

Tuberculosis outcomes during the COVID-19 pandemic in two high-burden countries

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FRONT MATTER

Abstract

The COVID-19 pandemic has disrupted tuberculosis (TB) services globally. Measuring the extent of these disruptions is critical to mitigate their impact and provide valuable information for TB program improvement, particularly in settings hard-hit by both COVID-19 and TB, such as Peru and India. The overall aim of this manuscript-based thesis was therefore to evaluate TB care and outcomes during the COVID-19 pandemic in Peru and India and compare them to pre-pandemic trends.

In **Manuscript 1**, we introduced TB care cascades and outlined data gaps for constructing them. Care cascades are a representation of the proportion of people reaching key milestones in TB care and are a valuable tool, particularly in the context of COVID-19, for measuring TB care delivery disruptions across the care pathway. This provides important context for **Manuscript 2**, in which we constructed the drug-susceptible (DS) and drug-resistant (DR) TB care cascades prior to and during COVID-19 in Lima province, Peru. We also collected data from patient registries of n=1,513 people receiving TB care in a district of Lima to identify predictors of cascade completion. The final gap in the cascade (those initiating vs. those completing treatment) was the largest gap across all cascades except for in the group receiving TB care entirely during COVID-19, in which the pre-diagnosis gap (estimated burden vs. number diagnosed) was the largest for both the DS-TB and DR-TB cascades. Receiving TB care entirely during COVID-19 was associated with a lower likelihood of cascade completion (OR:0.51, 95%CI:0.29-0.88).

Given that COVID-19-related setbacks have made it even more urgent to focus TB elimination efforts on key populations, in **Manuscript 3**, we further investigated the effect of COVID-19 disruptions on TB specifically in incarcerated populations in Peru, who face a particularly high burden of TB, and who may have experienced COVID-19 disruptions differently than the non-incarcerated population. Using Peruvian National TB Program (NTP) data we conducted interrupted time series analyses in the non-incarcerated, incarcerated and overall population to

assess pre- and during COVID-19 trends in TB case notifications compared to their counterfactual values (in the absence of COVID-19). The start of COVID-19 was defined as 16 Mar 2020 (declaration of the national emergency due to COVID-19 in Peru). Our findings indicate a 61.2% (95%CI: 59.9-62.7%) drop in TB case notifications in the first week of the COVID-19 pandemic in the non-incarcerated population and a 17.7% (95%CI: 17.5-17.9%) drop in the incarcerated population.

Finally, in **Manuscript 4**, we assessed in-treatment and post-treatment case-fatality among people diagnosed with TB and enrolled in a private sector TB program in India in the first year of the COVID-19 pandemic (Mar 2020-Mar 2021) and compared this to pre-pandemic estimates among people enrolled in the same program. We collected follow-up data through phone surveys of n=4,000 individuals, of which n=2,962 (74.1%) responded to the survey. We used inverse probability of selection (IPS) weighting to correct for selection bias. We estimated an IPS weighted in-treatment case fatality ratio (CFR) of 6.07% (95%CI: 5.22-6.93%), significantly lower ($p=0.036$) than the pre-COVID-19 CFR (7.27%, 95%CI: 5.97-8.49%).

In conclusion, large pre-diagnosis gaps in the during-COVID-19 TB care cascades in Peru highlight that efforts to increase case detection are urgently needed to regain lost progress on TB elimination. Furthermore, TB burden is extremely high in Peruvian prisons, but TB case notifications were less impacted by COVID-19 disruptions than the general population. Lastly, the observed TB case-fatality in an Indian private sector cohort treated during COVID-19 is above the level needed to reach the 2025 and 2030 End TB Strategy targets for reductions in TB deaths, further highlighting the need to get on track to TB elimination.

Résumé

La pandémie de COVID-19 a perturbé les services de lutte contre la tuberculose (TB) dans le monde. Il est essentiel de mesurer l'étendue de ces perturbations pour atténuer leur impact et fournir des informations utiles pour l'amélioration des programmes de lutte contre la TB, en particulier dans les pays durement touchés à la fois par la COVID-19 et la TB, comme le Pérou et l'Inde. L'objectif général de cette thèse était donc d'évaluer les interruptions de soins et les résultats de traitement pour la TB pendant la pandémie de COVID-19 au Pérou et en Inde.

Dans le **manuscrit 1**, nous avons souligné les défis liés à l'estimation précise des cascades de soins pour la TB, qui sont une représentation de la proportion de personnes atteignant des étapes clés dans le parcours de soins pour la TB, et qui sont un outil précieux, en particulier dans le contexte de la pandémie de COVID-19, pour mesurer les perturbations de la prestation des soins antituberculeux à travers le parcours de soins. Cela fournit un contexte important pour le **manuscrit 2**, dans lequel nous avons construit les cascades de soins pour la TB sensible aux médicaments (SM) et résistante aux médicaments (RM) avant et pendant la pandémie de COVID-19 dans la province de Lima, au Pérou. Nous avons également collecté des données à partir de registres de patients de $n = 1\,513$ personnes ayant reçu des soins antituberculeux dans un district de Lima afin d'identifier les prédicteurs d'achèvement de la cascade de soins. L'écart final dans la cascade (entre le nombre de personnes commençant le traitement et le nombre qui le terminent) était le plus grand écart dans toutes les cascades, sauf dans le groupe ayant reçu des soins antituberculeux entièrement pendant la pandémie de COVID-19, dans lequel l'écart avant le diagnostic (la charge de tuberculose estimée par rapport au nombre de personnes diagnostiquées) était le plus important pour les cascades de TB SM et RM. Le fait de recevoir des soins antituberculeux entièrement pendant la pandémie était associé à une probabilité plus faible d'achèvement de la cascade (OR: 0,51, 95CI%: 0,29-0,88).

Étant donné que les revers liés à la COVID-19 ont rendu encore plus urgent de concentrer les efforts d'élimination de la TB sur les populations clés, dans le **manuscrit 3**, nous avons étudié plus en détail l'effet des perturbations de la COVID-19 sur la TB, en particulier dans les

populations incarcérées au Pérou, qui font face à un fardeau particulièrement élevé de la TB et qui peuvent avoir vécu les perturbations liées à la COVID-19 différemment de la population non incarcérée. À l'aide des données du Programme national péruvien de lutte contre la tuberculose, nous avons effectué des analyses de séries chronologiques interrompues dans la population non incarcérée, incarcérée et dans l'ensemble des populations pour évaluer les tendances dans les notifications de cas de TB avant et pendant la pandémie, par rapport à leurs valeurs contrefactuelles (en l'absence de la COVID-19). Le début de la COVID-19 a été défini comme le 16 mars 2020 (déclaration d'urgence nationale due à la COVID-19 au Pérou). Nos résultats indiquent une baisse de 61,2% (95%CI: 59,9-62,7%) au cours de la première semaine de la pandémie dans la population non carcérale et une baisse de 17,7% (95%CI: 17,5-17,9%) dans la population carcérale.

Enfin, dans le **manuscrit 4**, nous avons évalué la létalité pendant et après le traitement chez les personnes traitées pour la TB au cours de la première année de la pandémie de COVID-19 (mars 2020-mars 2021) dans un programme du secteur privé en Inde, et nous avons comparé cette estimation aux estimations pré-pandémiques parmi les personnes inscrites au même programme. Nous avons recueilli des données de suivi à partir d'enquêtes téléphoniques auprès de $n = 4\,000$ personnes, dont $n = 2\,962$ (74,1%) ont répondu à l'enquête. Nous avons utilisé la pondération par probabilité inverse de sélection (PIS) pour corriger le biais de sélection. Nous avons estimé un taux de mortalité en cours de traitement (pondéré par PIS) de 6,07% (IC à 95%: 5,22-6,93%), significativement inférieur ($p = 0,036$) au taux de mortalité pré-COVID-19 (7,27%, IC à 95% : 5,97-8,49%).

En conclusion, les grandes lacunes pré-diagnostiques dans les cascades de soins de la TB pendant la COVID-19 au Pérou soulignent que des efforts pour augmenter la détection des cas sont nécessaires de toute urgence pour regagner les progrès perdus dans l'élimination de la TB. De plus, le fardeau de la TB est extrêmement élevé dans les prisons péruviennes, mais les notifications de cas de TB dans les prisons ont été moins touchées par les perturbations liées à la COVID-19 que dans la population générale. Enfin, le taux de mortalité observé dans une

cohorte du secteur privé indien traitée pendant la COVID-19 était supérieur au niveau nécessaire pour atteindre les objectifs de la stratégie de lutte contre la TB de 2025 et 2030 en matière de réduction des décès dus à la TB, soulignant davantage la nécessité de se mettre sur la bonne voie vers l'élimination de la TB.

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Contribution of authors

As first author on all included manuscripts, I developed study protocols, oversaw data collection, communicated with data collection teams in India and Peru, and conducted data analyses for all studies, with input from my supervisor, committee members, and the co-authors of each manuscript. With feedback from mentors, I also interpreted study findings, and wrote all chapters in this thesis. Contributions of co-authors to each manuscript are described below.

Manuscript 1: Improving measurement of tuberculosis care cascades to enhance people-centered care

Dr. Ramnath Subbaraman conceptualised the study, with input from me. I led meetings with all co-authors to aggregate their experiences with care cascade estimation challenges in their respective settings. I conducted data visualization, with input from Dr. Ramnath Subbaraman and co-authors. Supervision for this project was jointly provided by Dr. Ramnath Subbaraman and Dr. Madhukar Pai. I drafted the manuscript, with input provided by all co-authors.

Manuscript 2: TB care cascades and predictors of cascade completion prior to and during the COVID-19 pandemic in Lima province, Peru

I conceptualised the study and drafted the protocol, with input from Dr. César Ugarte-Gil, Dr. Madhukar Pai, Dr. Ramnath Subbaraman, Dr. Andrea Benedetti, and Dr. Sophie Huddart. A panel of five TB survivors and advocates also provided feedback on the protocol. Cascade estimation methods were based on guidelines developed and published by Dr. Ramnath Subbaraman.¹ For the primary data collection component of the project, I oversaw data collection, communicated with the data collection team in Lima, Peru, and conducted a site visit to Lima. Dr. César Ugarte-Gil locally supervised the data collection team, which was led by Dr. Guillermo Caceres-Cardenas. Ms. Naomi Urbina Suyu collected the data. Other study objectives utilized existing data provided by the Peruvian NTP.² I conducted all data analyses, with input from co-authors. The overall project was jointly supervised by Dr. César Ugarte-Gil and Dr. Madhukar Pai. I drafted the manuscript, with critical input from co-authors.

Manuscript 3: Tuberculosis case notifications and outcomes in Peruvian prisons prior to and during the COVID-19 pandemic: A national-level interrupted time series analysis

I conceptualised the study and drafted the protocol, with input from Dr. César Ugarte-Gil, Dr. Madhukar Pai, and Dr. Leonardo Martinez. The study used existing data provided by the Peruvian NTP.² Dr. Guillermo Caceres-Cardenas and I visited two prisons in Lima, Peru, for contextual understanding of TB management in prisons. I conducted all data analyses, with input from co-authors. Dr. Leonardo Martinez provided expertise on TB in prisons, and Dr. Sophie Huddart and Dr. Andrea Benedetti provided guidance on data analysis, in particular on the specification of models for the interrupted time series. The overall project was jointly supervised by Dr. César Ugarte-Gil and Dr. Madhukar Pai. I drafted the manuscript, with critical input from co-authors.

Manuscript 4: Case fatality among people with TB enrolled in a private health sector TB treatment support program in Bihar, India during the first year of the COVID-19 pandemic

Dr. Madhukar Pai and I conceptualised the study, with critical guidance from Dr. Sophie Huddart, who led a similar study prior to the COVID-19 pandemic, to which the current study's estimates were compared. Methods used in this study were therefore based on methods used in Dr. Huddart's prior work.³ I drafted the protocol, with input from Dr. Sophie Huddart, Dr. Madhukar Pai, Dr. Nita Jha, and Dr. Andrea Benedetti. A panel of four TB survivors and advocates also provided feedback on the protocol. Baseline data were from the World Health Partners program, and follow-up data were collected by Dr. Ayushi Ranjan, who conducted the follow-up calls. I conducted all data analyses, with input from co-authors, in particular from Dr. Sophie Huddart, to ensure comparability of methods in our two studies. I drafted the manuscript, with critical input from co-authors.

Statement of originality

Each of the four manuscripts in this thesis are original scholarship and make contributions to knowledge. Detailed contributions of co-authors are described below for each manuscript.

Manuscript 1 aggregates the experiences and expertise of researchers who have estimated TB care cascades across six countries, to discuss critical data gaps that hinder accurate TB care cascade measurement. This work serves as a consensus statement on these data gaps and their potential solutions, which are needed to facilitate the use of care cascades as a tool for evidence-based TB program planning and improvement.

Manuscript 2 represents the first estimation of an active TB care cascade in Peru. In addition, it provides valuable insight into TB care delivery disruptions during COVID-19 in this setting across the full cascade of care, rather than focusing solely on single indicators (e.g., treatment outcomes).

