIV (PLHIV) compared to HIV-negative individuals (treatment success: aOR 0.58 [95%CI 0.43-0.80], p<0.001; and case-fatality: aOR 3.00 [95%CI 1.54-5.84], p<0.001 respectively). In this observational study, TB screening was not associated with TB treatment outcomes. TB treatment outcomes were poor among PLHIV despite UTT, highlighting their continued need for TB-prevention interventions.

Word count: **298/300**

INTRODUCTION

Despite the widespread availability of effective, curative treatment, tuberculosis (TB) remains a leading infectious cause of morbidity and mortality worldwide. An estimated ~30% of people with TB are either not diagnosed through routine services or not notified.[1] Systematic community-wide TB screening (henceforth called TB screening) is now recommended by the World Health Organization (WHO) in general populations where TB prevalence is ≥0.5%.[2] TB screening, which is healthcare provider-initiated, aims to identify and treat people with infectious undiagnosed TB earlier in their clinical course: individuals who do not have or do not recognise they have symptoms and symptomatic individuals who for whatever reason have not sought healthcare.[2] Tools for screening include symptoms, chest radiographs, and WHO recommended rapid molecular diagnostic tests.

By linking people with undiagnosed TB to treatment, TB screening should contribute to closing the detection gap; TB notifications should increase with TB screening identifying a large proportion of all notifications, which should decrease onward TB transmission.[3] Earlier treatment should also improve the individual's clinical outcomes.[2] But, despite the large number of TB screening interventions implemented globally to date, there are very few data on the effect of TB screening on clinical outcomes.[4]

HPTN 071 (PopART) was a cluster-randomised trial of universal testing and treatment for HIV (or UTT), conducted in 21 Zambian and South African communities.[5,6] The intervention package delivered included TB screening.[5,6] Using data from the Zambian intervention communities, we investigated the association between TB screening and TB treatment outcomes.

METHODS

Ethical approval for the study was obtained from the London School of Hygiene and Tropical Medicine UK and the University of Zambia.

Study setting and the HPTN 071 (PopART) trial design.

The HPTN 071 (PopART) trial design has been described in detail elsewhere[5,6] and is briefly summarised here. In Zambia, 12 urban/peri-urban communities, with high HIV prevalence (10-25%) and TB case notification rates (≥400/100,000 population), were purposively selected. Each community was served by a health facility. Communities were first matched into triplets (groups of three communities) based on geography and HIV prevalence giving four triplets (Appendix-S1). Communities in each triplet were then randomly allocated to one of three trial arms (two intervention arms [A and B] and a control arm).

In the two intervention arms comprising eight communities, between November 2013 and December 2017, a door-to-door, community-wide, HIV/TB prevention intervention was delivered over three intervention rounds by trained community HIV care providers (or CHiPs; Figure 1). In both arms, a symptom questionnaire (cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month) was used to screen for TB at each annual intervention round. If symptomatic, CHiPs collected and delivered sputum samples to a laboratory serving the study community, for testing using Xpert MTB/RIF if HIV positive/status unknown or smear if HIV negative. Sputum results were returned to the CHiPs. If sputum positive, CHiPs linked individuals to TB treatment at the health facility with follow-up during treatment. CHiPs also collected sputum from individuals on TB treatment if needed (e.g. for TB treatment monitoring). Information on sputum samples collected by CHiPs was documented in presumptive TB registers maintained by the intervention team (from Quarter-4 2014). Information on all individuals started on TB treatment was recorded in TB treatment registers maintained by the health facility TB clinic. Complete TB treatment register data were available from December 2015.

In both arms, at each intervention round, CHiPs also offered universal HIV testing using rapid tests, as part of a comprehensive HIV prevention package of care. If HIV positive, CHiPs linked individuals to HIV care. In Arm A, antiretroviral therapy (ART) initiation was universal (irrespective of CD4 count) from 2013; i.e. UTT was provided from 2013. In arm B, ART initiation followed national guidelines, becoming universal (i.e. UTT), in April-May 2016. As the

TB screening intervention was the same in both intervention arms from the start of the trial, from Quarter-2 2016, both intervention arms received the same intervention.

Data sources, data collection, variables, and definitions

All presumptive TB register and health facility TB treatment register data from the Zambian intervention communities were captured onto electronic databases. For five communities, TB treatment register data from other nearby health facilities, known to be frequently accessed by intervention community members, were also captured. Presumptive TB register data collected included name, sex, age, address, sputum registration date, sputum sample source (CHiP or other [e.g. ART clinic, outpatient clinic]), sputum result, and TB treatment start date. The presumptive TB registers were used to identify all CHiP positive TB results, defined as Xpert/smear positive with a CHiP sputum sample source, between 1st December 2015 (mirroring the start of TB treatment register data) to 31st December 2017 (intervention end). TB treatment register data collected included name, sex, age, address, treatment start date, patient type (new or previous treatment), HIV-status, and treatment outcomes. Data between 1st December 2015 and 31st December 2018 (to allow maximum time for matching) were used.

There was no unique identifier for individuals in the two registers. Therefore names of individuals with CHiP positive TB results identified in the presumptive TB registers were matched to names in the TB treatment registers using the stata “matchit” command, which allows automated approximate matching between string variables (Figure 1, Appendix-S2).[7] A definite match was defined as name match AND any two of sex, age +/-3 years, address or TB treatment start month/year match AND the treatment start date was the same as or after the sputum registration date. A TB treatment before sputum registration match was defined as meeting all definite criteria except TB treatment was started in the 6 months before the date of sputum registration; compatible with CHiPs collecting sputum from people on TB treatment. Following matching, the characteristics (age, sex, and sputum results) of individuals with CHiP positive TB results who could and could not be matched to TB treatment registers, were explored using information available in the presumptive TB registers.

By matching, all individuals in the TB treatment registers were categorised by mode of diagnosis as screen-identified (definite match to a CHiP positive TB result) or clinic-identified (not matched to a CHiP positive TB result): the exposure for this analysis. TB treatment before sputum registration matches were classified as clinic-identified. Data in the TB treatment registers were then used for the primary analysis among new, Xpert/smear positive, adults (≥15 years), starting TB treatment between 1st January 2016 and 31st December 2017, who resided within community areas where all households in the area were eligible for the intervention (Figure 1). A secondary analysis also included those previously treated for TB.

Sputum results were classified as high-grade (Xpert medium and high or smear 2+ and 3+) or low-grade (Xpert low, very low and trace or smear scanty and 1+) and considered a mediator of the association between TB screening and treatment outcomes, as screening aims to identify individuals earlier in their clinical course when sputum-grade may be lower. The study outcomes were treatment success (cured and treatment completed combined) and case fatality (death from all causes while on TB treatment) among all individuals who started treatment. The denominator for all analyses included all individuals started on TB treatment, including those for whom a TB treatment outcome was not known at the end of the treatment period.

Statistical methods

Data were analysed using STATA version-15 (StataCorp LP, Texas, USA). To explore the characteristics of individuals with CHiP positive TB results who could and could not be matched to TB treatment registers, univariable and multivariable conditional logistic regression matched on community was used because of the small number of individuals with data on sputum-grade. Multivariable analysis adjusted for age, sex, and sputum-grade.

To investigate the association between mode of diagnosis and sputum-grade, and between mode of diagnosis and treatment success, logistic regression was used. 'Univariable analysis' consisted of base models adjusted for age, sex, and community. Multivariable

analysis consisted of base models and HIV-status. Due to the small number of deaths, conditional logistic regression, matched on community, was used to investigate the association between mode of diagnosis and case fatality. 'Univariable analysis' consisted of base models adjusted for age and sex. Multivariable analysis consisted of base models and HIV status.

RESULTS

Matching CHiP positive TB results in presumptive TB registers to TB treatment registers

Between 1st December 2015 and 31st December 2017, 7,595 sputum samples from the eight intervention communities were recorded as having a CHiP sputum sample source in the presumptive TB registers. From these 430 CHiP positive TB results were identified. On matching, eight individuals met the TB treatment before sputum registration match criteria. Of the remaining 422 CHiP positive TB results, 316/422 (75%) could be matched to TB treatment registers (definite matches) and 106/422 (25%) could not. On univariable analysis, only age ≤24 years was associated with not being matched to TB treatment registers (Appendix-S3); sex and sputum-grade were not associated. On multivariable analysis, there was no association between age, sex, and sputum-grade and not being matched to TB treatment registers. The median time between sputum registration and treatment start among individuals that could be matched was 6 days (interquartile range [IQR] 3-11).

Of all matched CHiP positive TB results, 205/316 (65%) were eligible for the primary analysis (Figure 2) which was restricted to adults with new, Xpert/smear positive TB, starting TB treatment between 1st January 2016 and 31st December 2017, who resided within community areas where all households in the area were eligible for the intervention. TB screening contributed 205/1,374 (15%) of all treatment starts meeting the eligibility criteria for the primary analysis. The contribution of TB screening varied by community and arm (Appendix-S4); it was higher in arm A communities (12-27%) than in arm B communities (7-12%).

Among all 1,374 meeting the eligibility criteria for the primary analysis (Table 1), the median age was 33 (IQR 27-40) years; 949/1,374 (69%) were male; and 731/1,354 (54%) were people living with HIV (PLHIV). After adjusting for community, female sex was associated with a higher odds of being screen-identified (females 78/425 [18%] vs males 127/949 [13%]; odds ratio [OR] 1.61 [95% confidence interval [CI] 1.17-2.23]; p=0.004). Community was associated with mode of diagnosis; the odds of being screen-identified was lower in arm B communities compared to most arm A communities. There was no association between age or HIV-status, and mode of diagnosis.

Table 1: Characteristics of individuals eligible for the primary analysis[1]; overall and by mode of diagnosis.

Characteristic		Total N (%)[2,3] N=1374	Clinic-identified n(%)[4] n=1169	Screen-identified n(%)[4] n=205	OR[5] (95% CI)	p-value
Age/years	median (IQR)	33 (27-40)	33 (27-40)	33 (27-39)		
	≤24	208 (15%)	178 (86%)	30 (14%)	0.85 (0.51-1.40)	0.60
	25-29	257 (19%)	221 (86%)	36 (14%)	0.77 (0.48-1.25)	
	30-34	300 (22%)	251 (84%)	49 (16%)	1	
	35-39	265 (19%)	224 (85%)	41 (15%)	0.88 (0.56-1.40)	
	40-44	165 (12%)	147 (89%)	18 (11%)	0.62 (0.34-1.12)	
	≥45	179 (13%)	148 (83%)	31 (17%)	1.01 (0.61-1.68)	
Sex	Female	425 (31%)	347 (82%)	78 (18%)	1.61 (1.17-2.23)	0.004
	Male	949 (69%)	822 (87%)	127 (13%)	1	
HIV status[N=1354]	Positive	731 (54%)	618 (85%)	113 (15%)	1.18 (0.87-1.61)	0.29
	Negative	623 (46%)	532 (85%)	91 (15%)	1	
Community[6]	1A	89 (6%)	74 (83%)	15 (17%)	0.55 (0.30-1.01)	<0.001
	1B	188 (14%)	174 (92%)	14 (7%)	0.22 (0.12-0.40)	
	2A	168 (12%)	136 (81%)	32 (19%)	0.64 (0.40-1.01)	
	2B	117 (9%)	103 (88%)	14 (12%)	0.37 (0.20-0.68)	
	3A	301 (22%)	220 (73%)	81 (27%)	1	
	3B	168 (12%)	155 (92%)	13 (8%)	0.23 (0.12-0.42)	
	4A	181 (13%)	160 (88%)	21 (12%)	0.36 (0.21-0.60)	
	4B	162 (12%)	147 (91%)	15 (9%)	0.28 (0.15-0.50)	

OR=odds ratio; CI=confidence interval; IQR=interquartile range;[1]adults (≥15 years) with new, Xpert/smear positive TB, starting TB treatment between 1/1/2016 and 31/12/2017 and living in the Zambian HPTN 071 (PopART) intervention community areas where all household in the area were eligible for the intervention; [2]column percentages shown; [3]denominator=1374 unless otherwise indicated; [4]row percentages shown; [5]adjusted for community; [6]communities shown by triplet (1 to 4) and arm (A or B)

Association between mode of diagnosis and treatment outcomes

Among those with data, sputum-grade was high in 798/1,267 (63%). In base models (Table 2), mode of diagnosis, age, and community were not associated with sputum-grade. A lower

proportion of females and PLHIV had high sputum-grade. On multivariable analysis, there was no association between mode of diagnosis and high sputum-grade (screen-identified 119/194 [61%] vs clinic-identified 679/1,073 [63%]; adjusted OR [aOR] 0.94 [95%CI 0.67-1.30]; p=0.71). But sex and HIV-status remained associated with sputum-grade.