Manuscript 3 is the first study comparing TB case notifications and treatment outcomes prior to and during the COVID-19 pandemic in the incarcerated and non-incarcerated populations of Peru. This is a valuable contribution to knowledge given that incarcerated populations are at particularly high risk for TB, shoulder a large proportion of the total TB burden in South America, and may have experienced COVID-19 disruptions differently than non-incarcerated populations.

Manuscript 4 provides selection-bias-corrected estimates of case fatality among people with TB enrolled in a private sector TB treatment support program in Bihar, India during the COVID-19 pandemic, and takes advantage of a unique opportunity to compare these during-COVID-19 estimates to existing pre-COVID-19 estimates³ derived from a cohort enrolled in the same program, using analogous methods.

List of abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
DOT	Directly observed therapy
DR-TB	Drug resistant TB
DST	Drug susceptibility testing
EPTB	Extrapulmonary TB
HIV	Human immunodeficiency virus
HR	Hazard ratio
INH	Isoniazid
INPE	Instituto nacional penitenciario (Peruvian national penitentiary institute)
IPS	Inverse probability of selection
IRR	Incidence rate ratio
ITS	Interrupted time series
MDR-TB	Multidrug-resistant tuberculosis
MICE	Multiple imputation by chained equations
NTP	National TB program
OR	Odds ratio
PPM	Public Private Mix
PPSA	Private provider support agency
PTB	Pulmonary TB
QI	Quality improvement
RIF	Rifampicin
SIGTB	Sistema de información gerencial de tuberculosis (Peruvian NTP database)
TB	Tuberculosis
VDOT	Video directly observed therapy
WHO	World Health Organization
WHP	World Health Partners
XDR-TB	Extensively drug resistant tuberculosis

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CHAPTER 1: INTRODUCTION

1.1 Introduction

“...[a person with pulmonary TB] presented numerous times with pleurisy and cough over months and had three COVID-19 tests and no TB assessment or testing. [They were] finally picked up to have smear positive TB. [They] died during treatment.”

~ TB program lead, Stop TB Canada Report on the Impact of COVID-19 on Tuberculosis Programs in Canada⁴

Tuberculosis (TB) is a bacterial infectious disease and an urgent global public health concern, being responsible for more annual deaths worldwide than any other infectious disease prior to the COVID-19 pandemic.⁵ In 2021, there were an estimated 10.6 million new cases of TB, and 1.6 million deaths due to TB.⁶ Being inextricably linked to social determinants of health,⁷ the global burden of TB continues to be unequally distributed, with 87% of the incident cases worldwide in 2021 occurring in just 30 high-burden countries.⁶

The World Health Organisation (WHO)’s End TB Strategy has outlined goals to reduce TB incidence by 90% and TB-associated deaths by 95% by 2035, compared to 2015 levels, but we are not on track to meet these goals.⁸ Concerningly, the COVID-19 pandemic has significantly disrupted TB programs globally,⁹ setting back already slow progress on ending TB. For example, in 2020, the WHO reported the first year-on-year increase in TB deaths since 2005¹⁰ erasing over a decade of progress on TB elimination.¹¹

Importantly, however, the nature of COVID-19-related disruptions to TB programs are context-specific and vary by setting in timing and extent (see **Chapter 2** for details). Better understanding and measuring these disruptions in specific settings and sub-populations is therefore critical to mitigate their impact, improve TB programs, and transparently track progress towards TB elimination targets.

1.2 Research gaps addressed by this thesis

The overall aim of this manuscript-based thesis is to investigate the impact of the COVID-19 pandemic on TB care in two countries in two continents, both hard-hit by TB and COVID-19 (Peru and India), using a variety of methodological approaches and considering different indicators of TB care disruptions (such as TB case notifications, TB treatment outcomes, case fatality, and losses along the cascade of care for TB). Although multiple modelling studies on the impact of COVID-19 on TB care disruptions and outcomes exist,¹²⁻¹⁴ empirical data on these disruptions are limited.¹⁵ Measuring these disruptions therefore provides a valuable basis for efforts towards their mitigation.

The first approach used in this thesis to assess the impact of COVID-19 on TB care is the care cascade model (a representation of the proportion of patients reaching specific milestones in care for a disease). To make progress on TB elimination, especially in light of COVID-19-related setbacks to elimination efforts, it is critical to understand bottlenecks throughout the entire cascade of care for TB, rather than measuring only downstream indicators (such as treatment outcomes). However, care cascade analyses have been under-utilized in the TB field, and their estimation is complicated by longstanding gaps in routine TB program data.¹ **Manuscript 1** therefore outlines the cascade of care model, and the data gaps and challenges for TB care cascade measurement, while also underlining the importance of cascades as a quality improvement tool, particularly now as TB programs recovering from COVID-19 look to optimize efforts to regain lost progress on TB elimination. This work represents a consensus statement by international experts on TB cascade estimation in six countries, providing calls to action for TB programs, funders, and global bodies such as the WHO to address TB data gaps. It also provides important context leading up to **Manuscript 2**, which applies the TB care cascade model to real-world data.

In **Manuscript 2**, the TB care cascades prior to and during the COVID-19 pandemic are constructed for Lima province, Peru. In addition to being the first estimation of an active TB care cascade in Peru, this work also highlights COVID-19-related disruptions to TB services

throughout the full pathway of care, representing an important value-add to existing studies that have focused their analyses of the effect of COVID-19 on TB care primarily on specific indicators, such as drops in TB case notifications or treatment outcomes.^{10,12,14,16}

Next, given that COVID-19-related disruptions to TB services have made it even more urgent to focus TB elimination efforts on the most vulnerable populations, the effect of COVID-19 disruptions on TB specifically in incarcerated populations in Peru is examined in **Manuscript 3**. This adds to our understanding of the impacts of the pandemic in a population which faces a particularly high burden of TB, and which may have experienced COVID-19 disruptions differently than the non-incarcerated population.

Lastly, in **Manuscript 4**, case-fatality is estimated among patients diagnosed with TB during the COVID-19 pandemic and enrolled in a private sector TB treatment adherence support program in urban India. The use of inverse probability of selection weighting for bias-corrected estimates of case fatality in this population addresses the problem of underreporting of deaths in TB patients cohorts,³ which is particularly relevant in light of pandemic-related disruptions to TB programs.

1.3 Objectives

To address the overall goal of the thesis, investigating the impact of the COVID-19 pandemic on TB care in two high TB burden settings, the following specific aims are addressed:

Manuscript 1: Improving measurement of tuberculosis care cascades to enhance people-centered care

1. To describe the value of expanding the use of TB care cascades and identify common data gaps and measurement challenges for accurate cascade estimation
2. To outline an agenda for rectifying these measurement challenges

Manuscript 2: TB care cascades and predictors of cascade completion prior to and during the COVID-19 pandemic in Lima province, Peru

1. To construct the drug-susceptible and drug-resistant TB care cascades for Lima province, Peru, prior to and during the COVID-19 pandemic.
2. To identify predictors of completing the TB care cascade (i.e., successfully completing TB treatment) pre- and during-COVID-19 in a sample of people with TB from San Juan de Lurigancho, a high-burden district of Lima province, Peru.

Manuscript 3: Tuberculosis case notifications and outcomes in Peruvian prisons prior to and during the COVID-19 pandemic: A national-level interrupted time series analysis

1. To describe DS-TB case notifications in the overall population and the incarcerated population in each department of Peru, prior to and during the COVID-19 pandemic.
2. To assess trends in weekly national DS-TB case notifications prior to and during COVID-19 in Peru in the overall population and in the incarcerated and non-incarcerated populations via interrupted time series (ITS) analyses.
3. To assess predictors of DS-TB treatment success (treatment completion or cure) in incarcerated and non-incarcerated people in Peru, prior to vs. during COVID-19.

Manuscript 4: Case fatality among people with TB enrolled in a private health sector TB treatment support program in Bihar, India during the first year of the COVID-19 pandemic

1. To estimate in-treatment and post-treatment case fatality among people diagnosed with TB in the private sector within the first year of the COVID-19 pandemic in Bihar, India
2. To identify predictors of in-treatment and post-treatment case fatality among people diagnosed with TB in the private sector within the first year of the COVID-19 pandemic in Bihar, India
3. To compare the during-COVID-19 in-treatment and post-treatment case fatality estimates with existing pre-COVID-19 estimates.

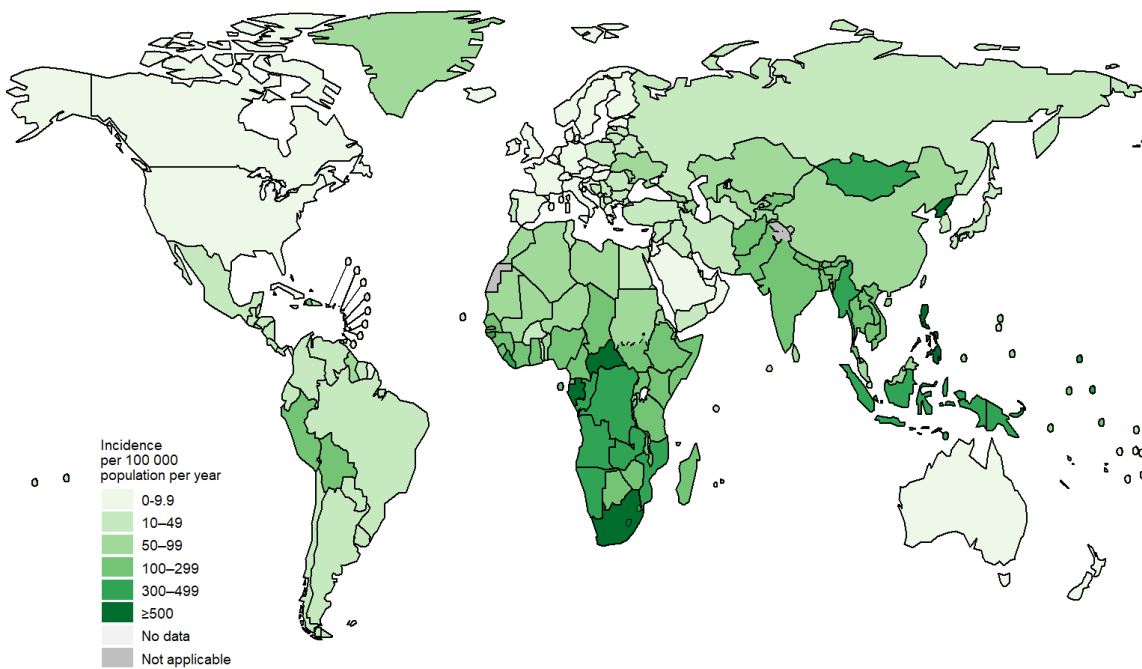
CHAPTER 2: REVIEW OF THE LITERATURE

2.1 The global epidemiology of tuberculosis

TB is a bacterial infectious disease caused by *Mycobacterium tuberculosis* (*M. tb*). Although the most common form of TB is pulmonary TB, extrapulmonary disease can also occur.¹⁷ In addition, it is important to differentiate between TB infection (previously referred to as latent TB) and active TB disease. Individuals with TB infection have been exposed to *M. tb* bacteria but are not symptomatic and do not transmit the infection to others. TB infection may progress to active TB, in which case individuals become symptomatic and can transmit TB.¹⁷ Often regarded as a biological manifestation of social inequities,¹⁸ factors such as poverty, undernutrition, crowded housing, and barriers to access to care all favour TB transmission.^{19,20} Key populations at risk for TB include people with comorbidities such as diabetes and HIV, with TB being the most common AIDS-defining illness.²¹ People living in congregate settings (including places of detention) are also at increased risk of TB.²²⁻²⁴

As mentioned previously, the WHO estimates that in 2021, there were 10.6 million new cases of TB, and 1.6 million TB-associated deaths.⁶ However, the burden of TB is predominantly concentrated in 30 high-burden countries responsible for 87% of global cases. **Figure 1** shows the estimated incidence of TB by country in 2021.⁶

Figure 1. Estimated incidence of tuberculosis globally in 2021



Source: 2022 Global Tuberculosis Report. Geneva: World Health Organization; 2022.⁶

2.2 Progress towards TB elimination targets

The WHO defines TB elimination as one TB case per million people (by country).²⁵ To reach TB elimination by 2050, the WHO's End TB Strategy outlines goals to reduce TB incidence by 90% and TB-associated deaths by 95% by 2035, compared to 2015 levels.⁸ Although the United Nations High-Level Meeting²⁶ on TB in 2018 provided a forum for global leaders to re-affirm their commitments to TB elimination, there remains a wide gap between the targets to which countries have committed and the efforts and investments made towards meeting them.²⁷ Although global incidence and mortality was slowly declining between 2016 and 2019, we are not on track to meet the End TB goals.⁸ In light of disruptions to TB programs globally due to the COVID-19 pandemic,⁹ already-slow progress on ending TB has suffered further setbacks. For example, in 2020, the WHO reported the first year-on-year increase in TB deaths since 2005¹⁰ erasing over a decade of progress on TB elimination.¹¹

Key challenges for TB elimination include addressing the underlying inequities that increase not only the risk of developing TB but also the risk of unfavourable TB treatment outcomes. This includes addressing social determinants of health,²⁰ such as poverty, gender-based disempowerment, undernutrition, food and housing insecurity, and lack of access to free, high-quality health care. Other challenges include outdated diagnostic tools used for TB and their limited sensitivity, especially in specific populations such as children or people living with HIV,^{28,29} as well as ongoing cost barriers to implementation of newer tools in low-income settings.³⁰ Similarly, long TB treatment regimens and regulatory challenges to access to newer regimens in some countries³¹ continue to jeopardize optimal treatment outcomes and TB elimination efforts. Lastly, barriers to the collection, digitization and management of timely, granular and high-quality data in routine TB program databases³² hinder the identification of areas for program improvement and the measurement of progress towards TB elimination goals.