Table 2: Logistic regression analysis of the association between mode of diagnosis and sputum-grade among individuals eligible for the primary analysis[1].

Characteristic		High-grade[2] n/N	%[3]	Base model OR (95% CI)[4]	p-value	Multivariable analysis[5] aOR (95% CI)	p-value
		798/1267	63%				
Mode of diagnosis	Screen-identified	119/194	61%	0.91 (0.66-1.26)	0.58	0.94 (0.67-1.30)	0.71
	Clinic-identified	679/1073	63%	1		1	
Age/years	≤24	127/193	66%	1.32 (0.90-1.97)	0.18	1.11 (0.74-1.67)	0.47
	25-29	161/238	68%	1.36 (0.94-1.97)		1.28 (0.88-1.87)	
	30-34	170/276	62%	1		1	
	35-39	150/244	61%	0.98 (0.69-1.40)		1.04 (0.72-1.50)	
	40-44	93/150	62%	1.01 (0.67-1.54)		1.02 (0.67-1.56)	
	≥45	97/166	58%	0.85 (0.57-1.27)		0.82 (0.55-1.23)	
Sex	Female	221/394	56%	0.62 (0.48-0.79)	<0.001	0.70 (0.54-0.91)	0.009
	Male	577/873	66%	1		1	
HIV-status[6,]	Positive	372/660	56%	0.59 (0.46-0.75)	<0.001	0.59 (0.46-0.75)	<0.001
	Negative	413/588	70%	1		1	
Community[7]	1A	63/86	73%	1.55 (0.90-2.66)	0.19	1.50 (0.86-2.59)	0.25
	1B	110/186	59%	0.78 (0.53-1.15)		0.77 (0.52-1.14)	
	2A	110/165	67%	1.15 (0.77-1.73)		1.04 (0.68-1.59)	
	2B	66/117	56%	0.74 (0.47-1.15)		0.73 (0.47-1.15)	
	3A	191/292	65%	1		1	
	3B	75/125	60%	0.81 (0.52-1.25)		0.74 (0.48-1.16)	
	4A	98/161	61%	0.91 (0.61-1.36)		0.92 (0.61-1.39)	
	4B	85/135	63%	0.95 (0.62-1.47)		0.96 (0.62-1.48)	

OR=odds ratio; 95%CI=95% confidence interval; aOR=adjusted odds ratio; [1]adults (≥15 years) with new, Xpert/smear positive TB, starting TB treatment between 1/1/2016 and 31/12/2017 and living in the Zambian HPTN 071 (PopART) intervention community areas where all household in the area were eligible for the intervention [2]high grade defined as Xpert medium and high or smear 2+ and 3+; [3]row percentages shown; [4]adjusted for community, age and sex; [5]adjusted for community, age, sex and HIV-status among n=463 with low grade and n=785 with high grade who have complete information; [6]among 1248 with complete information of whom 785 had a high sputum-grade; [7]communities shown by triplet (1 to 4) and arm (A or B)

Treatment outcomes were not known for 182/1,374 (13%; Appendix-S5). After adjusting for community, none of mode of diagnosis, age, sex, or HIV-status were associated with treatment outcomes being unknown. Community was however associated with treatment outcomes being unknown; most arm B communities had a lower proportion of treatment outcomes that were unknown, compared to most arm A communities. In four communities (2B, 3B, 4A, and 4B), treatment outcomes were known for >90% of people with TB. Among all individuals treated, a high proportion had documented treatment success: 1,133/1,374 (82%). In base models, mode of diagnosis was not associated with treatment success (Table 3). Age and sex were also not associated with treatment success. But treatment success was lower among PLHIV compared to those who were HIV-negative. Community was associated with treatment success; the odds of treatment success was higher in communities which had the lowest proportion of treatment outcomes that were unknown. On multivariable analysis there was no association between mode of diagnosis and treatment success (screen-identified 171/205 [83%] vs clinic-identified 962/1,169 [82%]; aOR 1.26 [95%CI 0.83-1.91]; p=0.28). Female sex was associated with a higher odds of treatment success (females 359/425 [84%] vs males 774/949 [81%]; aOR 1.36 [95%CI 0.97-1.90]; p=0.07), while treatment success remained lower among PLHIV (PLHIV 591/731 [81%] vs HIV-negative 530/623 [85%]; aOR 0.58 [95%CI 0.43-0.80]; p<0.001). Community also remained associated with treatment success on multivariable analysis.

Table 3: Logistic regression analysis of the association between mode of diagnosis and TB treatment success among individuals eligible for the primary analysis[1].

Characteristic		Treatment success[2] n/N	%[3]	Base model OR (95% CI)[4]	p-value	Multivariable analysis[5] aOR (95% CI)	p-value
		1133/1374	82%				
Mode of diagnosis	Screen-identified	171/205	83%	1.22 (0.81-1.85)	0.32	1.26 (0.83-1.91)	0.28
	Clinic-identified	962/1169	82%	1		1	
Age/years	≤24	165/208	79%	0.84 (0.53-1.32)	0.55	0.65 (0.40-1.05)	0.17
	25-29	214/257	83%	1.11 (0.71-1.73)		0.99 (0.63-1.57)	
	30-34	246/300	82%	1		1	
	35-39	219/265	83%	1.07 (0.69-1.66)		1.05 (0.67-1.65)	
	40-44	143/165	87%	1.45 (0.84-2.50)		1.44 (0.82-2.52)	
	≥45	146/179	81%	0.99 (0.61-1.61)		0.91 (0.55-1.50)	
Sex	Female	359/425	84%	1.21 (0.88-1.67)	0.24	1.36 (0.97-1.90)	0.07
	Male	774/949	81%	1		1	
HIV-status[6]	Positive	591/731	81%	0.59 (0.43-0.80)	<0.001	0.58 (0.43-0.80)	<0.001
	Negative	530/623	85%	1		1	
Community[7]	1A	64/89	72%	0.72 (0.42-1.24)	<0.001	0.73 (0.42-1.28)	<0.001
	1B	148/188	79%	1.06 (0.68-1.65)		1.09 (0.69-1.73)	
	2A	136/168	81%	1.20 (0.75-1.93)		1.11 (0.68-1.80)	
	2B	98/117	84%	1.46 (0.83-2.57)		1.52 (0.86-2.71)	
	3A	234/301	78%	1		1	
	3B	149/168	89%	2.24 (1.29-3.88)		2.43 (1.37-4.30)	
	4A	165/181	91%	2.88 (1.60-5.17)		3.29 (1.79-6.03)	
	4B	139/162	86%	1.67 (0.99-2.81)		1.79 (1.05-3.04)	

OR=odds ratio; 95%CI=95% confidence interval; aOR=adjusted odds ratio; [1]adults (≥15 years) with new, Xpert/smear positive TB, starting TB treatment between 1/1/2016 and 31/12/2017 and living in the Zambian HPTN 071 (PopART) intervention community areas where all household in the area were eligible for the intervention; [2]treatment success defined as treatment outcomes of cured and treatment completed combined among all individuals treated; [3]row percentages shown; [4]adjusted for community, age and sex; [5]adjusted for community, age, sex and HIV-status among n=1,121 with treatment success and n=233 without documented treatment success who had complete information; [6]among 1354 with complete information of whom 1121 successfully completed treatment; [7]communities shown by triplet (1 to 4) and arm (A or B)

There were 55/1,374 (4%; Table 4) documented deaths among all individuals treated. In base models, mode of diagnosis was not associated with case fatality (Table 4). Sex was also not associated with case fatality. But case fatality was more common among people

aged ≥45 years and PLHIV. On multivariable analysis (Table 4) there was no association between mode of diagnosis and case fatality (screen-identified 6/205 [3%] vs clinic-identified 49/1,169 [4%]; aOR 0.79 [95%CI 0.32-1.92]; p=0.59). Older age remained associated with case-fatality (≥45 years 12/179 [7%] vs <45 years 43/1,195 [4%]; aOR 1.94 [95%CI 0.99-3.80]; p=0.07). The odds of case fatality was three times higher among PLHIV compared to those who were HIV-negative (PLHIV 42/731 [6%] vs HIV-negative 12/623 [2%]; aOR 3.00 [95%CI 1.54-5.84]; p<0.001).

Table 4: Conditional logistic regression analysis of the association between mode of diagnosis and case fatality among individuals eligible for the primary analysis[1]

Characteristic		Died n/N 55/1374[3]	%[2] 4%	Base model[4] OR (95% CI)[5]	p-value	Multivariable analysis[6] aOR (95% CI)	p-value
Mode of diagnosis	Screen-identified	6/205	3%	0.74 (0.31-1.78)	0.49	0.79 (0.32-1.92)	0.59
	Clinic-identified	49/1169	4%	1		1	
Age/years	≥45	12/179	7%	1.83 (0.94-3.56)	0.09	1.94 (0.99-3.80)	0.07
	<45	43/1195	4%	1		1	
Sex	Female	16/425	4%	0.86 (0.47-1.56)	0.57	0.75 (0.41-1.39)	0.35
	Male	39/949	4%	1		1	
HIV-status[N=54/1354]	Positive	42/731	6%	3.01 (1.55-5.85)	<0.001	3.00 (1.54-5.84)	<0.001
	Negative	12/623	2%	1		1	

OR=odds ratio; 95%CI=95% confidence interval; aOR=adjusted odds ratio; [1]adults (≥15 years) with new, Xpert/smear positive TB, starting TB treatment between 1/1/2016 and 31/12/2017 and living in the Zambian HPTN 071 (PopART) intervention community areas where all household in the area were eligible for the intervention; [2]row percentages shown; [3]number of deaths=55 and denominator=1374 unless otherwise indicated; [4]when matched on community, the analysis was restricted to 1186 with complete information on age and sex (among whom 55 deaths were reported), and 1168 with complete information on age, sex, and HIV-status (among whom 54 deaths were reported), as community 1B was excluded because no deaths were reported over the 2 year period; [5]adjusted for community, age, and sex; [6]adjusted for community, age, sex, and HIV-status among n=54 who died and n=1114 with no death documented who have complete information.

Findings were similar on secondary analysis, where the TB case definition included both new and previously treated TB (Appendix-S6 to S9).

DISCUSSION

In this observational study, embedded within the intervention arms of a cluster randomised trial of community wide UTT and TB screening, there was no association between TB symptom screening and sputum-grade, treatment success, or case fatality, among people with TB on treatment. In our study sample, the proportion with documented treatment success was high, and the proportion of documented deaths was low. Therefore, our power to detect small but clinically significant differences would have been low. While the point estimate for the association between TB screening and treatment success and TB screening and case fatality suggested some potential benefit, the confidence intervals around these estimates were very wide and crossed one and the p-values were very large, suggesting no evidence of an effect.

Our findings were also consistent with other TB screening studies (four observational and one trial) conducted in general populations, which also showed no association between TB screening (using different screening modalities including symptoms, chest radiographs, and sputum smear/cultures on all) and on-treatment outcomes.[8-12] Limitations to consider when interpreting our findings and those of the previously published literature include the observational design of most studies. Ultimately definitive evidence for the effect of TB screening on treatment outcomes require trials comparing screened and unscreened populations; only one trial has reported population-level findings to date, showing no effect.[12] Routine TB treatment data were used in all studies, which have inherent limitations, such as missing data, possible misclassifications, potential over-ascertainment of good outcomes, and limited information on potential confounders, both at the individual and clinic-level, limiting the adjustment for these. Alternatively, the results may indicate a true finding: TB screening may not improve treatment outcomes.

Our analysis showed female sex and younger age were associated with better TB treatment outcomes, in keeping with the published literature.[13-18] Further our results also showed PLHIV had poorer TB treatment outcomes, which while consistent with the published literature,[19] was against the backdrop of an UTT intervention being delivered throughout the communities. The proportion of PLHIV that died on TB treatment in our study (6%) was lower than previously published estimates when ART initiation for PLHIV was not universal (~11-15%).[19,20] Nonetheless, the odds of death among PLHIV on TB treatment was unacceptably high, compared to those who were HIV-negative. The HPTN 071 (PopART) intervention data showed the odds of being newly diagnosed with TB was higher among those who were also newly diagnosed with HIV compared to those who were HIV negative.[21] These individuals were more likely to represent a population with more severe immunosuppression, which may in part explain the poorer outcomes among PLHIV with TB. The HPTN 071 (PopART) intervention data also showed that while overall ART coverage was >80%, there were gaps in coverage: especially among men and the young (aged 18-34 years),[6,22] which are populations with a high prevalence of TB.[23,24] This highlights the need for different strategies to target hard-to-engage at-risk groups within a population. It also highlights the continued need of PLHIV for early HIV/TB diagnosis, treatment, and other TB prevention interventions such as TB preventive therapy, alongside ART. Limitations of our analysis include the limited information on potential confounders, limiting the adjustment for these. We also did not have reliable ART data for the study sample and therefore do not know what proportion of PLHIV were on ART prior to or during TB treatment.

We were unable to match 25% of CHiP positive TB results to TB treatment registers (with matching to treatment registers for a full calendar year following the end of the HPTN 071 [PopART] intervention), commensurate with other reports in the literature.[4] The unmatched proportion may be an over-estimate. Despite efforts to maximise the sensitivity and specificity of the matching algorithm, it is possible some people who did start treatment were missed. Further, individuals may have sought treatment from health facilities not included in

this study. We do not have outcomes for those we could not match. There are also very few published data on outcomes of people lost to follow-up pre-treatment who were diagnosed through TB screening.[4] In an Indian study, individuals diagnosed with TB through TB screening and routine services who were lost to follow-up pre-treatment were investigated[4]. Among those diagnosed through routine services for whom outcomes were known, nearly 20% had died, and only ~10% had commenced treatment elsewhere (i.e. at a different health facility to the study health facility).[4] While no deaths were reported among people lost to follow-up pre-treatment who were diagnosed through TB screening, none had commenced TB treatment at other health facilities.[4] While these findings are not generalisable, they do have broader implications. If countries consider TB screening in general populations, all screening activities must be coupled with systems to maximise linkage-to-care. Impacts on TB burden demonstrated in TB screening trials driving WHO recommendations,[25] may not be realised if all individuals identified through screening are not linked to care. Further, trials comparing treatment outcomes among all people diagnosed with TB (as opposed to on-treatment outcomes) in screened and unscreened populations, will help identify whether TB screening has an effect on important clinical outcomes.

TB screening contributed only 15% of all those eligible for our study. This is in keeping with cross-arm comparisons showing no increase in self-reported TB treatment in the HPTN 071 (PopART) research cohort in intervention arms A and B, compared to the control arm.[26] This contrasts with other community-wide TB screening studies, where TB screening contributed a larger proportion of overall notifications.[3,27] Possible reasons for this include using symptom screening, known to have low sensitivity for prevalent undiagnosed TB,[2] and smear for diagnosis, which has lower sensitivity compared to other diagnostic methods.[28] The intervention was also less good at reaching men, who are more likely to have prevalent TB[6,22,23]; we found females were more likely than males to be screen-identified. Use of more sensitive screening and diagnostic algorithms such as chest-

radiographs and Xpert MTB/RIF coupled with additional strategies to engage hard-to-reach, high-risk groups such as men, may therefore yield different results.

Additional limitations of our study include the use of routine presumptive TB register data to determine CHiP positive TB results. It is possible that some CHiP positive TB results were not recorded, or that CHiP and clinic diagnoses were misclassified. We only matched CHiP positive TB results with documented positive smear/Xpert results; we did not confirm all negative sputum results documented in the presumptive TB register against laboratory records.

In conclusion, in this observational study, there was no association between TB screening and TB treatment outcomes. Treatment outcomes were poor among PLHIV despite UTT, highlighting their continued need for prevention and care interventions.

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COMPETING INTERESTS

All authors declare no competing interests

AUTHOR CONTRIBUTION

Study design: LT, SF, RJH, HMA

Data collection, cleaning, and preparation: LT, ML, OS, BK, AS

Data matching and analysis: LT with input from SF and RJH.

Drafted manuscript: LT

Edited manuscript: LT, SF, KS, ML, OS, BK, MP, AS, PB, SF, RJH, HMA

Approved final draft: LT, SF, KS, ML, OS, BK, MP, AS, PB, SF, RJH, HMA

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SUPPORTING INFORMATION

Appendix-S1 Figure: The three study arms in Zambia.

Appendix-S2 Figure: Matching algorithm used to match presumptive TB registers to TB treatment registers in the Zambian HPTN 071 (PopART) intervention communities.

Appendix-S3 Table: Characteristics of individuals with CHiP positive TB results between 1/12/2015 -31/12/2017 who could and could not be matched to individuals in the TB treatment registers.

Appendix-S4 Table and Figure: Contribution of TB screening to new, Xpert/smear positive TB, among adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, and living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention; by community, arm, and year.

Appendix-S5 Table: Association between demographic and clinical characteristics and having treatment outcomes which were not known among new, Xpert/smear positive, adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, and living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention.

Appendix-S6 Figure: Matching CHiP positive TB results to TB treatment registers to determine people with screen-identified TB in the TB treatment registers and forming the sample for the secondary analysis among all (new and previously treated), Xpert/smear positive, adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, who resided within community areas where all households in the area were eligible for the intervention.

Appendix-S7 Table: Characteristics of all (new and previously treated), Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian

HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention; overall and by case-finding method.

Appendix-S8 Table: Logistic regression analysis of the association between mode of diagnosis and sputum-grade and mode of diagnosis and TB treatment success among all (new and previously treated) Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention.

Appendix-S9 Table: Conditional logistic regression analysis of the association between mode of diagnosis and case fatality among all (new and previously treated), Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention.

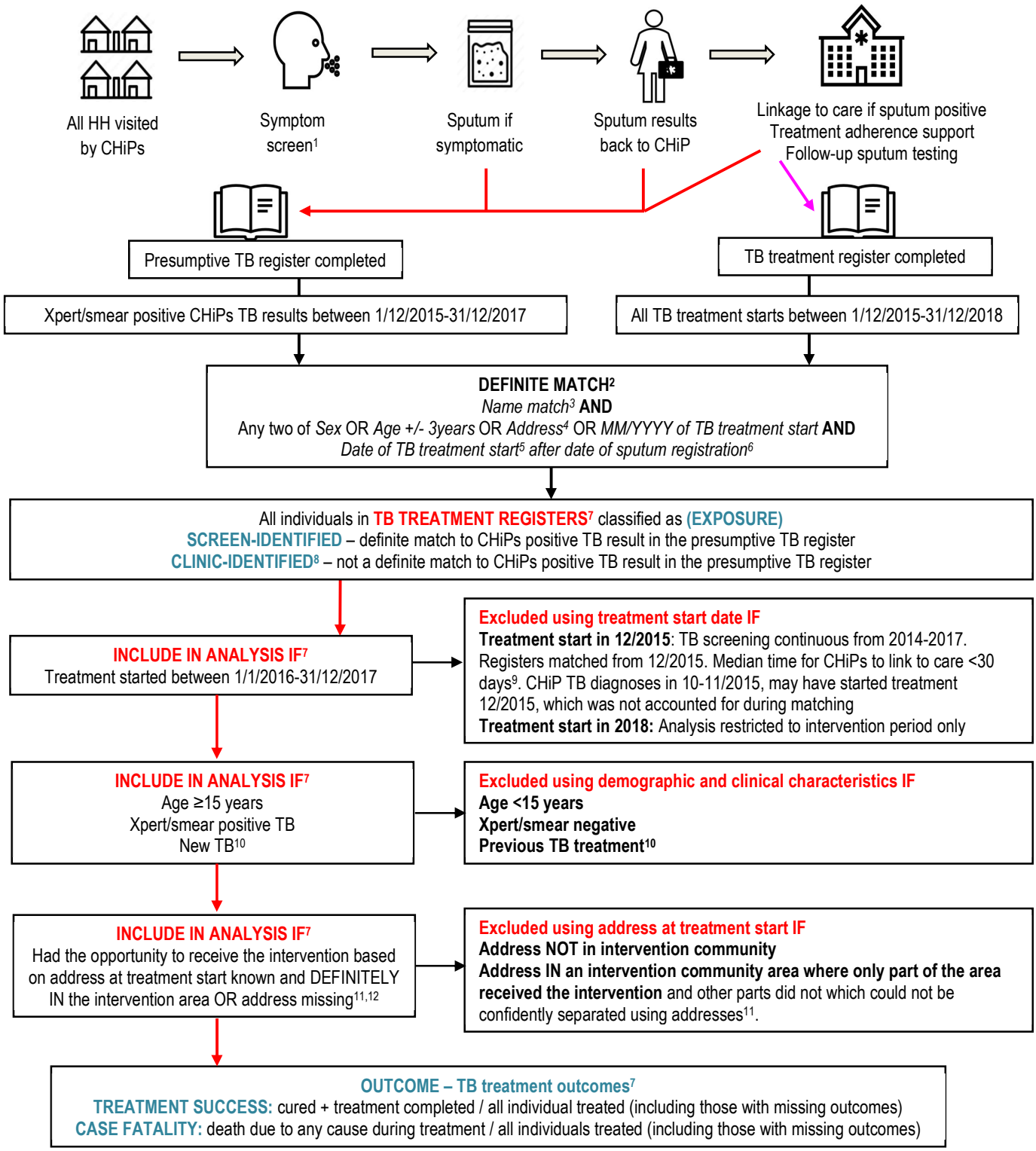

Figure 1: The systematic TB screening intervention, data sources, matching algorithm, exposure, inclusion/exclusion criteria for TB case definition and outcome. HH=household; CHiPs=community HIV-care providers; TB=tuberculosis; [1]TB screening (using

symptoms [cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month] or household contact of a person with TB disease) with all households visited at least 3 times between 2014-2017; [2]Matching also identified individuals meeting definite criteria except treatment was started in the 6 months before sputum registration (compatible with follow-up sputum testing, testing symptomatic people on treatment). These individuals were not considered CHiPs TB screen identified people with TB disease; [3]Matching done using the stata matchit command which allows automated approximate matching between string variables. Matching includes exact matches or "sounds like" and allowing for misspelling and surname forename switch. Matching produces a similarity score between 0-1 (1 is a perfect match). A threshold of ≥0.7 was used to define a match; [4]allowing for minor spelling errors, house number switch; [5]in TB treatment register; [6]in presumptive TB register; [7]Following matching the analysis was restricted to information held in the TB treatment registers; [8]Included those not matched to CHiPs positive TB results in the presumptive TB registers or individuals meeting definite match criteria except TB treatment was started in the 6 months before sputum registration; [9]CHiPs intervention data showed the median time to link to treatment was ~20 days in 7/2015-9/2016 and ~14 days in 10/2016-12/2017; [10]secondary analysis included individuals with new and previous TB treatment; [11]All communities had areas within their boundaries. In the large Lusaka province communities, the intervention was only delivered to part of the community. In some areas, all households received the intervention – people with TB disease starting TB treatment whose addresses were in these areas were included in the analysis. In some areas only some of the households received the intervention - households receiving the intervention could not be clearly separated from those not receiving the intervention in these areas. People with TB disease starting TB treatment whose addresses were in these areas were excluded. Outside the Lusaka province, the intervention was delivered throughout community areas that were clearly demarcated. [12]Individuals with missing addresses (8% of the study sample) – who could not be categorized as living at an address definitely in or not in the intervention community areas - were included in the analysis.