2.3 The impact of the COVID-19 pandemic on TB programs and TB care globally

2.3.1 The global burden of COVID-19

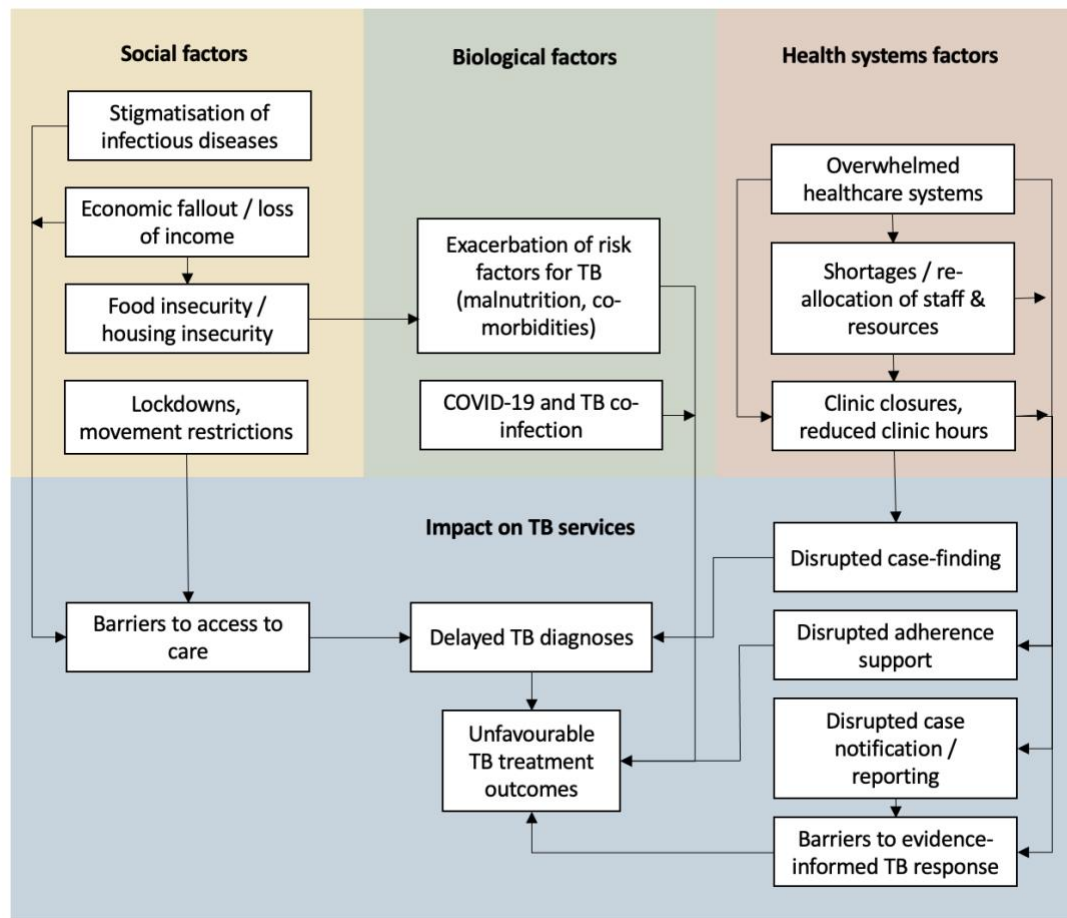
The WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) on 30 Jan 2020, and subsequently declared it a pandemic on 11 Mar 2020.³³ Since January 2020, there have been over 760 million cases of COVID-19 and over 6.9 million associated deaths worldwide, although these numbers are known to be under-estimated.³⁴ Although, all countries have been affected by COVID-19, its impacts across countries are heterogeneous, driven by varying outbreak responses,³⁵ differences in health systems capacity, and most concerningly, deep inequities in access to vaccines and other counter-measures.³⁶ The pandemic has over-burdened health systems globally, but has particularly disrupted care for other airborne infectious diseases, such as TB.⁹ The nature and extent of these disruptions to TB care differ by setting and context, and are explored in more detail in the next section.

2.3.2 The impact of COVID-19 on TB:

Before discussing the impact of COVID-19 on TB care and programs, ‘impact’ must first be defined. As the impact of COVID-19 on TB is multi-faceted, various indicators can be used to define and measure this impact. Specifically, the impact of COVID-19 on TB services, or the factors that drive this impact, include the exacerbation of social inequities and risk factors for TB, the diversion of staff and resources away from TB programs, barriers to care-seeking for TB during the pandemic, subsequent delays in TB diagnoses, drops in case detection and case notification, and reductions in TB treatment success (including increased mortality).^{9,12,14,15,37-39} The interconnectedness of these indicators is shown in **Figure 2**. Evidence from the existing literature for the contributions of each to the overall disruptive impact of the pandemic on TB care are further discussed below.

It should also be noted, however, that although the pandemic has disrupted health systems - and TB services in particular - it is also possible that changes in TB transmission dynamics during the pandemic (due to infection control measures implemented) reduced new TB infections to some extent.⁴⁰ Although this is not expected to have outweighed the adverse consequences of large-scale under-detection of TB cases during the pandemic,^{12,13,41} the role of this within the overall impact of COVID-19 on TB burden is also discussed.

Figure 2. Disruptions to TB care during the COVID-19 pandemic



Drops in TB case notifications:

One indicator of TB program disruptions is the global drop in TB case notifications during the pandemic. The WHO reports that TB case notifications dropped across all regions of the world in 2020 as a result of COVID-19 (**Figure 3**). Importantly, given the significant and rapid drops in case notifications reported, it is likely that they indicate missed TB cases rather than actual decreases in TB burden (discussed further in the next section). In addition, these drops reflect not only that people with TB experienced barriers to access to TB diagnosis and care, but also that TB programs struggled to maintain TB services, including case detection, reporting and notification.⁶ Importantly, only three countries (India, Indonesia, and the Philippines) accounted for the majority (67%) of the global shortfall in TB case notifications, and 10 countries accounted for 90% of the shortfall.⁶

The timing and extent of disruptions to TB case notifications however differ between countries, with the WHO reporting that some high TB burden countries have (as of 2021) made a partial recovery in notifications compared to 2019 levels, whilst others have fully recovered to 2019 levels or above, and others have continued to see a decline in notifications in 2021.⁶

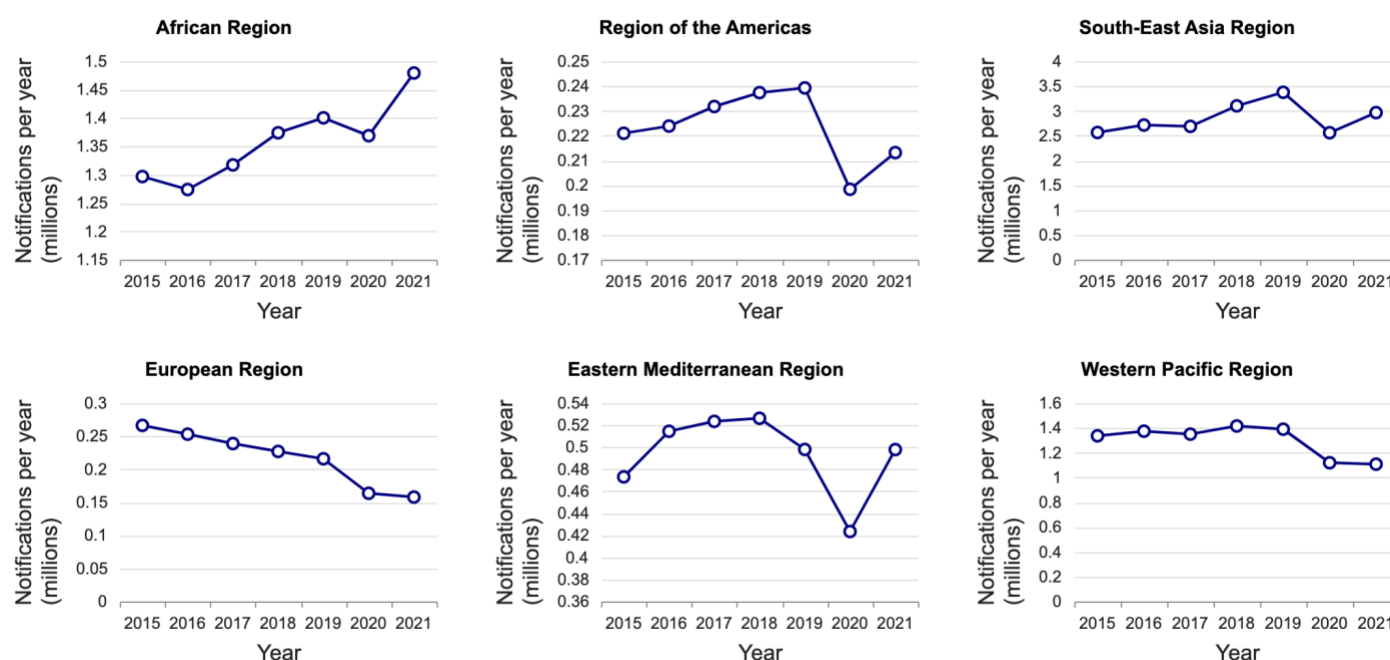
A 2021 study assessing the impact of the COVID-19 pandemic on reported TB cases in 43 TB centres across 19 countries implementing lockdowns at different times found that reductions in reported TB cases co-occurred with the initiation of lockdowns in the majority of these countries.¹⁶ TB centres in only two countries (USA and Australia) reported increases in notified TB cases, possibly due to increased surveillance for both TB and COVID-19 during the pandemic.¹⁶

A time series analysis from Eswatini found a significant decrease in TB case notifications during the pandemic (Mar 2020 - May 2021) compared to prior to COVID-19 (Dec 2018 - Feb 2020), (IRR 0.71, 95% CI: 0.60-0.83).⁴² Similarly, a study using TB program data from one district of Indonesia found that although TB notifications had been increasing between 2015 and 2019 (with a 67% increase occurring in this period), notifications decreased by 19% in 2020 compared to 2019.⁴³

Apart from differing impacts on TB notifications across countries, it is also important to consider how pandemic disruptions may have been experienced differently in specific population subgroups. For example, considering childhood TB specifically, a time series analysis on 215 countries (using TB data notified to WHO) found an increasing trend in notifications from 2014 to 2019 for all childhood age groups and across all six WHO regions, but large decreases in observed compared to predicted notifications in 2020 (35.4%, 27.7%, and 18.8% decreases in the 0-4, 5-14 and ≥ 15 year age groups, respectively).⁴⁴ Interestingly however, the magnitude of the drop in notifications did not differ by extent of COVID-19 restrictions in place in all high TB burden countries analysed (28/28, as Liberia and North Korea were excluded for this analysis objective).⁴⁴ This differs from a modelling study in Mozambique, Malawi, Peru,

Kyrgyzstan and Indonesia, which found that stricter pandemic-related movement restrictions were related to greater reductions in TB notifications.¹²

Figure 3. Trends in case notifications of people newly diagnosed with TB by WHO region, 2015–2021.