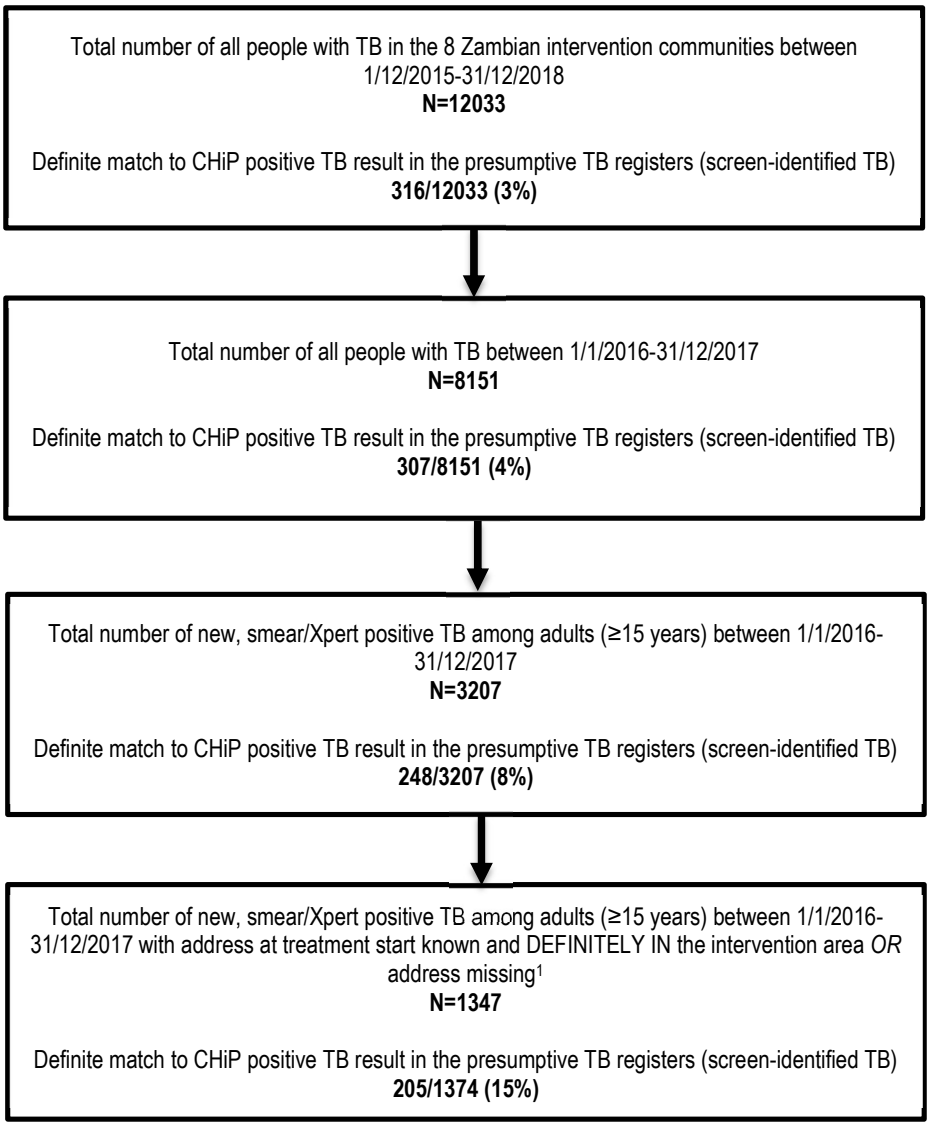

Figure 2 Matching CHiP positive TB results to TB treatment registers to determine people with screen-identified TB in the TB treatment registers and forming the sample for the primary analysis. TB=tuberculosis; CHiP=Community HIV-care providers; [1]excluding individuals with addresses NOT in intervention community *OR a*ddress IN an intervention community area where only part of area received the intervention and other parts did not which could not be confidently separated using the available addresses and landmarks

Supplementary Appendix-S1

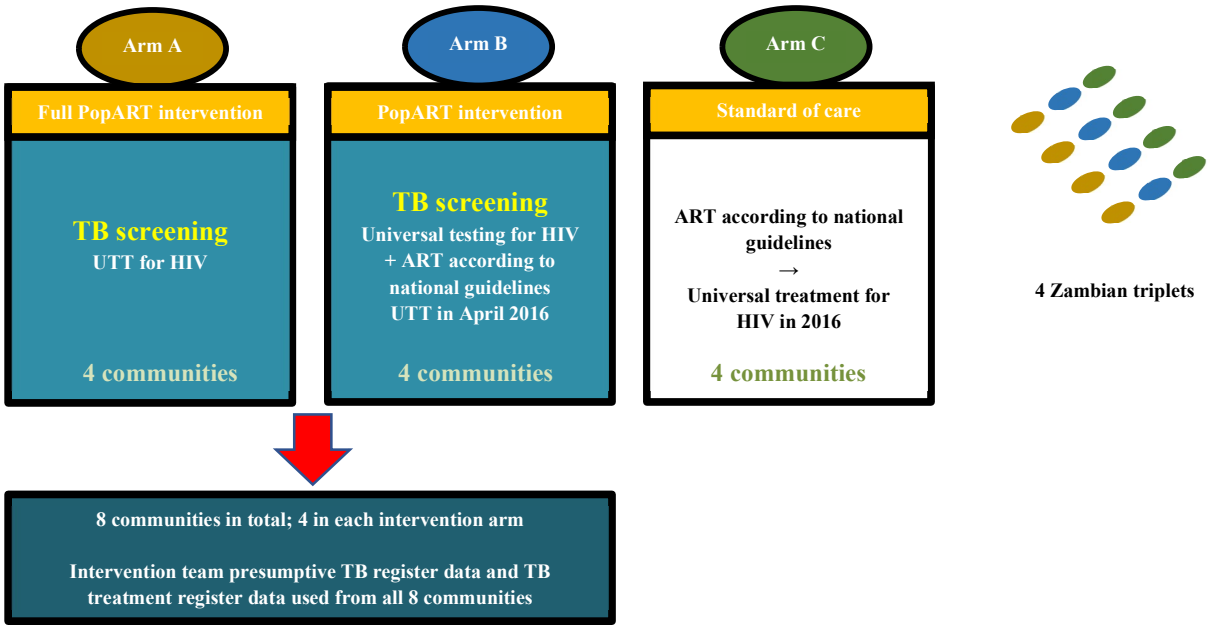

Figure: The three study arms in Zambia

TB=tuberculosis; UTT=universal testing and treatment for HIV; ART=antiretroviral therapy.

There were 2 intervention arms – arm A (4 communities in Zambia) and B (4 communities in Zambia). There were x3 community-wide intervention rounds between 11/2013 and 12/2017 in arms A and B. Round 1 was from Nov-2013 to Jun-2015. Round 2 was from Jul-2015 to Sept-2016. Round 3 was from Oct-2016 to Dec-2017. Arm A received the full intervention package, which included community-wide systematic TB screening using a symptom questionnaire (cough ≥2 weeks, night sweats or unintentional weight loss ≥1.5 Kg in the preceding month) AND universal testing for HIV, with universal treatment for HIV (irrespective of CD4 cell count) from 2013. In arm B there was community-wide systematic TB screening from 2013. There was universal testing for HIV, but ART start was according to national guidelines, which changed to universal treatment in April 2016. Therefore, from April 2016 in Zambia, the arm A and B communities received the same intervention. Intervention team paper presumptive TB register data and health facility paper TB treatment register data in the 8 Zambian intervention communities were captured electronically.

Supplementary Appendix-S2

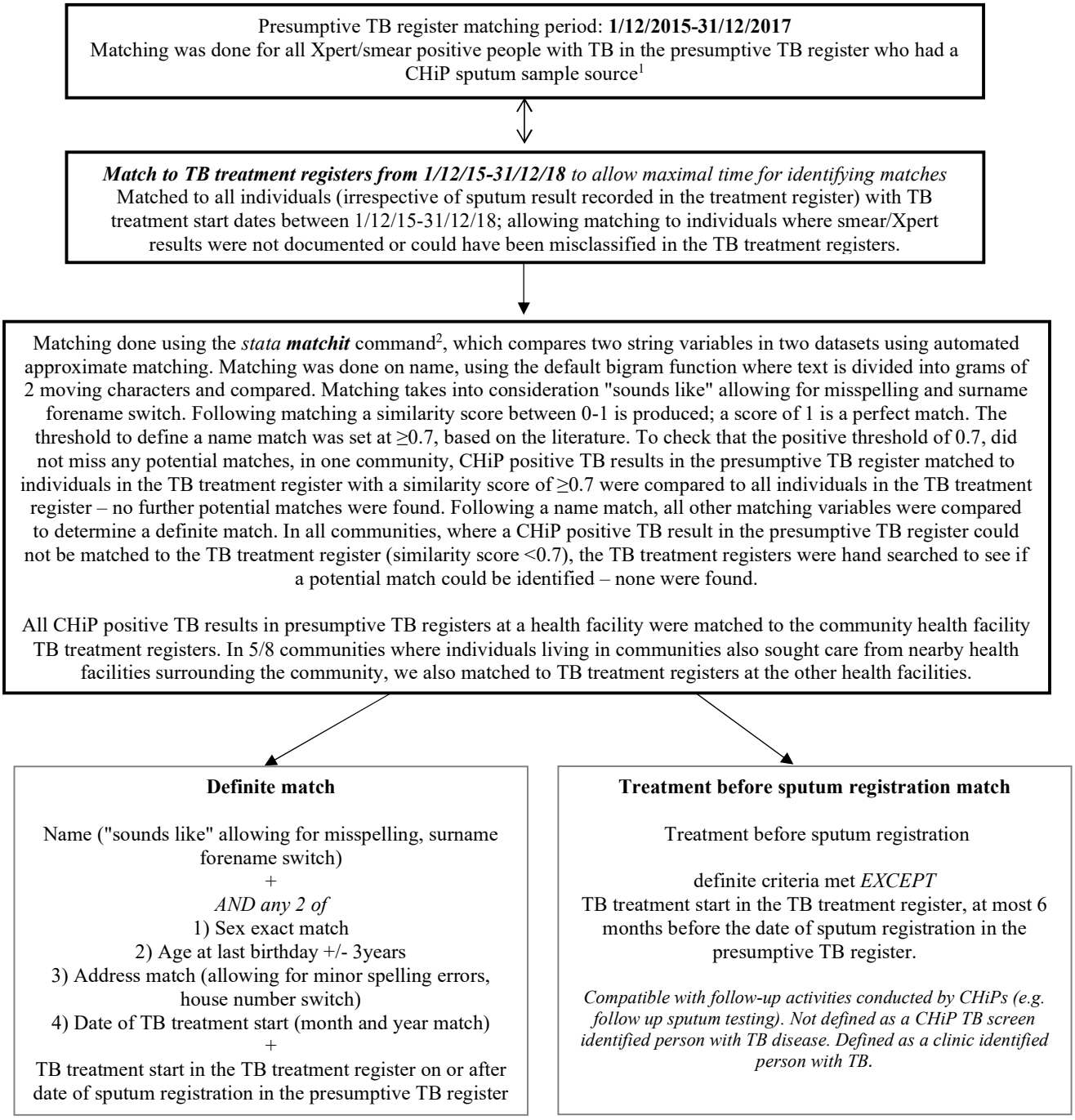

Figure: Matching algorithm used to match presumptive TB registers to TB treatment registers in the Zambian HPTN 071 (PopART) intervention communities.

CHiP=community HIV-care providers; [1]Variable in the presumptive TB register which identified the origin of the sputum sample; [2]Julio Raffo, 2015. "MATCHIT: Stata module to match two datasets based on similar text patterns," Statistical Software Components S457992, Boston College Department of Economics, revised 20 May 2020

Supplementary Appendix-S3

Characteristic		Total[1] N (%) N=422	Definite match[2] n(%)[4] N=316 (75%)	No match[3] n(%)[4] N=106 (25%)	Unadjusted OR[5] (95% CI)	p-value	Adjusted OR[6] (95% CI) n/N=41/177	p-value
Age/years[n=384]	≤24	79 (20%)	59/79 (75%)	20/79 (25%)	2.17 (1.11-4.24)	0.07	0.96 (0.33-2.79)	0.60
	25-39	194 (50%)	164/194 (84%)	30/194 (15%)	1		1	
	≥40	111 (29%)	88/111 (79%)	23/111 (21%)	1.54 (0.82-2.87)		1.47 (0.66-3.28)	
Sex[n=393]	Female	158 (40%)	125/158 (79%)	33/158 (21%)	1.14 (0.67-1.91)	0.63	1.30 (0.60-2.76)	0.50
	Male	235 (60%)	191/235 (81%)	44/235 (19%)	1		1	
Sputum grade[n=189]	Low	85 (45%)	59/85 (69%)	26/85 (30%)	1.62 (0.81-3.22)	0.17	1.24 (0.59-2.59)	0.57
	High	104 (55%)	80/104 (77%)	24/104 (23%)	1		1	
Community	1A	34 (8%)	18/34 (53%)	16/34 (47%)	-		-	
	1B	30 (7%)	17/30 (57%)	13/30 (43%)	-		-	
	2A	70 (17%)	43/70 (61%)	27/70 (39%)	-		-	
	2B	20 (5%)	18/20 (90%)	2/20 (10%)	-		-	
	3A	139 (33%)	123/139 (88%)	16/139 (11%)	-		-	
	3B	70 (17%)	49/70 (70%)	21/70 (30%)	-		-	
	4A	38 (9%)	30/38 (79%)	8/38 (21%)	-		-	
	4B	21 (5%)	18/21 (86%)	3/21 (14%)	-		-	

Table: Characteristics of individuals with CHiP positive TB results between 1/12/2015 -31/12/2017 who could and could not be matched to individuals in the TB treatment registers. CHiP=Community HIV-care providers; OR=odds ratios; aOR=adjusted odds ratios; 95%CI=95% confidence interval; Sputum grade=Low grade defined as Xpert low, very low and trace or smear scanty and 1+. High grade defined as Xpert medium and high or smear 2+ and 3+. [1]column percentages shown; [2]definite match between CHiP positive TB results in the presumptive TB registers and individuals in the TB treatment registers; [3]no definite match between CHiP positive TB results in the presumptive TB registers and individuals in the TB treatment registers; [4]row percentages shown; [5]univariable analysis using conditional logistic regression matched on community; [6]multivariable analysis using conditional logistic regression matched on community among N=177 with complete information on age, sex, and smear/Xpert grade of whom, n=41 with CHiP positive TB results in the presumptive TB registers could not be matched to individuals in the TB treatment registers.

Supplementary Appendix-S4

	2016			2017			Total		
Community	**Screen-identified**	**Total N**	**%**	**Screen-identified**	**Total N**	**%**	**Screen-identified**	**Total N**	**%**
1A	7	35	20%	8	54	15%	15	89	17
2A	14	90	16%	18	78	23%	32	168	19
3A	30	153	20%	51	148	34%	81	301	27
4A	7	102	7%	14	79	18%	21	181	12
Total in arm A	**58**	**380**	**15%**	**91**	**359**	**25%**	**149**	**739**	**20%**
1B	2	91	2%	12	97	12%	14	188	7
2B	7	65	11%	7	52	13%	14	117	12
3B	5	83	6%	8	85	9%	13	168	7
4B	8	87	9%	7	75	9%	15	162	9
Total in arm B	**22**	**326**	**7%**	**34**	**309**	**11%**	**56**	**635**	**9%**

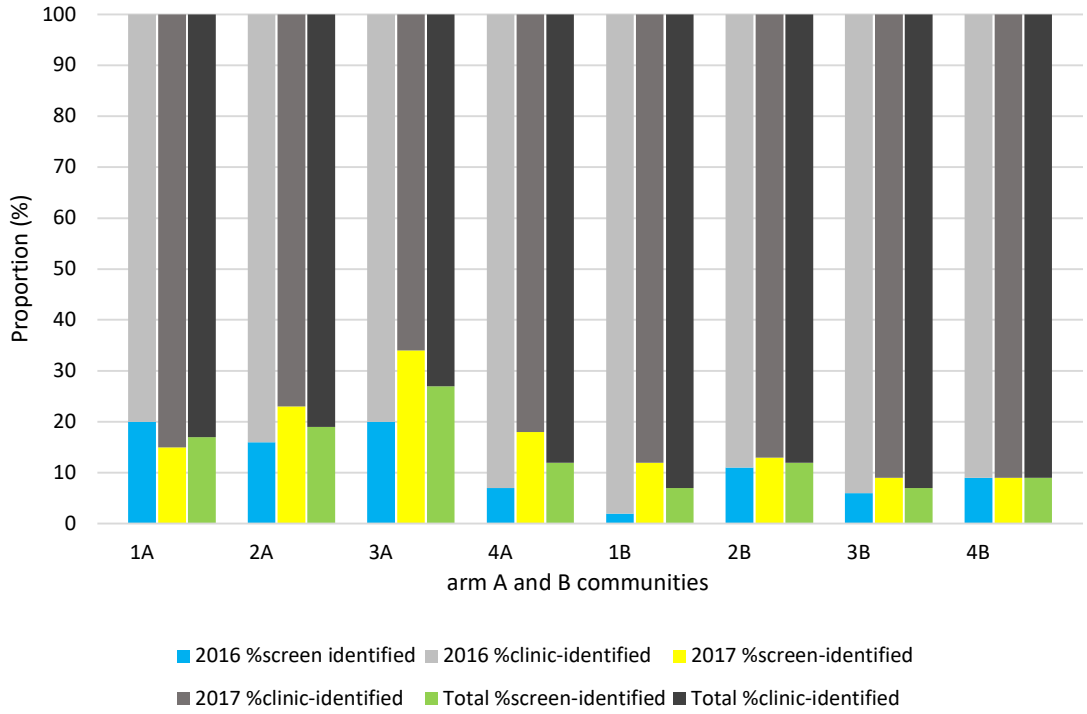

Table and Figure: Contribution of TB screening to new, Xpert/smear positive TB, among adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, and living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention; by community, arm, and year.

Supplementary Appendix-S5

Characteristic		Treatment outcomes[1]		OR[5] (95% CI)	p-value
		Not known[2] n(%)[4] n=182	Known[3] n(%)[4] n=1192		
Mode of diagnosis	screen-identified	28 (14%)	177 (86%)	0.87 (0.55-1.36)	0.54
	clinic-identified	154 (13%)	1015 (87%)	1	
Age/years	≤24	36 (17%)	172 (83%)	1.27 (0.77-2.09)	0.54
	25-29	35 (14%)	222 (86%)	0.95 (0.58-1.57)	
	30-34	41 (14%)	259 (86%)	1	
	35-39	31 (12%)	234 (88%)	0.81 (0.49-1.35)	
	40-44	18 (11%)	147 (89%)	0.76 (0.42-1.40)	
	≥45	21 (12%)	158 (88%)	0.83 (0.47-1.47)	
Sex	Female	50 (12%)	375 (88%)	0.91 (0.63-1.30)	0.59
	Male	132 (14%)	817 (86%)	1	
HIV status[N=1354]	Positive	97 (13%)	634 (87%)	1.23 (0.89-1.72)	0.20
	Negative	78 (13%)	545 (87%)	1	
Community[6]	1A	22 (25%)	67 (75%)	1.34 (0.77-2.36)	<0.001
	1B	40 (21%)	148 (79%)	1.11 (0.71-1.74)	
	2A	23 (14%)	145 (86%)	0.65 (0.38-1.10)	
	2B	11 (9%)	106 (91%)	0.43 (0.22-0.84)	
	3A	59 (20%)	242 (80%)	1	
	3B	10 (6%)	158 (94%)	0.26 (0.13-0.52)	
	4A	5 (3%)	176 (97%)	0.12 (0.05-0.30)	
	4B	12 (7%)	150 (93%)	0.33 (0.17-0.63)	

Table: Association between demographic and clinical characteristics and having treatment outcomes which were not known among new, Xpert/smear positive, adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, and living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention

OR=odds ratio; 95%CI=95% confidence interval; [1]denominator=1374 unless otherwise indicated; [2]combines outcomes of lost to follow-up (44/1374 [3%]), transferred out (33/1374 [2%]), not evaluated (4/1374 [<1%]) and missing (101/1374 [7%]); [3]combined outcomes of cured (1090/1374 [79%]), treatment completed (43/1374 [3%]), treatment failure (4/1374 [<1%]) and died (55/1374 [4%]); [4]row percentages shown; [5]adjusting for community; [6]communities shown by triplet (1 to 4) and arm (A or B)