Source: 2022 Global Tuberculosis Report. Geneva: World Health Organization; 2022.⁶

Increases in estimated TB incidence:

Although global TB incidence (as estimated by the WHO)⁴⁵ had been in decline for decades, incidence increased by 4.5% in 2021 (from 10.1 million in 2020 to 10.6 in 2021).⁶ The estimated global incidence of drug-resistant (multidrug-resistant and rifampin-resistant) TB also increased by 3.1% in 2021.⁶

A modelling study conducted in the first year of the pandemic, focusing on three high TB burden countries (India, Kenya and Ukraine) estimated 1.19 million additional TB cases in India, over 24,000 additional cases in Kenya, and over 4,000 additional cases in the Ukraine in the following five years (2020-2025), assuming a 3-month lockdown.¹³ Another study modelling the

impact of COVID-19 on TB incidence in five countries estimated increases in incidence over the five years (2020-2024) ranging from 3% (in Mozambique, Peru, Kyrgyzstan and Indonesia) to 11% (in Malawi).¹² Both of these studies hypothesized that the main driver of the increase in TB incidence is the build-up of undetected cases during lockdowns.^{12,13}

Importantly, although COVID-19-related infection control interventions (e.g., lockdowns) may have reduced TB transmission,⁴⁰ the aforementioned modelling study¹³ predicts the stated increase in TB burden when assuming a 50% reduction in TB transmission during COVID-19. This suggests that cases remaining undetected due to barriers to care-seeking is the stronger of these two opposing forces with regards to the role of altered transmission dynamics during the pandemic in the resulting TB burden. Only under a scenario of mild TB service disruptions and strong reductions in TB transmission as a result of lockdowns would the expected effect be reversed (i.e., result in a decrease in estimated TB burden), although specific thresholds for this vary across the three countries analysed in the study.¹³

Exacerbation of risk factors for TB:

Apart from jeopardizing progress on TB elimination through direct disruptions to TB programs, the COVID-19 pandemic has also exacerbated risk factors for TB in the population, resulting in a concerning indirect impact that is difficult to quantify and complex to mitigate. The economic consequences of the pandemic, such as loss of income during and following lockdowns have worsened poverty,⁴⁶ especially in low- and middle-income countries.³⁹ Given that social determinants of health underpin TB risk,²⁰ rising poverty levels and subsequent undernutrition, under housing, and increased barriers to access to health care put more people at risk for TB and for poor TB outcomes. In India for example, the COVID-19 pandemic is expected to have increased poverty and malnutrition, both critical and interconnected drivers of the local TB epidemic, with malnutrition responsible for 30-50% of new TB cases.^{15,47}

Care for co-morbidities such as HIV has also been disrupted during the pandemic.¹⁵ For example, the number of people being tested for HIV has declined across high TB burden

countries, as has the number of people being initiated on treatment.¹⁵ This further exacerbates TB risk and reduces the likelihood of successful treatment outcomes, representing an additional burden to already overwhelmed health systems.

TB program staff and resource diversions:

Given the overlap in equipment, infrastructure and training required for the COVID-19 response in comparison to other airborne infectious diseases such as TB, diversions of TB program staff and resources to COVID-19 teams were common.⁹ A global survey including responses from 76 healthcare workers from Global Fund eligible countries found 44% reporting that they or their colleagues were diverted from TB to COVID-19 work.⁹ In a survey of TB staff at private clinical and laboratory facilities in Nigeria, 11% of respondents reported staff layoffs during COVID-19.⁴⁸ In Canada, TB staff diversions to COVID-19 were reported by 68% of n=25 NTP staff members responding to a survey.⁴ This resulted in scale-backs of essential TB services, including reduced active case finding and contact tracing activities (reported by 36% and 56% of NTP staff, respectively).⁴

Barriers to care-seeking for TB:

In the context of TB staff re-allocation, lockdowns and transportation restrictions, the barriers to care faced by people with TB during the COVID-19 pandemic are manifold. First of all, amid lockdowns and restrictions on public transport services, patients were less able to get to clinics. In addition, if they did present for care, staff shortages, reduced clinic hours or clinic closures further hindered timely care.^{4,9,48,49} Moreover, there is evidence that the pandemic increased stigma around infectious diseases, which increased reluctance to seek care,^{50,51} as did fears of COVID-19 infection at health facilities.³⁹ Food insecurity and indirect costs of treatment (e.g., costs of transportation to clinics) were also barriers to care-seeking for TB during the pandemic.⁵¹

Diagnostic delays for TB:

The barriers to TB-care-seeking outlined above all contribute to delays in TB diagnoses. In addition, apart from demand-side barriers (barriers faced by those requiring care), supply-side challenges (challenges faced by those providing care) also exacerbated diagnostic delays. For example, many TB programs scaled-down essential TB management activities such as active case-finding and contact tracing.⁴ Lower case detection by TB programs,¹² compounded by care-seeking barriers faced by patients increase the likelihood of people presenting to care with more advanced TB disease,⁴ delaying diagnosis and treatment initiation, and increasing the risk of poor TB treatment outcomes. For example, in a survey of Canadian NTP leads and staff, 41% reported that TB diagnoses in their programs were significantly delayed during COVID-19, and qualitative data from these respondents suggests that TB care providers were seeing patients at more advanced stages of disease during the pandemic, due to delays in access to care.⁴

A modelling study in five countries (Malawi, Mozambique, Indonesia, Kyrgyzstan, and Peru) found that demand-driven TB diagnosis, i.e., diagnoses following presentation to TB clinics for care was the most disrupted aspect of TB service delivery during the pandemic,¹² from a 11% decrease in passive TB diagnoses in the second quarter of 2020 in Mozambique, to a 64% reduction in Peru. These disruptions to diagnosis translate to treatment initiation delays, with a Korean study finding a small but significant increase in time to treatment initiation of three additional days in the first year of the pandemic (2020) compared to the previous three years ($p < 0.0001$).⁵² A Turkish study however found a larger, 49-day increase in TB treatment initiation delays in 2020 compared to in the three years prior to the pandemic.⁵³

Increases in unfavourable TB treatment outcomes:

The various disruptions to TB programs and TB care discussed above have contributed to worse treatment outcomes for people with TB, including increases in TB mortality. Most alarmingly, the WHO has reported that in 2020, annual TB deaths increased for the first time since 2005,⁶ representing over a decade of lost progress on improving outcomes for people with TB. The estimated number of TB deaths per 100,000 people across WHO regions over the past two

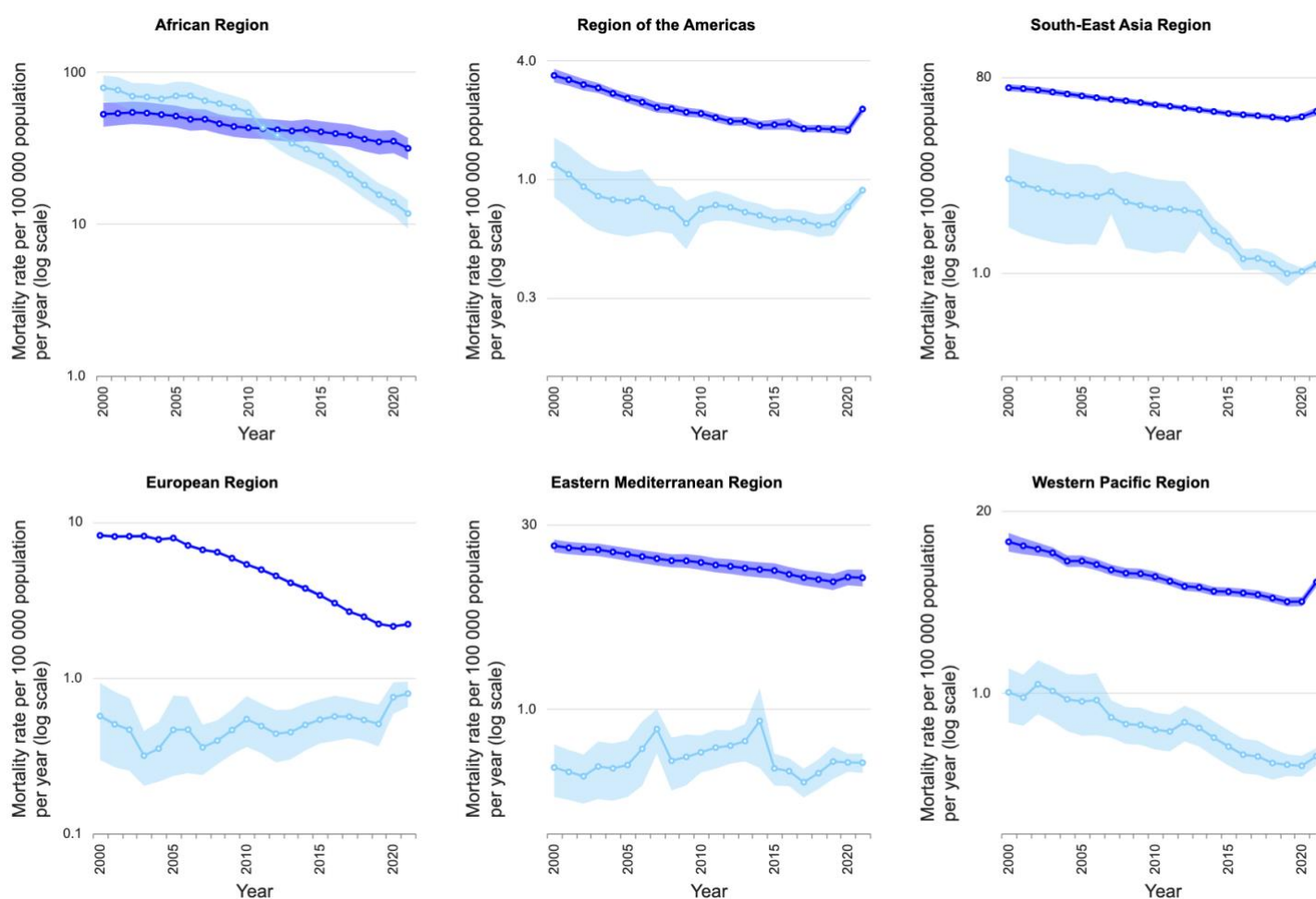
decades are shown in **Figure 4**. Concerningly, although six of the 30 high TB burden countries met the 2020 milestone of a 35% reduction in TB deaths relative to 2015, it was estimated that countries with large drops in TB notifications, including India, also experienced large increases in TB deaths.⁶ Importantly, an underlying assumption of these WHO TB mortality estimates is that drops in TB notifications are due to fewer people accessing TB care, rather than due to actual reductions in TB burden.⁴⁰ Although the validity of this assumption is difficult to determine, evidence in the sections above (on TB notifications and estimated burden) suggests that it is unlikely that reductions in TB transmission due to COVID-19 public health measures outweighed increases in TB burden due to undetected cases.^{12,13,41} In addition, it should be noted that estimates of TB deaths in many settings are likely to be under-estimates, due to under-reporting of TB deaths.³⁹

A study on TB treatment outcomes in the first year of COVID-19 compared to the three previous years (2017-2019) in a region of Turkey found significant increases in unfavourable treatment outcomes, including treatment failure ($p=0.018$) and relapse ($p=0.022$).⁵³ Regarding TB mortality, the previously mentioned 2020 modelling study focusing on India, Kenya and Ukraine, assuming a lockdown period of 3 months, estimated over 360,000, over 12,000 and over 1,300 additional TB deaths in these countries, respectively,¹³ between 2020 and 2025. A further study estimates a 20% increase in global TB deaths in the same period.⁵⁴ The modelling study on Malawi, Mozambique, Indonesia, Peru and Kyrgyzstan mentioned in previous sections also projected increases in TB deaths in these countries from 2020 to 2024 that ranged from 10% to 20%.¹² Lastly, a study ($n=2,400$) based on TB treatment registry data from 8 healthcare facilities in Eswatini also found significantly higher TB deaths during the pandemic compared to prior to the pandemic (21.3% vs 10.8%, respectively, $p<0.01$).⁴²

Apart from under-detection of TB cases during the pandemic, a further contributor to TB mortality is the disruption in TB prevention services, such as BCG vaccination. A study modelling the impact of disruptions to BCG vaccinations during COVID-19 on TB outcomes estimated over 33,000 additional deaths among children due to missed or delayed vaccination.⁵⁵ This is

concerning given that large disruptions in BCG vaccination are reported in different settings. For example, in Indonesia, BCG vaccination is thought to have dropped by 60%,¹² and in India, one million fewer children are expected to have received the BCG vaccine³⁹ in the first month after the start of the pandemic (April 2020) compared to the same month in the previous year. Fortunately however, BCG vaccination is reported to have remained similar to pre-COVID-19 levels in Peru, Malawi, Mozambique and Kyrgyzstan.¹²

Figure 4. Trends in estimated TB mortality rates by WHO region, 2000–2021



Dark blue = TB mortality among HIV-negative people. Light blue = TB mortality among HIV-positive people.

Source: 2022 Global Tuberculosis Report. Geneva: World Health Organization; 2022.⁶

COVID-19 and TB co-infection

Lastly, apart from the societal and health systems impacts of the COVID-19 pandemic on TB, a further, direct impact is that of co-infection with COVID-19 itself. Given the evidence for higher mortality among people co-infected with COVID-19 and TB,⁵⁶⁻⁵⁸ with a systematic review finding a mortality rate of 13% among 146 people co-infected with TB and COVID-19,⁵⁸ this represents a dual concern for countries with a high burden of both TB and COVID-19.