Supplementary Appendix-S6

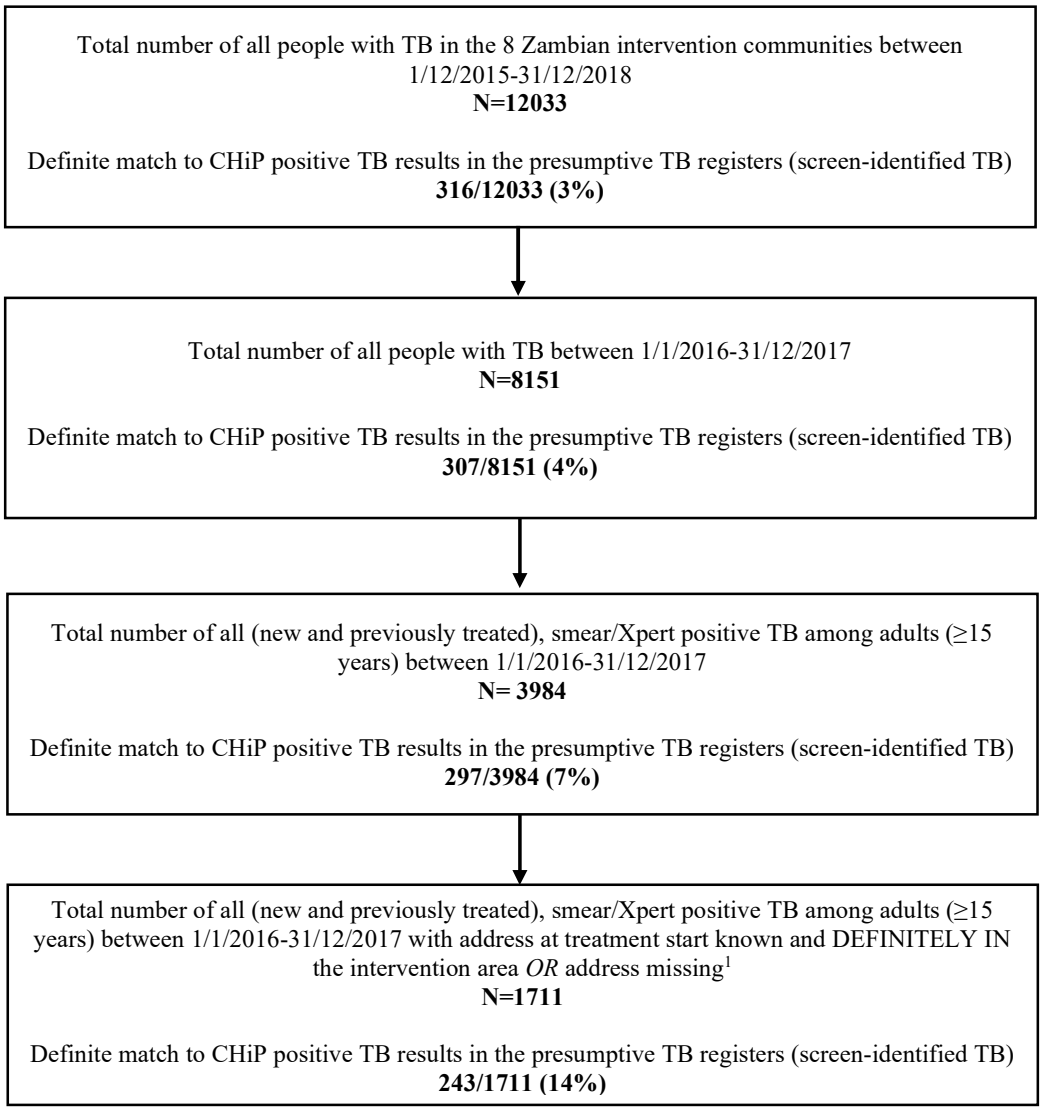

Figure: Matching CHiP positive TB results to TB treatment registers to determine people with screen-identified TB in the TB treatment registers and forming the sample for the secondary analysis among all (new and previously treated), Xpert/smear positive, adults (≥15 years), starting TB treatment between 1/1/2016-31/12/2017, who resided within community areas where all households in the area were eligible for the intervention.

TB=tuberculosis; CHiP=Community HIV-care providers; [1]excluding individuals with addresses NOT in intervention community OR address IN an intervention community area where only part of the area received the intervention and other parts did not which could not be confidently separated using the available addresses and landmarks

Supplementary Appendix-S7

Characteristic		Total N (%)[1,2] N=1711	Clinic-identified n(%)[3] n=1468	Screen-identified n(%)[3] n=243	OR[4] (95% CI)	p-value
Age/years	≤24	236 (14%)	202 (86%)	34 (14%)	0.98 (0.61-1.57)	0.85
	25-29	304 (18%)	265 (87%)	39 (13%)	0.80 (0.51-1.27)	
	30-34	360 (21%)	307 (85%)	53 (15%)	1	
	35-39	336 (20%)	291 (87%)	45 (13%)	0.84 (0.54-1.30)	
	40-44	233 (13%)	200 (86%)	33 (13%)	0.93 (0.58-1.51)	
	≥45	242 (14%)	203 (84%)	39 (16%)	1.07 (0.68-1.70)	
Sex	Female	517 (30%)	428 (83%)	89 (17%)	1.52 (1.13-2.05)	0.006
	Male	1194 (70%)	1040 (87%)	154 (13%)	1	
HIV status[N=1685]	Positive	954 (57%)	816 (86%)	138 (14%)	1.14 (0.86-1.52)	0.36
	Negative	731 (43%)	627 (86%)	104 (14%)	1	
Community	1A	106 (6%)	90 (85%)	16 (15%)	0.50 (0.28-0.89)	<0.001
	1B	252 (15%)	236 (94%)	16 (6%)	0.19 (0.11-0.33)	
	2A	219 (13%)	179 (82%)	40 (18%)	0.62 (0.41-0.95)	
	2B	152 (9%)	135 (89%)	17 (11%)	0.35 (0.20-0.61)	
	3A	353 (21%)	260 (74%)	93 (26%)	1	
	3B	215 (12%)	199 (93%)	16 (7%)	0.22 (0.13-0.39)	
	4A	212 (12%)	185 (87%)	27 (13%)	0.41 (0.26-0.65)	
	4B	202 (12%)	184 (91%)	18 (9%)	0.27 (0.16-0.47)	

Table: Characteristics of all (new and previously treated), Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention; overall and by case-finding method

OR=odds ratio; CI=confidence interval; [1]column percentages shown; [2]denominator=1711 unless otherwise indicated; [3]row percentages shown; [4]adjusting for community

Supplementary Appendix-S8

Characteristic		Sputum-grade						Treatment success					
		High[1]		Base model		Multivariable analysis[4]		Yes[6]		Base model		Multivariable analysis[7]	
		n/N	%[2]	OR (95% CI)[3]	p-value	aOR (95% CI)	p-value	n/N	%[2]	OR (95% CI)[3]	p-value	aOR (95% CI)	p-value
		978/1570	62%					1372/1711	80%				
Mode of diagnosis	Screen-identified	141/231	61%	0.92 (0.69-1.25)	0.61	0.95 (0.70-1.28)	0.74	196/243	81%	1.12 (0.78-1.60)	0.53	1.13 (0.79-1.64)	0.48
	Clinic-identified	837/1339	62%	1		1		1176/1468	80%	1		1	
Age/years	≤24	146/219	67%	1.35 (0.93-1.95)	0.03	1.14 (0.78-1.66)	0.17	180/236	76%	0.84 (0.56-1.25)	0.23	0.66 (0.44-1.01)	0.04
	25-29	188/282	67%	1.29 (0.92-1.80)		1.23 (0.88-1.74)		248/304	81%	1.16 (0.79-1.72)		1.10 (0.73-1.63)	
	30-34	204/328	62%	1		1		283/360	79%	1		1	
	35-39	192/308	62%	1.00 (0.72-1.38)		1.06 (0.76-1.47)		267/336	79%	1.08 (0.74-1.56)		1.09 (0.75-1.60)	
	40-44	121/210	58%	0.82 (0.58-1.18)		0.87 (0.60-1.24)		194/233	83%	1.39 (0.90-2.14)		1.44 (0.92-2.24)	
	≥45	127/223	57%	0.79 (0.56-1.12)		0.78 (0.54-1.11)		200/242	83%	1.35 (0.89-2.06)		1.27 (0.83-1.96)	
Sex	Female	265/476	56%	0.63 (0.50-0.79)	<0.001	0.72 (0.57-0.91)	0.006	432/517	83%	1.37 (1.04-1.82)	0.02	1.54 (1.15-2.07)	0.003
	Male	713/1094	65%	1		1		940/1194	79%	1		1	
HIV-status[5,8]	Positive	478/856	56%	0.58 (0.46-0.73)	<0.001	0.58 (0.46-0.73)	<0.001	750/954	79%	0.58 (0.44-0.76)	<0.001	0.58 (0.44-0.76)	<0.001
	Negative	485/691	70%	1		1		607/731	83%	1		1	
Community	1A	71/100	71%	1.37 (0.84-2.24)	0.22	1.33 (0.81-2.18)	0.35	73/106	69%	0.66 (0.41-1.07)	<0.001	0.66 (0.40-1.08)	<0.001
	1B	147/246	60%	0.80 (0.57-1.13)		0.81 (0.57-1.15)		197/252	78%	1.08 (0.73-1.60)		1.14 (0.76-1.71)	
	2A	140/214	65%	1.09 (0.75-1.56)		1.00 (0.69-1.46)		163/219	74%	0.86 (0.58-1.27)		0.81 (0.54-1.22)	
	2B	88/152	58%	0.77 (0.52-1.14)		0.80 (0.53-1.19)		125/152	82%	1.38 (0.85-2.24		1.48 (0.90-2.44)	
	3A	223/342	65%	1		1		271/353	77%	1		1	
	3B	91/157	58%	0.75 (0.51-1.11)		0.70 (0.47-1.05)		185/215	86%	1.87 (1.18-2.97)		2.01 (1.25-3.23)	
	4A	111/188	59%	0.84 (0.58-1.22)		0.86 (0.59-1.25)		191/212	90%	2.61 (1.55-4.38)		2.92 (1.71-4.99)	
	4B	107/171	62%	0.93 (0.63-1.37)		0.95 (0.64-1.40)		167/202	83%	1.40 (0.90-2.18)		1.49 (0.94-2.33)	

Table: Logistic regression analysis of the association between mode of diagnosis and sputum-grade and mode of diagnosis and TB treatment success among all (new and previously treated) Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention.

OR=odds ratio; 95%CI=95% confidence interval; aOR=adjusted odds ratio; [1]high grade defined as Xpert medium and high or smear 2+ and 3+; [2]row percentages shown; [3]adjusted for community, age and sex; [4]adjusted for community, age, sex and HIV-status among n=584 with low grade and n=963 with high grade who have complete information; [5]among 1547 with complete information of whom 963 had a high sputum-grade; [6]treatment success defined as treatment outcomes of cured and treatment completed combined among all individuals treated; [7]adjusted for community, age, sex and HIV-status among n=1357 with treatment success and n=328 without documented treatment success who had complete information; [8]among 1685 with complete information of whom 1357 successfully completed treatment.

Supplementary Appendix-S9

Characteristic		Died					
		Yes		Base model		Multivariable analysis[4]	
		n/N 74/1711[2]	%[1] 4%	OR (95% CI)[3]	p-value	aOR (95% CI)	p-value
Mode of diagnosis	Screen-identified	8/243	3%	0.82 (0.38-1.76)	0.61	0.87 (0.40-1.88)	0.72
	Clinic-identified	66/1468	4%	1		1	
Age/years	≥45	14/242	6%	1.42 (0.78-2.60)	0.27	1.49 (0.81-2.75)	0.21
	<45	60/1469	4%	1		1	
Sex	Female	21/517	4%	0.82 (0.49-1.39)	0.46	0.71 (0.42-1.21)	0.21
	Male	53/1194	4%	1		1	
HIV-status[N=73/1,685]	Positive	60/954	6%	3.59 (1.93-6.66)	<0.001	3.58 (1.93-6.64)	<0.001
	Negative	13/731	2%	1		1	

Table: Conditional logistic regression analysis of the association between mode of diagnosis and case fatality among all (new and previously treated), Xpert/smear positive, adults (≥15 years) starting TB treatment between 1/1/2016-31/12/2017 living in the Zambian HPTN 071 (PopART) intervention community areas where all households in the area were eligible for the intervention

OR=odds ratio; 95%CI=95% confidence interval; aOR=adjusted odds ratio; [1]row percentages shown; [2]number of deaths=74 and denominator=1711 unless otherwise indicated; [3]adjusted for community, age, and sex; [4]adjusted for community, age, sex and HIV-status among n=73 who died and n=1612 with no death documented who have complete information

Chapter 8: Discussion, implications, and future directions.

Overview

This section summarises the findings that are presented in Chapters 3 to 7 in relation to the objectives that this thesis aimed to address. It also describes the findings in the broader context of the HPTN 071 (PopART) trial.

Objective 1: To investigate the effect of increasing ART coverage on measures of population-level TB.