TB program adaptations to the COVID-19 pandemic

TB programs have adapted to the pandemic in a variety of ways. First of all, tele-health and remote consultations, as well as virtual treatment adherence monitoring (video directly observed therapy, VDOT), or other alternatives to traditional DOT (such as home delivery of medications) were used in many settings to replace in-person clinic visits.^{4,12,59,60} In addition, some facilities enacted additional infection control measure or increased intervals between appointments (to facilitate physical distancing).⁴⁹ Although some programs reported that active case finding activities were scaled back due to staff shortages during the pandemic,⁴ other countries reported increasing active case finding, particularly through mobile screening units, to adapt to pandemic restrictions.^{12,61} Taking advantage of existing diagnostic capacity, some settings also evaluated integrated testing for COVID-19 and TB.⁶²⁻⁶⁴

Interestingly, COVID-19-related disruptions to TB programs has also led to increased emphasis on people-centered care. TB care providers in a variety of countries, including Bangladesh, India, Indonesia, Myanmar, Nigeria, Pakistan, and the Philippines reported increasing efforts to ensure a safer clinical environment for patients and staff,^{49,65} and moving from directly observed therapy (DOT) to more patient-friendly protocols (e.g., giving patients a supply of medication to take home,⁴⁸ or delivering medications to patients' homes).⁶⁵ Lastly, given that existing fragmentation in health systems and TB programs, particularly in countries with large private sector TB care provision, pandemic disruptions further underlined the need for better integration of public and private sector TB care. In Pakistan, for example, this led to increased

support and resources (medication supplies and equipment) being provided to private TB care providers by intermediary agencies (non-governmental organisations that work towards closing gaps between public and private sector care).⁶⁵

2.3.3 Cascades of care as a model for measuring the impact of COVID-19 on TB

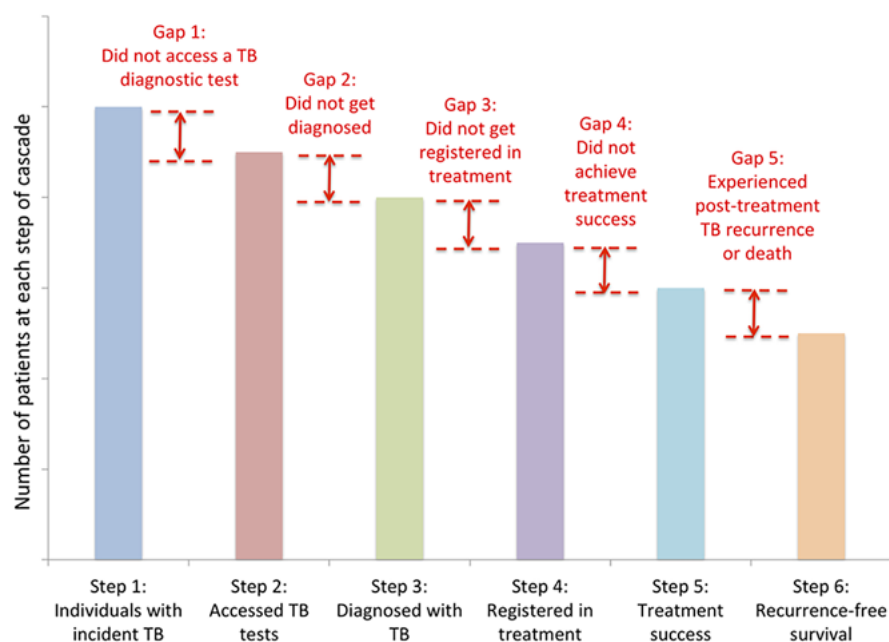
The multiple disruptions to TB care described above impact different stages of the TB care pathway. Therefore, care cascades, which are a representation of the proportion of people reaching specific milestones in care for a disease,⁶⁶ are a useful tool for understanding widening gaps in care delivery across the whole continuum of care, rather than single indicators such as drops in case notifications or treatment success rates. As the care cascade approach will be used in **Manuscript 2 (Chapter 4)**, a brief overview of care cascades is provided here. A more extensive discussion of the challenges of estimating accurate care cascades and possible solutions to improve cascade measurement is provided in **Manuscript 1 (Chapter 3)**.

Although the care cascade model has been widely used, particularly in the field of HIV, to understand shortfalls in care delivery and measure progress towards HIV prevention goals,⁶⁷⁻⁶⁹ it has not yet been applied routinely to TB care. A few studies in recent years have estimated national or subnational TB care cascades (including for India,⁷⁰ South Africa,⁷¹ Nigeria,⁷² Madagascar,⁷³ and Zambia⁷⁴), but care cascade analyses are not routinely included in national TB program reports or elimination strategies, representing a lost opportunity for quality improvement (QI) in TB care. Leveraging the potential of care cascades to inform public health strategy and advocacy is particularly important now, to facilitate identification and mitigation of COVID-19-related disruptions to TB programs in specific settings.

As shown in **Figure 5** from Subbaraman et al,¹ for active TB, the care cascade consists of the following steps: (1) the number of people with TB in the population, (2) the number who access screening or testing, (3) the number diagnosed with TB, (4) the number who start treatment, (5) the number who complete treatment, and (6) the number who achieve one-year recurrence-free survival.¹ These steps can be estimated based on published methods,¹ but

given that only treatment initiation and completion are routinely captured by NTPs, the accurate measurement of other steps is complicated by limitations in data availability, quality, and granularity.

Figure 5. A generic care cascade for active TB



Source: Subbaraman et al., 2019.¹

Specifically, the lack of data on the population-level burden of TB, for example acquired through national prevalence surveys (which have indicated substantial discrepancies in prior estimates of TB burden)⁷⁵, hinders the accurate estimation of the first step in the cascade. The heterogeneity and imperfect sensitivity^{28,29} of tests in the diagnostic algorithm for TB further challenges the measurement of cascade steps, making data on test performance under local NTP conditions important for accurate cascade estimation. In addition, under-reporting is a major data quality issue in NTPs.⁷⁶⁻⁸² This limits the accuracy of TB care cascade estimates, especially if patients who are more likely to have unfavourable treatment outcomes are also less likely to be reported in program databases. Lastly, the lack of data digitization is a challenge affecting the estimation of multiple steps in the cascade. Electronic data capture would not only

improve data quality and standardization,^{83,84} but also allow data linkage across care facilities and databases, enabling comprehensive data capture across the care pathway (including post-treatment follow-up⁸⁵), especially as patients are transferred between facilities or between public and private sector care.^{71,74}

Addressing these data gaps would facilitate not only accurate TB care cascade estimation, but also improvements in people-centered TB care. Working towards this will involve efforts to accurately measure population-level TB burden, digitize data, improve routine TB data quality and reduce under-notification, requiring multi-sectoral action from funders, global bodies such as the WHO, and local NTPs. For example, indicators allowing the estimation of TB cascade steps should be made reportable to WHO, and capacity-building for routine care cascade estimation by NTPs should be supported by funders.

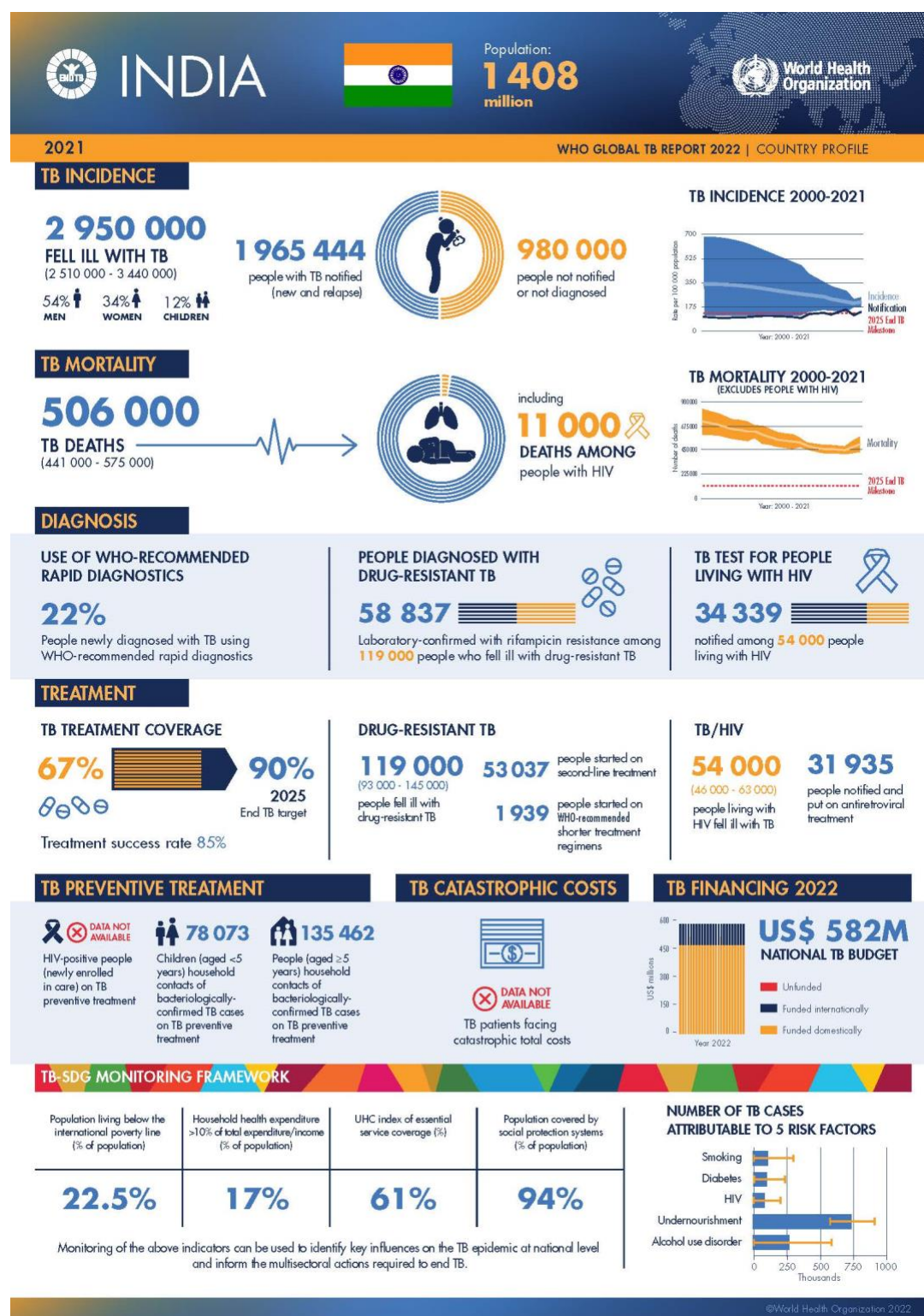
2.4 Tuberculosis in India

India has the largest TB epidemic in the world (**Figure 6**), experiencing 28% of the global TB burden in 2021,⁶ with an estimated TB incidence of 210 (178-244) cases per 100,000 people.⁸⁶ Particular challenges to TB elimination in India include high rates of poverty and malnutrition, which exacerbate TB transmission and poor TB outcomes.²⁰ A care cascade analysis in India's public sector identified the pre-evaluation gap (prior to accessing TB testing) as the largest gap in the TB care pathway, with only 72% of the estimated number of people with TB reaching diagnostic facilities.⁷⁰ In addition, India's large private sector plays a significant role in TB care, also contributing to health system fragmentation and variability in quality of care.⁷⁷

Approximately two thirds of TB-related prescriptions in India originate from the private sector,⁸⁷ highlighting that many patients in the country seek care for TB in the private sector. However, standardized patient studies assessing quality of TB care have found that care providers often fail to adhere to standard practices (e.g., ordering inappropriate tests based on TB symptoms,⁸⁸ or prescribing inappropriate medications⁷⁷), and that incorrect patient management is more common among private sector providers.^{88,89} This has highlighted the

need for private provider engagement in TB elimination efforts, and closer integration with public sector services. Intermediary agencies, also called private provider support agencies (PPSAs) working to close this gap have emerged,^{90,91} providing free TB diagnosis and treatment, linkage between private and public testing and care facilities, and treatment adherence support services.

Figure 6. WHO Global TB Report country profile for India (2021 data, 2022 reporting year)



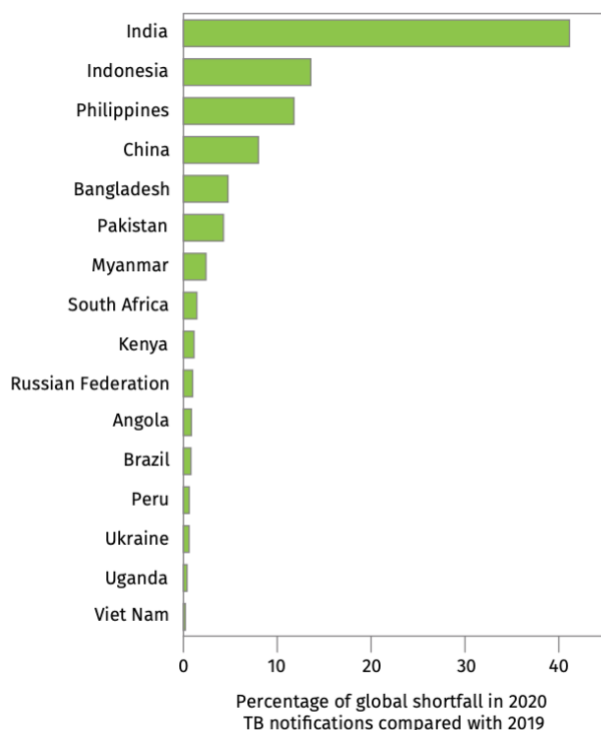
Source: 2022 Global Tuberculosis Report. Geneva: World Health Organization; 2022.⁶

2.5 Disruptions to TB care during the COVID-19 pandemic in India

India has reported almost 45 million COVID-19 cases and over 500,000 COVID-19 associated deaths between Jan 2020 and July 2023,⁹² however, these deaths are expected to be highly undercounted.⁹³ Given the high burden of both COVID-19 and TB in India, the country has suffered particularly severe disruptions to TB care during the pandemic. For example, it suffered the largest shortfall in TB case notifications of all countries at the beginning of the pandemic (**Figure 7**), representing a 38% reduction in notifications in 2020 compared to 2019.⁹⁴

Specific impacts of the pandemic on TB prevention in India include increases in poverty and malnutrition, important drivers of the local TB epidemic.⁴⁷ In addition, it is estimated that one million fewer children in India received the BCG vaccine in April 2020 compared to April 2019.³⁹ People with TB in India have also experienced longer diagnostic delays,⁹⁵ likely to have resulted in poorer TB treatment outcomes, as suggested by a modelling study predicting a 19.5% (14.5-24.7%) increase in TB deaths in 2020 due to the accumulation of missed TB cases.⁴⁷ Another modelling study projecting the impact of COVID-19 related disruptions on TB outcomes over 5 years suggests that disruptions during an expected lockdown duration of 3 months (and taking into account the time required for services to gradually recover to pre-lockdown levels) would result in 1.19 million (1.06-1.33 million) additional TB cases and 361,000 (333,000-394,000) additional TB deaths in India between 2020 and 2025.¹³

Figure 7. The 16 countries with the largest contributions to the global shortfall in TB notifications in 2020 compared with 2019



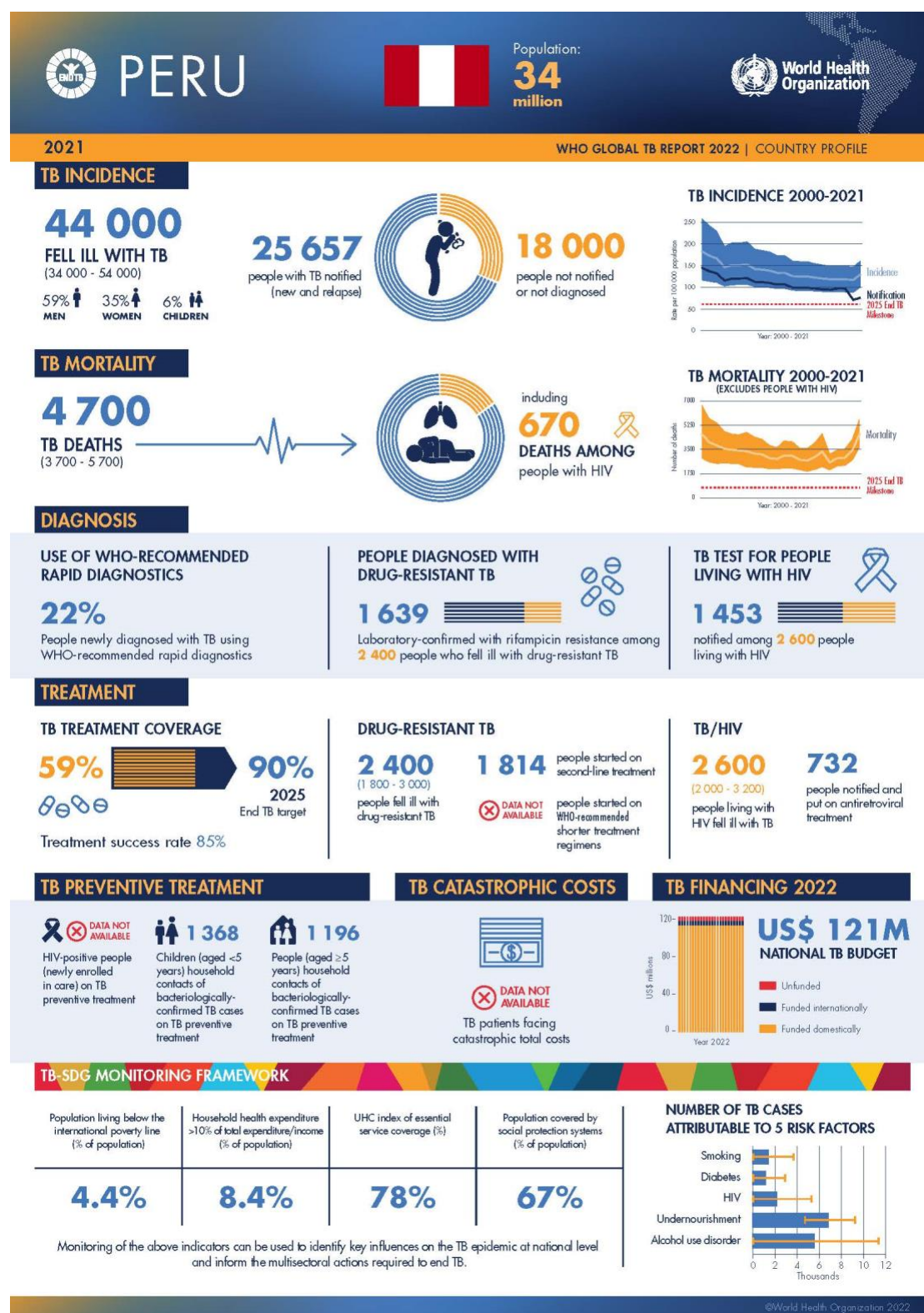
Source: 2021 Global Tuberculosis Report. Geneva: World Health Organization; 2021.⁹⁴

2.6 Tuberculosis in Peru:

In 2021, Peru had an estimated 44,000 (34,000-54,000) cases of TB (**Figure 8**), corresponding to an incidence of 130 (102-161) cases per 100,000 people.⁹⁶ Peru is one of 30 high-burden countries for DR-TB,⁹⁷ with an estimated burden of 2,400 (1,800-3,000) cases (7.1 [5.4-8.8] cases per 100,000 people) of rifampicin-resistant (RR) and multidrug-resistant TB (resistant to rifampicin and isoniazid) in 2021.⁹⁶

TB care in Peru is provided through the public health sector. Despite political unrest and frequent changes in Health Ministry leadership in recent years creating challenges for the health system, important progress has been made with regard to TB management in Peru,⁹⁸ including the scale-up of rapid molecular diagnostics for TB. Diagnostic capacity however continues to be concentrated in the country's capital region of Lima.⁹⁹

Figure 8. WHO Global TB Report country profile for Peru (2021 data, 2022 reporting year)



Source: 2022 Global Tuberculosis Report. Geneva: World Health Organization; 2022.⁶

2.7 Disruptions to TB care during the COVID-19 pandemic in Peru

Peru shoulders not only a high incidence of TB but has also suffered the highest per capita COVID-19 death toll in the world.¹⁰⁰ With over 4.5 million confirmed cases of COVID-19 and over 221,000 COVID-19 deaths in Peru between January 2020 and July 2023,¹⁰¹ overburdening of the health system poses alarming threats to TB control in the country.¹⁰² Concerningly, within the first months of the pandemic, 8,000 fewer TB were identified in Peru compared to the same period in 2019⁹⁸ and the country had the 13th largest drop in TB case notifications from 2019 to 2020 globally (**Figure 7**).¹⁰ Specifically, a recent analysis of the impact of COVID-19 disruptions on TB services in five countries, including Peru, shows that passive case-finding was most severely impacted by COVID-19 related disruptions, with a 64% decrease in the second quarter of 2020 (the largest drop of the five countries analysed, with the others being Mozambique, Malawi, Kyrgyzstan and Indonesia).¹²

A study among people with TB in Carabayllo district (Lima province) found that delays from symptom onset to diagnosis among those diagnosed within the first year of the COVID-19 pandemic (acute phase) were more than twice as long as among those diagnosed after the first year of the pandemic (post-acute phase).¹⁰³ Qualitative findings from the study show that the pandemic altered care-seeking behaviour (e.g. hesitation to seek care due to fear of COVID-19) and presented barriers to care even when it was sought (due to lack of staff capacity and evaluation of patients for COVID-19 prior to consideration of TB).¹⁰³ Importantly, however, COVID-19 disruptions were differentially experienced by specific subgroups in Peru, with men having a significantly larger proportion of missed diagnoses compared to women (RR: 0.82, 95%CI: 0.76-0.89), and children experiencing a larger (but not significantly different) proportion of missed diagnoses compared to adults (RR: 1.12, 95%CI: 0.96-1.30).¹⁰⁴

Adaptations by the Peruvian NTP to COVID-19 disruptions included increasing active case finding through mobile chest X-ray campaigns,⁶¹ and adaptations to DOT, including administration of DOT via home visits.⁵⁹

2.8 A closer look at a key population: people with TB experiencing incarceration

As **Chapter 5** of this thesis explores the impact of COVID-19 on TB case notifications and outcomes among the incarcerated and non-incarcerated populations of Peru, the final section of this literature review focuses on TB in incarcerated populations, including a brief global overview and particular emphasis on Peru and the South American region.

2.6.1 incarceration and health

The 2022 Global Prison Trends Report estimated that over 11.5 million people were incarcerated worldwide that year, one third of whom were pre-trial detainees.¹⁰⁵ The number of people experiencing incarceration globally is growing, with a 24% increase since 2000, however, the problem is most severe in the South American region, which has seen a 200% increase in the same period.¹⁰⁵ Overcrowding in prisons is therefore a growing concern for population health. In 2021, 121 countries had prisons operating at more than 100% of their capacity, and in 13 countries, prison facilities are at over 250% capacity.¹⁰⁵ This presents obvious challenges for the prevention of communicable infectious diseases such as TB, and is at odds with international standards affirming the rights – and right to health – of prisoners. Although the United Nations Revised Minimum Standards for the Treatment of Prisoners, also known as the Mandela Rules, state that prisoners have the right to prompt access to health services, to a standard of healthcare equal to that available in the community, to receive specialized care outside of prison where needed, and to continuity of care beyond incarceration,¹⁰⁶ these standards are not legally binding,¹⁰⁷ and health in prison settings continues to be neglected.

As disenfranchised communities are overrepresented in the world's incarcerated population,¹⁰⁵ safeguarding health in detention is an ethical imperative that not only recognizes detainees' right to health¹⁰⁸ but also supports health equity.¹⁰⁹ In addition, particularly with respect to communicable diseases, good prison health is integral to good public health more broadly,¹¹⁰⁻¹¹² as prison populations are dynamic. This means that failure to prevent infectious disease transmission in prisons is a lost opportunity for prevention in the community as a whole.¹¹³⁻¹¹⁵

Unfortunately, however, in many settings, prison health at the state level may fall under the purview of the Ministry of justice rather than the Ministry of Health. Competing priorities and health service fragmentation in prisons therefore pose ongoing challenges for addressing factors such as overcrowding, malnutrition and poor ventilation that create conditions that favour the transmission of airborne infectious diseases such as COVID-19 and TB in places of detention.^{107,116}

2.6.2 Incarceration during the COVID-19 pandemic

As the COVID-19 pandemic continues to disrupt life outside prisons, it has also had a unique impact in prison settings in several ways. First, although conditions of imprisonment have put incarcerated populations at higher risk of COVID-19,¹¹⁷ and the WHO has issued guidance regarding the management of COVID-19 in detention,^{110,118} prisons were de-prioritized in the overall pandemic response.^{113,116} For example, the 2022 Global Prison Trends Report found that only 38% of countries (out of 131 with available data) considered detainees a priority population for COVID-19 vaccine rollout plans.¹⁰⁵ This is alarming because the confluence of neglect in the crisis response combined with existing risk factors in this population, such as confinement,¹¹⁹ overcrowding,^{120,121} undernutrition,¹¹⁰ and a high burden of comorbidities among people experiencing incarceration^{117,119,120} makes detainees highly vulnerable to COVID-19. In fact, multiple studies across countries have demonstrated that COVID-19 cases and deaths have been much higher in prisons compared to the general population.¹²²⁻¹²⁴ For example, a US-based study comparing COVID-19 case and mortality rates estimates that cases and deaths in prisons were 5 and 2.5 times higher than in the general population, respectively.¹²² Similar disparities between COVID-19 death rates in prisons compared to the general population are mirrored in other countries.^{123,124} The lack of transparent, timely, high-quality and disaggregated data on COVID-19 testing, cases, and deaths in prisons however obscures our understanding of the impact of COVID-19 in prisons and hinders an evidence-informed response.^{125,126}

Apart from the direct impacts of COVID-19 in prisons, the pandemic has also severely disrupted other aspects of health in prisons.¹²⁴ Just as COVID-19 has over-burdened health systems worldwide, health services in prisons have similarly suffered from significant diversions of resources towards the pandemic response,¹²⁷ to the detriment of care for other conditions.¹²⁶ Such indirect impacts include the discontinuation of family visits,^{125,126} the suspension of detainees' medical appointments outside of prison, a scale-back—in some settings—of access to health services to emergency-only levels,¹⁰⁵ and delays in care for other conditions. A state-wide study of prison healthcare delivery in California showed that referrals and timeliness for both routine and urgent care in state prisons decreased significantly during the pandemic.¹²⁷

Several measures were taken to temper the risk of COVID-19 in prisons, but most were temporary. For example, release measures implemented in some settings to reduce overcrowding in prisons during the pandemic^{109,113,117,119} only reduced prison populations in the short-term, before being discontinued.¹⁰⁵ At the same time, the slow-down of court proceedings during the COVID-19 pandemic temporarily lowered new prison admissions^{105,109} but they are now rising as proceedings return to pre-COVID-19 schedules. In addition, COVID-19 has also put further strain on prison staff shortages, which were already a challenge prior to the pandemic.¹⁰⁵ Lastly, although the pandemic presented a fitting opportunity to expand the use of alternatives to incarceration (such as community service and home detention¹¹⁷) widespread uptake was limited.