A literature review, presented in Chapter 3, identified 18 observational studies[1-18] from sub-Saharan Africa which consistently showed that TB notifications and diagnoses decreased coincident with increasing ART coverage through routine services, and increasing ART coverage was associated with decreased measures of population-level TB. Decreases were greater among people living with HIV (PLHIV) than those who were HIV negative. A single trial of universal testing and treatment for HIV (UTT) in Uganda and Kenya, the Sustainable East Africa Research in Community Health (SEARCH) trial, found on post-hoc analysis, an ~60% decrease in TB notifications among PLHIV in the UTT arm compared to the control arm in the third intervention year [19]. While formal comparisons were not made, the data also showed a steep fall in TB notification rates in the intervention arm during the second intervention year (i.e. following the roll-out of UTT). Among those HIV negative, there was no difference in TB notification rates. While study limitations prevent causal inferences, the totality of the evidence suggests that ART could contribute to TB control in sub-Saharan Africa.

Objective 2: To investigate changes to routine TB notifications with general population TB screening.

A systematic review presented in Chapter 4[20], identified seven before-after studies of different TB screening strategies in the general population (targeted vs population-wide screening, with screening mainly using symptoms but with more sensitive diagnostic

algorithms compared to routine care). The data suggest screening was associated with initial increases in TB case notification rates. Increases were greatest with population-wide screening (two studies), where screening identified ~55-65% of people with bacteriologically confirmed TB who were notified through routine services, during the screening period.

This contrasted with HPTN 071 (PopART) trial data shown in Chapter 7, where population-wide TB screening (using symptoms and diagnostic testing which followed routine practice), only identified ~15% of new bacteriologically confirmed adults with TB, notified from the Zambian intervention communities during the last two intervention years (2016-2017). This was during the intervention period when TB screening yield in Zambia was highest[21]. Zambian community HIV-care Provider (CHiPs) data presented in Chapter 1 showed the proportion of individuals identified with presumptive TB (i.e. had a positive symptom screen) increased over each intervention round, being 1.2%, 1.2% and 2.7% in intervention rounds 1, 2, and 3 respectively, and the yield of TB screening increased over each intervention round, being 81, 93, and 110 per 100,000 people screened in intervention rounds 1, 2, and 3 respectively[21].

Objective 3: To investigate the effect of the HPTN 071 (PopART) interventions of UTT and TB screening on the incidence of self-reported TB.

Self-reported TB was measured in the research cohort, called the Population Cohort or PC, established to measure the primary outcome of the HPTN 071 (PopART) trial. Large increases in self-reported TB were anticipated in intervention arm A and B communities with population-wide TB screening. But this was not seen and was in keeping with the low proportion of TB notifications identified through TB screening in Zambia, presented in Chapter 7.

Instead of an increase, the analysis presented in Chapter 5, showed an ~45-50% decrease in self-reported TB incidence among PLHIV in arm A compared to arm C. There was also some evidence this translated to a decrease in self-reported TB incidence overall in the population in arm A compared to arm C. The effect of the interventions on self-reported TB

incidence among those who were HIV negative could not be determined due to the small number of events. The findings were consistent with the body of literature[1-18] and mathematical model predictions[22] of the effect of increasing ART coverage on TB notifications. Further the estimated effect and the timing of the effect of UTT on self-reported TB incidence among PLHIV was consistent with findings from the SEARCH trial[19], and together these studies provide evidence to support the hypothesis that UTT could contribute to controlling TB in high TB/HIV burden settings.

Self-reported TB incidence was similar in arms B and C, overall and among PLHIV. The trial occurred during a period when the ART eligibility criteria for PLHIV through routine services rapidly changed; from <350 cells/μL, to <500 cells/μL, and then universal ART. Universal ART was established in all arm B and C communities in Zambia and South Africa in 2016 (in April-May 2016 in Zambia and in October-November 2016 in South Africa). Following the transition, in 2017/18, there was an ~20-30% reduction in the incidence of self-reported TB among PLHIV and overall, in arm B compared to arm C. But the confidence intervals around estimates were wide and crossed one. There were no further follow-up data to determine whether these changes were sustained, and therefore results should be interpreted with caution. Given the population-wide HIV testing and linkage to care activities in arm B, we anticipated some differences in self-reported TB incidence in arm B compared to arm C during the trial. CD4+ T-lymphocyte count data for PLHIV starting ART, which would have helped unpick these findings, were not available. But the proportion of PLHIV in the PC with viral suppression at PC24 (which spanned August 2016 to July 2017) in arm A compared to C was 72% versus 60%; aPR 1.16 (95% CI 0.99–1.36); p=0.07 and in arm B compared to C was 67% versus 60%; aPR 1.08 (95%CI 0.92–1.27); p=0.30[23]. HIV viral suppression while not directly related to TB disease incidence risk, does provide a measure of ART use, which is the pathway through which UTT decreases TB risk. The viral suppression data within the PC show that the difference between arm B and C was small, suggesting ART use may

have been more similar between these arms, which may in part explain their similar self-reported TB incidence.

Objective 4: To investigate whether TB screening can identify people with TB disease earlier in their clinical course and improve their clinical outcomes.

A systematic review presented in Chapter 6[24], identified very few studies investigating the effect of TB screening on clinical outcomes. From 919 articles on screening for all forms of TB, only 18 studies were eligible. Indeed, the main finding from this large review was that there were insufficient data to address the research questions. Despite this, there were some consistent findings worth noting. Studies in general populations and risk groups consistently showed no difference in treatment success between screened groups and routine health care groups. Studies in general populations showed no difference in case fatality among screened groups and routine health care groups. Four studies, all in risk groups (two observational [in miners and migrants] and two trials [in neonates and post-hoc analysis among household contacts of TB patients]), found TB screening was associated with lower case fatality and all-cause mortality. But due to study limitations (e.g. generalisability to all risk groups and the general population, study design and methods), it was not possible to draw any conclusions.

Objective 5: To investigate the association between how TB disease was diagnosed (TB screening versus self-presentation to health services) and the clinical outcomes of people with TB disease on TB treatment in the eight Zambian HPTN 071 (PopART) intervention communities.

This observational study was conducted in Zambian intervention communities during 2016-2017. Zambian arm B communities transitioned to universal ART in the 2nd Quarter of 2016; therefore, both arm A and B communities provided UTT from this point. As shown in Chapter 7, there was no association between mode of TB diagnosis (through systematic community-wide TB screening versus routine health services) and sputum-grade, treatment success or case fatality, among people with TB on treatment. Findings were consistent with data from general population TB screening studies identified through the systematic review presented in Chapter 6[24]. Despite UTT for most of the study period, treatment success was 40% lower

and case fatality three times higher among PLHIV, compared to those who were HIV negative. This underscores the continued need of PLHIV for rapid TB diagnosis, treatment and care, and prevention services.

Study limitations

The limitations of each study undertaken to address the research objectives have been explored/presented in detail within the results chapters. Here, the overall/key limitations of this body of work are discussed.

The greatest limitation was the lack of quality assured notification data from the study communities before, during and after the trial, even though these were sought. In South Africa, there were shortfalls in TB notifications captured through the Electronic TB Registers, across multiple communities and multiple calendar years, during the study period. In Zambia, where registers were in paper form, there were missing registers for multiple communities over multiple calendar year. We were therefore unable, as originally planned, to compare TB notification rates across trial arms, link PC data to TB notification data and explore changes to bacteriologically confirmed TB within the PC or compare treatment outcomes across study arms. These analyses would have allowed us to draw much firmer conclusions about the effect of the HPTN 071 (PopART) interventions on notified TB incidence and on treatment outcomes during the trial period.

While not specifically an objective of this study, CHiPs intervention data for South Africa were only available for intervention round 3, due to some data quality issues in rounds 1-2[21, 25]. Therefore, it is unclear to what extent the findings from the Zambian intervention data can be generalised to South Africa. These data would have given us a better understanding of overall TB screening yield and UTT coverage against which self-reported TB incidence was being measured.

The PC was a large cohort, of ~38,500 individuals, recruited from all 21 communities and followed up ~annually over 3 years. Within the PC, individuals were offered HIV testing as part of study procedures. Therefore, it was possible that in this cohort with repeated follow-up, behaviour may have been altered in all study arms, with PC participants taking up the offer of HIV testing, and PLHIV accessing care and taking ART (i.e. a type of Hawthorne effect). This may in part explain the large decrease in self-reported TB incidence in arm A (which received universal ART from the start) compared to arm C (which received ART according to national guidelines) and the similar self-reported TB incidence in arms B and C (which both received ART according to national guidelines). However, the primary outcome (HIV incidence) and key secondary HIV outcomes of the trial suggest that there were differences between trial arms[23], which would also be relevant for understanding TB outcomes within the PC. First the proportion of PLHIV with viral suppression was, as already noted, higher in arms A and B than in arm C. HIV incidence was also lower in arms A and B than arm C. While these HIV metrics are not directly related to TB disease incidence risk per se, which is associated with immunosuppression as measured via CD4+ T-lymphocyte counts[26-28], it still suggests there were differences between arms which could be attributed to differences in taking ART. As already mentioned, the lack of CD4+ T-lymphocyte count data for the PC which were critical to understanding differences in self-reported TB incidence risk among PLHIV, was another limitation of this study.

Attrition during PC follow up was high. The primary reason PC participants were not seen was due to permanent relocation. There were no differences in the characteristics of those seen at least once and those not seen during follow up (i.e. only had a baseline PC0 visit), or of those seen and not seen at each PC visit/calendar year. Further the characteristics of those seen at each PC visit by study arm were similar. Given these observations, while selection bias cannot be excluded, it is less likely to be substantial.

While the PC was a large cohort, among those HIV negative, there were very few self-reported TB events, with no events in some communities over several calendar years.

Therefore, any estimate of the effect of the HPTN 071 (PopART) interventions on self-reported TB incidence among those HIV negative would have had very low precision and power; therefore, these calculations were not undertaken. Due to this, we were unable to evaluate the overall impact of the interventions.

Definitive evidence for the effect of TB screening on treatment outcomes requires trials comparing screened and unscreened populations. We were only able to undertake an observational analysis, comparing TB treatment outcomes among people with TB identified through TB screening and those identified through routine services, in the Zambian intervention communities alone. We used presumptive TB register data to identify individuals diagnosed through CHiPs TB screening, which may have been subject to information bias. But when compared to CHiPs intervention data (captured by CHiPs onto electronic data capture devices and used to monitor the CHiPs intervention processes [Table 1]), the numbers identified using presumptive TB registers were higher in intervention round 2 and similar in intervention round 3. This was compatible with feedback from the Zambian intervention team, where shortfalls in updating CHiPs intervention data were identified in intervention round 2 and corrected during round 3. Despite our efforts to increase the sensitivity and specificity of the matching algorithm, it was possible some people who did start treatment were missed. CHiPs intervention data also showed ~20% of those identified had not commenced TB treatment (based on self-report); again, similar to our finding that 25% of individuals could not be matched to TB treatment registers.

Table 1: Comparing the total number of people with TB identified through CHiPs TB screening in Zambia, in the CHiPs intervention database and in the presumptive TB registers, by intervention round.

	CHiPs intervention database	Presumptive TB register data
Intervention round 2	173	259
Intervention round 3	220	258

Evidence in the context of other HPTN 071 outcomes

The Tuberculosis Reduction through Expanded Anti-retroviral Treatment and Screening (TREATS) study was carried out to measure TB outcomes of the HPTN 071 (PopART) trial. A primary objective of TREATS was to conduct a TB disease prevalence survey in all 21 communities and compare prevalence in the intervention (A and B) and control (C) arms[29]. Due to the COVID-19 pandemic, the prevalence survey timelines were delayed, with the survey completed between 2019-2021, 2-4 years following the end of the HPTN 071 (PopART) intervention. TB disease prevalence across study communities was high at ~0.9%. The results showed no evidence that the HPTN 071 (PopART) interventions decreased TB disease prevalence (arm A versus C adjusted prevalence ratio [aPR] 1.29 [95% confidence interval (CI) 0.69-2.39], p=0.38; arm B versus C aPR 1.01 [95%CI 0.54-1.88], p=0.97). Given the self-reported TB incidence data from the PC, this was a surprising result.