2.6.3 Incarceration in Peru

As of August 2022, over 90,000 people are incarcerated in Peru¹²⁸, (incarceration rate: 268/100,000 people¹²⁹). Nationwide, 95.0% of detainees are male, and only 61.2% of all detainees currently incarcerated have received their sentence.¹²⁸ Of those sentenced, most (93.1%) are serving sentences longer than 5 years.¹³⁰ On average, prisons in the country are at 220% capacity,¹²⁸ creating aforementioned risks for increased transmission of TB, COVID-19, and other infectious diseases.¹³¹

In response to the COVID-19 pandemic, the national penitentiary institute of Peru (Instituto Nacional Penitenciaria, INPE) implemented a rapid response plan in prisons, and was granted additional funding via emergency decree.¹³² As part of this response plan, approximately 7,900 detainees have been released since 2020 under the decriminalization laws enacted to reduce the incarcerated population during the pandemic.¹³³ Despite these measures, the high risk of COVID-19 infection during incarceration sparked protests among detainees in Peru, including one that resulted in the deaths of nine people in custody.¹²⁵

2.6.4 Tuberculosis in incarcerated populations

Incidence of active TB in prisons:

People experiencing incarceration represent a key population for TB prevention because the carceral environment is conducive to TB transmission, facilitated by factors such as crowding,¹⁰⁵ poor ventilation¹³⁴, undernutrition, high barriers to accessing care,²² and fragmentation of health services.^{22,134,135} Studies in a variety of countries report an extremely high prevalence and incidence of TB in incarcerated populations.^{22,136-141} Prisons in South America, however, have been found to have a particularly high burden of TB. A study in Paraguay, for example, reported 3,459 TB case notifications per 100,000 population among detainees in 2018, representing 14.5% of all notifications in the country in the same year.¹³⁹ In Colombia, the prevalence of active TB among detainees was found to be 1,026 cases / 100,000 people¹⁴¹, while in Brazil, studies report prevalence rates ranging from 1,439 cases / 100,000 people¹⁴⁰ to as high as 3,973 cases / 100,000 people.^{22,23,142} In Peru, results of a 2016 survey of detainees found a prevalence of 2,510 cases / 100,000 people of detainee-reported TB diagnosis by a healthcare provider during incarceration.¹⁴³

A recent systematic review notes that the disparity in incidence of TB in the incarcerated compared to the general population is particularly large in South America (incidence rate ratio: 26.9, 95%CI: 17.1-40.1), and estimates a pooled TB prevalence of 1,680 cases / 100,000 people (95%CI: 830–2,970) in the region.²² A further study notes that although detainees constitute less than 1% of the population in Central and South America, they represent 11% of notified

tuberculosis cases,²³ underlining the importance of understanding TB in prisons to the wider epidemic in the region.

TB treatment outcomes in prisons:

TB treatment outcomes in prisons reported in prior studies vary by context. Barriers to successful TB treatment may be exacerbated in the prison setting by factors such as high rates of tobacco, drug and alcohol use among people in detention,¹⁴⁴ and some studies report low proportions of treatment success. For example, studies in prison populations in Ecuador,¹⁴⁵ Nigeria,¹⁴⁶ Thailand,¹⁴⁷ Malaysia¹⁴⁸ and Malawi¹⁴⁹ report treatment success proportions ranging from 72.9%¹⁴⁶ to 61.5%¹⁴⁹. In addition, a study of MDR-TB treatment outcomes in DOTS-plus programs, including participants from Peru (n=663) and four other countries (n=1,105), found history of incarceration to be associated with treatment drop-out (RR: 1.86, 95%CI: 1.42-2.45).¹⁵⁰

Other studies however report high treatment success among detainees, including a Thai study reporting that 94.9% of detainees with pulmonary TB were successfully treated.¹⁵¹ Several studies comparing treatment outcomes for populations in and outside of prison have also found higher treatment success among prisoners than among those not incarcerated. For example, a study in Malawi (n=1,652) shows that 93% of prisoners with TB were cured or had completed treatment, compared to 88% in the non-incarcerated population, thought to be due to closer treatment monitoring in prisons.¹⁵² Focusing on South American studies, a large study in Brazil including n=17,776 incarcerated and n=160,728 non-incarcerated individuals found higher treatment success in the incarcerated population (82.2% vs. 75.1% treatment success, p<0.0001) due to more widespread implementation of DOT in the prison setting.¹⁵³ Moreover, a study of TB treatment outcomes in unhoused (n=2,782) and incarcerated (n=7,462) people in Brazil reported 78.6% treatment success in prisons, and that incarceration was associated with favourable treatment outcomes (adjusted OR for treatment failure: 0.68, 95%CI: 0.63-0.73).¹⁵⁴

Transmission of TB from prisons to the community:

Considering the importance of prisons in TB transmission in the overall population,¹⁵⁵ the high burden of TB in prisons is an immense barrier to broader TB elimination efforts.²³ A genomic study in Brazil found that 50.6% of cases among people with no history of incarceration were linked to cases in people recently incarcerated, and that prison transfers were a driver of TB transmission in the area.¹⁵⁶ In addition, a study in Georgia (n=1,613) showed that compensatory mutations (mutations that correct for the fitness cost associated with drug-resistance and result in highly transmissible *Mycobacterium tuberculosis* strains) were more likely to be found in samples from the incarcerated population, suggesting prison settings as a driver of the MDR-TB epidemic in the country.¹⁵⁷

In Peru, an MDR-TB spillover region of over 5km from prisons in Lima to the general population was estimated.¹⁵⁵ Moreover, a further study linked the transfer of prisoners from Peru to a community outbreak in Spain,¹⁵⁸ and a case-control study in Lima, Peru found that people with TB were more likely to spend time around prisons than TB-free controls (OR: 11.55, 95% CI 1.48-90.13).¹⁵⁹

2.6.5 The management of TB in prisons in Peru

The following information on TB management in prisons in Peru is based on observations and discussions with penitentiary health staff during visits (by the author and collaborators) to two large prison facilities in Peru. It should therefore be noted that specifics pertaining to the availability of TB services may vary by facility, particularly in smaller or more remote prisons.

Depending on their size, prison establishments in Peru have dedicated TB care facilities and staff. Detainees receive a physical health evaluation and a chest X-ray at entry, and those with abnormal chest X-ray findings undergo sputum microscopy. GeneXpert platforms for TB testing, provided by the Global Fund, are available in 3 of the country's prisons (however, when availability of cartridges is limited, the use of GeneXpert is restricted to priority groups such as detainees with comorbidities). Large prisons may have laboratories for sputum microscopy on-

site, although samples are sent to external reference laboratories for culture and drug-susceptibility testing. Same-day smear and GeneXpert results are available to prison health through an electronic result reporting platform.

Detainees diagnosed with TB stay in cell blocks separate from healthy detainees (at least until smear negative) and receive additional food (4 meals per day for detainees with TB, compared to 3 for detainees without TB). In some facilities, DOT is provided to detainees directly in their cells, while in others, detainees report to a TB treatment area within the prison to receive DOT. Some prisons have a 'health promoter' program, in which detainees receive training on TB, and subsequently help identify TB symptoms among their cellmates, as well as providing peer support for treatment adherence. Treatment for extensively drug-resistant (XDR) TB is centralised, with all detainees diagnosed with XDR-TB being transferred to one specific prison. If a detainee is released during TB treatment, they are referred to their local primary care centre for continuation of treatment, although in practice ensuring continuity of care in this context is difficult. Although reduced staff and the attribution of respiratory symptoms to COVID-19 complicated TB care in prisons during the COVID-19 pandemic (likely reducing case detection), prison clinic hours, DOTS and treatment monitoring continued as normal.

CHAPTER 3: MANUSCRIPT 1:

Improving measurement of tuberculosis care cascades to enhance people-centered care

3.1 Preface:

In this article, we discuss measurement challenges and data gaps for the estimation of TB care cascades, which represent the proportion of people estimated to have TB in the population who reach specific stages in TB care (including accessing testing, receiving a diagnosis, initiating TB treatment, and completing treatment). We discuss potential solutions to these measurement challenges and highlight that addressing them would facilitate the use of accurate care cascades as quality improvement tools for TB programs.

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Improving measurement of tuberculosis care cascades to enhance people-centered care

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3.2 Abstract

Care cascades represent the proportion of people reaching milestones in care for a disease and are widely used to track progress toward global targets for HIV and other diseases. Despite recent progress in estimating care cascades for tuberculosis (TB) disease, they have not been routinely applied at national and subnational levels, representing a lost opportunity for public health impact. As researchers who have estimated TB care cascades in high-incidence countries (India, Madagascar, Nigeria, Peru, South Africa, and Zambia), we describe the utility of care cascades and identify measurement challenges, including the lack of population-based disease burden data and electronic data capture, under-reporting of people with TB navigating fragmented and privatized health systems, the heterogeneity of TB tests, and the lack of post-treatment follow-up. We outline an agenda for rectifying these gaps and argue that improving care cascade measurement is critical to enhancing people-centered care and achieving the End TB goals.

3.3 Introduction

Care cascades (also known as “care continuums”) are representations of the proportion of people reaching important milestones in the care pathway for a disease. Gaps between each milestone represent the proportion of people lost at each stage in care, from the number of people with a condition at the population level to those achieving optimal treatment outcomes. For this reason, care cascades are a valuable approach for evaluating the quality of care for a given condition within a health system.¹ The care cascade model has been applied to understand care delivery for several conditions, including hypertension,² diabetes,³ viral hepatitis B.⁴ Notably, in the field of HIV, this model has been used widely since 2017 to assess global progress towards the Joint United Nations Programme on HIV/AIDS (UNAIDS) goals⁵ and to monitor the test-and-treat strategy. As such, HIV care cascades have gone beyond merely being a measurement model to serving as a quality improvement (QI)^{6,7} and advocacy tool with public health impact.⁸

In contrast, despite recent methodological advances,⁹ care cascades for TB disease have not been routinely utilized by national TB programs (NTPs) to generate actionable data that can improve quality of care. In recent studies, care cascades for TB disease have been constructed for India,¹⁰ Madagascar,¹¹ Nigeria,¹² Peru,¹³ South Africa,¹⁴ Zambia¹⁵ but have not been routinely included in publicly-accessible national TB reports in these countries,¹⁶⁻¹⁸ except in South Africa, which has not published annual TB reports in recent years, but which included an updated (2020) care cascade in its TB Recovery Plan.¹⁹ Care cascades are also not reported in the annual World Health Organization (WHO) Global TB Reports.^{20,21} Identifying and closing gaps in the TB care cascade will be essential to accelerate the current slow global progress in reducing TB incidence.²² Failure to exploit the full potential of care cascades therefore represents a major missed opportunity for the global TB community.

Leveraging this model for public health impact is particularly important given the status of TB as the second leading cause of death from an infectious pathogen worldwide (after COVID-19, as of 2021), with TB having been responsible for about 1.6 million deaths in 2021.²¹ Given the

disruptive impact of the COVID-19 pandemic on TB programs globally, which has significantly set back progress on TB elimination efforts^{23,24} care cascades may help identify which care stages need to be targeted to mitigate these disruptions. The application of care cascade analyses to measure progress towards the End TB goals is also relevant ahead of the 2023 United Nations high-level meeting on TB. As we are not on track to meet the targets set at the 2018 high-level meeting,²² routine application of TB care cascades may facilitate transparent tracking of progress towards milestones to which member states have committed.

Although the need to improve TB care *cascade outcomes* is clear, and interventions for doing so have been explored,²⁵ our focus in this piece is specifically on *cascade measurement*. As a group of researchers who have estimated, or are estimating, care cascades for TB disease across various high-incidence countries,¹⁰⁻¹⁵ and therefore have a sense of the scope and diversity of challenges in quality, availability, granularity, and timeliness of data in these settings, we built consensus around the overarching challenges of accurate cascade measurement, and the value of care cascades for TB programs. This process included meetings at which all co-authors shared their experiences of cascade estimation in their setting, reviewed successive drafts of this work, and provided country-specific examples. In the resulting paper, we describe the value of expanding the use of TB care cascades, identify common measurement challenges, and outline an agenda for rectifying these problems.

We argue that the construction of care cascades needs to move beyond serving as a theoretical exercise or research publication that is unlinked to routine care delivery. Rather, enhancing the capacity of TB programs to measure care cascades routinely and accurately at multiple levels will require improvements in estimation of disease burden, data capture and management, and post-treatment follow-up, which are also essential to achieving high-quality person-centered care.