Table 2 summarises the characteristics of those who took part in the TREATS prevalence survey. Approximately 60% of those invited to participate across both countries were surveyed to meet the required sample size. Of those that took part, ~70-75% had been resident in the community for >5 years, with ~50% resident for >10 years. This suggests a population that would have been aware of the HPTN 071 (PopART) trial in the control arm and intervention arms (where they would have also had the opportunity to receive the intervention). A striking feature of the study sample was the similarity in all HIV indicators (known HIV positive at the time of the survey, current ART use among those with known HIV positive status, and newly testing HIV positive during the survey) across the study arms. Among those who knew their HIV positive status, a high proportion (>90%) self-reported current ART use in arm C. Indeed, this proportion was similar to the proportion that self-reported ART use among those who knew their HIV positive status in arm A following the 3rd (and final) round of the HPTN 071 (PopART) UTT intervention (data also shown in Table

2)[25], and similar to findings in the Arm A communities during the TREATS prevalence survey.

While surprising, it was possible that routinely available HIV testing services and targeted community testing campaigns along with universal ART since 2016, may have resulted in high ART uptake in arm C in 2019-2021, similar to that achieved through the HPTN 071 (PopART) UTT intervention. Alternatively, the population who took part in the survey, being mostly long-term residents who would have been aware of the HPTN 071 (PopART) trial and its overarching goals, may represent a population who were more likely to seek HIV testing and universal ART services, when available. Irrespective of the reason, if UTT was the main driver of decreases in self-reported TB incidence among PLHIV in the PC, the similar and high ART use among PLHIV across all arms by the time of the TREATS prevalence survey, would be expected to decrease any differences in TB disease prevalence between the intervention and control arms.

Table 2: Characteristics of individuals who took part in the HPTN 071 (PopART) CHiPs 3rd intervention round by country, and individuals who took part in the TREATS prevalence survey by study arm

	HPTN 071 (PopART): 3 intervention rounds between 2014-2017[1]		**TREATS prevalence survey 2019-2021[2]**	
	Zambia round 3	**SA round 3**	**Arm C**	**Arm A**
Residency in community >5 years[3]	-	-	70%	74%
Accepted HIV interview	-	-	96%	97%
% who knew their HIV positive status[4]	-		15%	16%
% newly testing HIV positive among those accepting testing			2.6%	2.5%
% of all who took part who knew their HIV positive status[5]	9% men 16% women	8% men 17% women	17%	17%
% who knew their HIV positive status who were on ART[6]	85% men 89% women	84% men 92% women	92%	93%

CHiPs=community HIV-care Providers; TREATS=Tuberculosis Reduction through Expanded Anti-retroviral Treatment and Screening; SA=South Africa; PLHIV=people living with HIV; ART=antiretroviral therapy. [1]CHiPs data shown for intervention arm A and round 3 alone unless

otherwise indicated; [2]TREATS survey conducted to measure the effect of the HPTN 071 (PopART) interventions on TB prevalence;; [3]~50% had resided in the community for >10 years; [4]Based on self-report during the TREATS prevalence survey; [5]based on self-report and HIV testing; [6]based on self-report at the end of the 3rd intervention round during the HPTN 071 (PopART) trial and includes all individuals who knew their HIV positive status (including those who newly tested HIV positive who were referred for ART). By self-report at the time of the TREATS prevalence survey, and therefore does not include individuals who newly tested HIV positive during the TREATS prevalence survey.

As the HPTN 071 (PopART) UTT intervention in arm A started in ~November 2013, ART coverage in arm A communities would have been higher for longer, than in arm C communities. Therefore, TB disease prevalence would have still been expected to be lower in arm A communities compared to those in arm C. But this was not observed. Indeed, overall TB disease prevalence was higher in arm A communities compared to those in arm C. By country, TB disease prevalence was consistently higher in Zambian arm A communities compared to arm C communities, while in South Africa, TB disease prevalence was consistently lower in arm A communities compared to arm C communities[(29)]. Routine Zambian Ministry of Health data on all bacteriologically confirmed TB notifications for three of the four arm A and arm C communities were available for 2013 (i.e. in the year before the start of HPTN 071 [PopART] trial). The geometric mean TB notification rates were 218 per 100,000 population for the three arm A communities and 159 per 100,000 population for the three arm C communities, suggesting some baseline (chance) imbalances in TB disease burden by study arm may have existed in Zambia. Similar data for South Africa were unavailable.

Further, the longer-term effects of UTT on TB disease incidence remain unclear. Mathematical modelling predicts that following steep initial decreases in HIV-associated TB disease incidence, incidence subsequently falls more slowly[(22)]. Arm C communities transitioned to universal ART during the course of 2016 (i.e. ~2-2.5 years before the start of

the TREATS prevalence survey which took ~3 years to complete). Therefore, if mathematical modelling predictions were correct, sufficient time at high ART coverage may have elapsed across all arms, for TB disease incidence in arm C to have fallen steeply, and the arm A versus C risk ratios to increase and move closer to one.

Finally, HIV in the absence of ART is more strongly associated with TB disease incidence than TB disease prevalence (which is influenced by both disease incidence and its duration) due to the shorter TB disease duration among PLHIV compared to those who are HIV negative[30, 31]. With increasing ART coverage, TB disease incidence among PLHIV is expected to fall. But the effect on TB disease prevalence may be variable and is unclear. If TB disease among PLHIV on ART resembles TB disease among those who are HIV negative (which is typically more infectiousness and has a longer duration)[32, 33], the effect of increasing ART coverage on TB disease prevalence may be smaller than its effect on incidence. This together with the similar high ART coverage across study arms by the time of the TREATS prevalence survey may have contributed to the differences observed between the survey and self-reported TB incidence in the PC.

Implications of findings and future research directions

The data presented in this thesis, together with the body of literature that precedes it, suggest that UTT can decrease TB disease incidence among PLHIV in sub-Saharan Africa at the population-level and contribute to TB control. The next step is to understand how these findings can be translated into routine practice. A key question is whether routine HIV testing services with linkage to universal ART are sufficient to achieve levels of ART coverage similar to those achieved through an intensive community wide UTT intervention delivered over 4 years. TREATS data[29] suggests that they may be; but it is unclear if these findings, from communities engaged in research for many years, are generalisable. Further the data are based on self-report. A study comparing ART coverage (using routine ART

data and population HIV projections) and TB notification rates in the HPTN 071 (PopART) study areas with surrounding non-study areas during the HPTN 071 (PopART) and TREATS study period, might help identify if community-specific characteristics played a part in the TREATS prevalence survey findings. Going forward, identifying models of universal HIV testing and linkage-to-care that are acceptable, cost-effective, and reflect the local TB/HIV epidemiology will also be important.

The long-term effects of universal ART on TB disease incidence are unclear. Ecological studies investigating trends in routine TB notification rates following the introduction of universal ART can generate data to address this question. Further, studies which investigate *Mycobacterium tuberculosis* transmission from PLHIV who are on ART at different CD4+ T-lymphocyte counts will help to determine whether immediate ART increases the infectiousness of PLHIV with TB disease. These data will be important to understand the likely long-term impact of universal ART on TB epidemiology.

Despite UTT, the incidence of self-reported TB and TB disease prevalence among PLHIV remained high. This was coupled with the higher case fatality and lower treatment success among PLHIV on TB treatment compared to those who were HIV negative. This suggests that further measures to prevent TB disease among PLHIV are warranted. TB preventive therapy is known to decrease the risk of TB disease among PLHIV on ART[34-37]. During the HPTN 071 (PopART) trial period, TB preventive therapy use was limited. However, in recent years, national TB programmes have focused on efforts to increase TB preventive therapy use among PLHIV, with a view to improving the morbidity and mortality associated with TB disease in this at-risk group. Combined with universal ART, this may result in further reductions in TB disease incidence among PLHIV.

In the HPTN 071 (PopART) trial, community wide systematic TB screening using a symptom questionnaire, coupled with smear and Xpert testing of those screening positive, did not result in large increases in self-reported TB or identify as large a proportion of notifications in

the intervention arms, as had been anticipated. Reasons for this are likely to be multifactorial and include the lower sensitivity of TB symptom screening for prevalent undiagnosed TB compared to other screening modalities[38], the highly pragmatic nature of this trial during which CHiPs focused on the HIV prevention activities during the early trial period, followed by TB screening activities later during the trial which may have been insufficient to significantly impact TB epidemiology[29], and the lower reach of the intervention to population groups at higher risk of TB, such as men[25, 39].

An estimated ~30% of those with incident TB disease, are either not diagnosed or not reported through national TB programmes annually[40], suggesting a need for provider-initiated TB screening efforts to identify “the missing millions”. There is some evidence from randomised and non-randomised studies that TB screening, in particular more intensive screening with tools such as chest radiographs or sputum Xpert MTB/RIF for all, if implemented with sufficiently high coverage, can be associated with decreases in TB disease prevalence[38, 41]. TB screening efforts must always be context specific. In settings with generalised high TB prevalence or barriers to accessing TB diagnostic and treatment services, a community wide TB screening approach may be considered appropriate if sufficient resources are available. In settings where high TB prevalence is restricted to risk groups within the population, a targeted approach will be most appropriate. Ultimately to scale-up TB screening to any population group (whole communities or risk groups) in sub-Saharan Africa and other low and middle income countries which achieves its maximum potential impact, will require simple to use screening/diagnostic tools and algorithms which are scalable, sustainable, and can be implemented by community health workers or those with little training, which ideally identify the full spectrum of TB disease (from incipient to symptomatic TB disease) with high sensitivity and specificity, are acceptable, and achieve high population coverage[42].

None of the current World Health Organization (WHO) recommended TB screening/diagnostic tools (symptom screen, chest radiographs, and rapid molecular

diagnostic tests) meet all these criteria[38]. WHO has released high priority TB target product profiles to identify biomarkers and tests for screening and diagnosis[43]. Several large international research groups are working with product developers to push the TB diagnostic pipeline forward and identify tests that meet the WHO specifications[44]. If successful, this may change the TB screening and diagnostic landscape and facilitate the scale-up of TB screening, globally. In the interim, implementation studies that generate data on models of how to cost-effectively scale-up and optimise the use of current WHO recommended TB screening tools, can help guide routine TB programmes.

In the WHO END-TB era, to monitor TB trends, and plan, implement and evaluate TB prevention interventions, routine programmes must have access to quality assured TB surveillance data. WHO encourages countries to adopt digital surveillance tools, with examples of improved notifications, and the potential benefits of improved data quality and timely information, which can be used for analysis and reporting, when moving from paper-based to electronic systems[45]. The greatest limitation of this current body of work, was the lack of quality assured TB notification data from the study communities. In Zambia, TB registers were in paper form, with missing registers over several years primarily preventing the use of these data; electronic registers may have mitigated these problems. However, in South Africa, where TB registers were electronic, shortfalls were still identified which prevented the use of these data, highlighting the need for quality assurance processes alongside electronic systems. As countries move towards digitizing TB recording and reporting systems, key considerations include opportunities for shared learning across country programmes, need for user-centred approaches, with capacity development and training to address identified skills gaps, effective and sustainable systems, timely and responsive quality assurance processes, and clear policies on data governance and management[46].

Conclusion

This thesis contributes to the evidence base on the effect of UTT and TB screening on TB epidemiology. The data suggest that UTT can contribute to TB control in high TB/HIV prevalence settings. But, despite community wide UTT, case fatality among PLHIV on TB treatment was high, highlighting their continued need for TB prevention interventions. Community wide TB screening using symptoms combined with sputum smear and Xpert MTB/RIF for diagnosis identified a low proportion of TB notifications and did not result in an increase in self-reported TB. This suggests the TB screening component of the intervention is likely to have contributed little to any intervention effect on TB epidemiology.

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