3.4 The value of the TB care cascade model

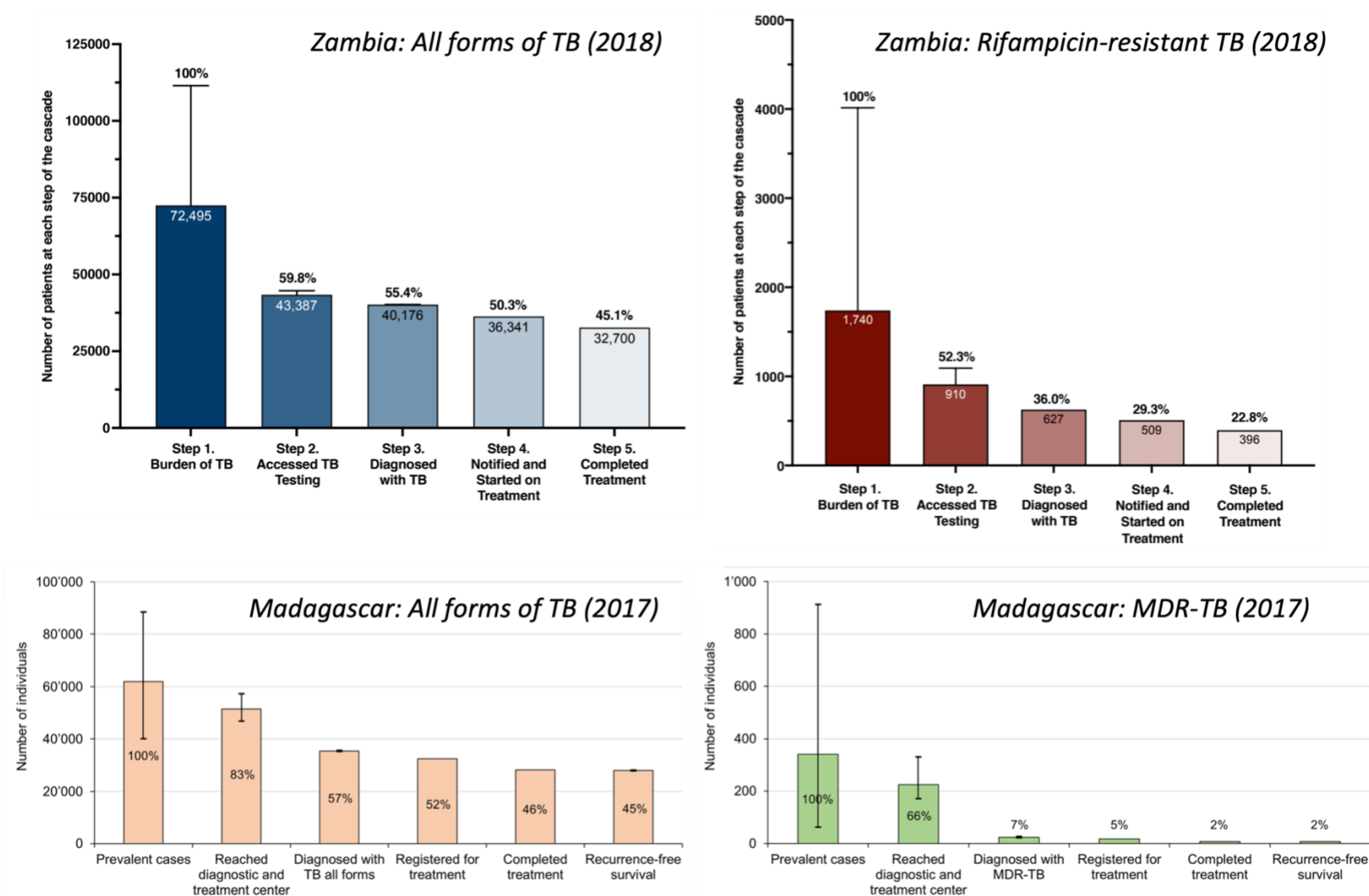
While approaches to estimating care cascades vary, based on recent guidance,⁹ a general model for TB disease includes the following steps: (1) the estimated TB burden (i.e., the number of people with TB in the population, comprising prevalence or incidence), (2) the number who access screening or testing, (3) the number diagnosed with TB, (4) the number who start treatment, (5) the number who complete treatment, and (6) the number who achieve one-year recurrence-free survival. Examples of recent TB care cascades from Zambia¹⁵ and Madagascar¹¹ are shown in **Figure 1**. In most NTPs, only Steps 4 and 5 (i.e., treatment initiation and completion) are routinely captured, creating challenges for estimating the remaining steps.

Regarding Step 2, it should be noted that this step represents people who *truly had TB* who accessed testing. It does not represent all people with symptoms who accessed testing based on TB program data. Step 2 therefore takes into account people who had bacteriological test-negative TB, which is estimated from subsequent steps based on the known imperfect sensitivity of bacteriological tests (e.g., sputum microscopy, Xpert MTB/RIF). Comparison of the number of people with bacteriological test-negative TB in Step 2 with the number of people who were actually diagnosed with test-negative TB in Step 3 therefore provides insights into whether TB programs are empirically diagnosing enough people with test-negative TB, which highlights another value-add of care cascade measurement.

By identifying bottlenecks in TB programs, care cascade analyses sometimes reveal unexpected findings, which could inform program priorities. For example, in India (in 2013)¹⁰, Zambia (in 2018),¹⁵ and South Africa (for all forms of TB in 2020),¹⁹ the largest gap comprised people who contracted TB disease but did not reach diagnostic facilities or access a TB test. In contrast, this gap had a smaller contribution to overall losses in Madagascar (in 2017),¹¹ as well as in South Africa's DR-TB cascade (in 2013)¹⁴ (**Table 1**). In addition, while the treatment stage of care has historically been the focus of TB programs, these national care cascade studies suggest that, even after people with TB engage with services, more people are lost during the diagnostic workup (in India and Madagascar) or after diagnosis and before treatment initiation (in India

and Zambia) than are lost during treatment. Furthermore, where estimates of post-treatment outcomes are available, such as in India, TB recurrence and death appear to be high under programmatic conditions.^{10,26} Care cascade analyses show that outcomes are particularly poor for people with multidrug-resistant (MDR) or rifampin-resistant (RR) TB. In all countries studied, the largest gaps occur before the treatment stage,^{10-12,14,15} and the least data is available for one-year recurrence-free survival. Such analyses therefore motivate TB programs to expand their focus beyond the treatment phase alone.^{6,27,28} Further, if evaluated serially over time, as was done for MDR-TB in Nigeria,¹² care cascades can help programs to set and track progress towards TB goals, and allocate resources based on needs. Apart from guiding QI efforts for program *operations*, care cascade estimation can also enhance quality control for program *data*, bringing to light data management issues that can then be rectified.

Figure 1. Examples of TB care cascades for Zambia¹⁵ and Madagascar¹¹



Figures taken from published TB care cascades for Zambia (Lungu et al. 2021, BMJ Open) ¹⁵ and Madagascar (Knoblauch et al. 2020, BMC Med). ¹¹ Both publishers (BMC and BMJ) allow reproduction of published figures.

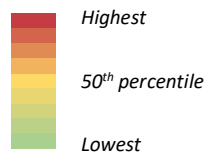
Brief description of estimation of each step and associated error bars (for the overall TB cascade, all forms of TB): (See original papers for more details):

- *Zambia: ¹⁵ Step 1) WHO TB incidence estimates. Error bars are the 95%CI around the WHO incidence estimates. Step 2) Missed cases + cases diagnosed (Step 3), where missed cases are true test-negative cases based on TB test sensitivity, correcting for those empirically treated. Error bars based on 95%CI for test sensitivity estimates and 95%CI for Step 3. Step 3) Number of people with TB notified and treated (Step 4) + those lost to follow-up prior to treatment initiation, based on the difference between detected cases (from laboratory data) and notified cases. Error bars based on 95%CI for pre-treatment loss to follow-up estimates. Step 4) Actual value from notification data (number started on treatment). No error bar as this represents the exact national value. Step 5) Actual value from notification data (number successfully completing treatment). No error bar as this represents the exact national value.*
- *Madagascar: ¹¹ Step 1) WHO TB incidence estimates. Error bars are the 95%CI around the WHO incidence estimates. Step 2) Missed cases + cases diagnosed (Step 3), where missed cases are based on local TB test sensitivity. Error bars based on 95%CI for test sensitivity estimates and 95%CI for Step 3. Step 3) Number of people with TB notified and treated (Step 4) + estimated pre-treatment loss to follow-up, based on trimestral TB program reports and laboratory data. Error bars based on 95%CI for pre-treatment loss to follow-up estimates. Step 4) Actual value from local clinical TB management data (number started on treatment). No error bar as this represents the exact national value. Step 5) Actual value from local clinical TB management data (number successfully completing treatment). No error bar as this represents the exact national value. Step 6) Step 5 minus the estimated number of those experiencing relapse, based on relapse proportions from the literature. Error bars are based on the 95%CI for the estimated proportion of relapse.*

Table 1. Findings from national-level care cascades for TB disease: Losses at each gap as a proportion of total estimated losses by country

	Total losses across all gaps ^a	Gap 1: Pre-evaluation losses ^b	Gap 2: Pre-diagnosis losses ^c	Gap 3: PTLFU ^d	Gap 4: On-treatment losses ^e	Gap 5: One-year post-treatment recurrence or death ^f
All forms of TB						
India (2013)^g						
n	1,650,763	761,973	308,121	212,068	196,074	172,527
%	100.0%	46.2%	18.7%	12.8%	11.9%	10.5%
Madagascar (2017)						
n	33,884	10,461	16,080	2,912	4,249	182
%	100.0%	30.9%	47.5%	8.6%	12.5%	0.5%
South Africa (2020)^h						
n	193,278	73,738	19,139	27,091	73,310	Not evaluated
%	100.0%	38.2%	9.9%	14.0%	37.9%	
Zambia (2018)						
n	39,795	29,108	3,211	3,835	3,641	Not evaluated
%	100.0%	73.1%	8.1%	9.6%	9.1%	
Drug-resistant TB						
India (2013)^g						
n	123,587	69,000	35,938	5,764	10,477	2,408
%	100.0%	55.8%	29.1%	4.7%	8.5%	1.9%
Madagascar (2017)						
n	333	117	200	6	10	0
%	100.0%	35.1%	60.1%	1.8%	3.0%	0.0%
Nigeria (2016)						
n	19,037	14,800	3,509	436	292	Not evaluated
%	100.0%	77.7%	18.4%	2.3%	1.5%	
South Africa (2013)^h						
n	19,097	3,870	2,396	6,736	6,095	Not evaluated
%	100.0%	20.3%	12.5%	35.3%	31.9%	
Zambia (2018)						
n	1,344	830	283	118	113	Not evaluated
%	100.0%	61.8%	21.1%	8.8%	8.4%	

Proportion of losses:



^aTotal losses = Cascade step 1 estimate minus final cascade step estimate (Step 5 or 6, as applicable)

^bPre-testing losses = Step 1 - Step 2

^cPre-diagnosis losses = Step 2 - Step 3

^dPre-treatment loss-to-follow-up = Step 3 - Step 4

^eOn-treatment losses = Step 4 - Step 5

^fOne-year post-treatment recurrence or death = Step 5 - Step 6

Where: Step 1 = TB burden estimate, Step 2 = accessed testing, Step 3 = diagnosed, Step 4 = started treatment, Step 5 = completed treatment, Step 6 = recurrence-free survival.

^gFor India's care cascade, Step 2 and later steps represent public sector estimates only.

^hEstimates for 2020 South Africa cascade (all forms of TB) are from South African National TB Recovery Plan,¹⁹ and 2013 estimates (DR-TB) are from the published cascade analysis.¹⁴

Critically, as care cascades are descriptive, their estimation will not translate into TB program improvements unless accompanied by the willingness to take evidence-based action in response to the findings. Encouragingly, recent care cascade analyses have guided some TB program priorities. Construction of the MDR-TB care cascade in Madagascar facilitated goal setting for MDR-TB surveillance and care delivery, and regional disaggregation of data allowed the targeting of additional MDR-TB centers in priority areas.¹¹ Care cascade analyses have been utilized in India to inform the country's national TB strategic plan for 2017-2025,²⁹ to inform differentiated care strategies,³⁰ and lastly, to understand loss to follow-up along the TB care pathway in India's 2007-2021 National Health Programme Guidelines,³¹ leading to the integration of data capture into India's online TB data management system.³² Furthermore, initiatives are underway in India to implement interventions with Private Provider Support Agencies (PPSAs), targeted at specific geographic areas, to translate care cascade findings into TB program practices.³³ In South Africa, the TB care cascade has contributed to TB program planning since 2017, having been included in the 2017-2022 National Strategic Plans for HIV, AIDS, TB and Sexually Transmitted Infections.³⁴ In general, however, few of the cascades shown

in **Table 1** have been directly used to inform program improvement in a manner documented in official reports.

3.5 Mapping data gaps across the care cascade

We identify five overarching data gaps that hinder accurate estimation of TB care cascades in high-incidence settings. Descriptions of specific data gaps and approaches to addressing these challenges to improve the accuracy of care cascades are shown in **Table 2**.

1. Lack of population-based data on TB burden:

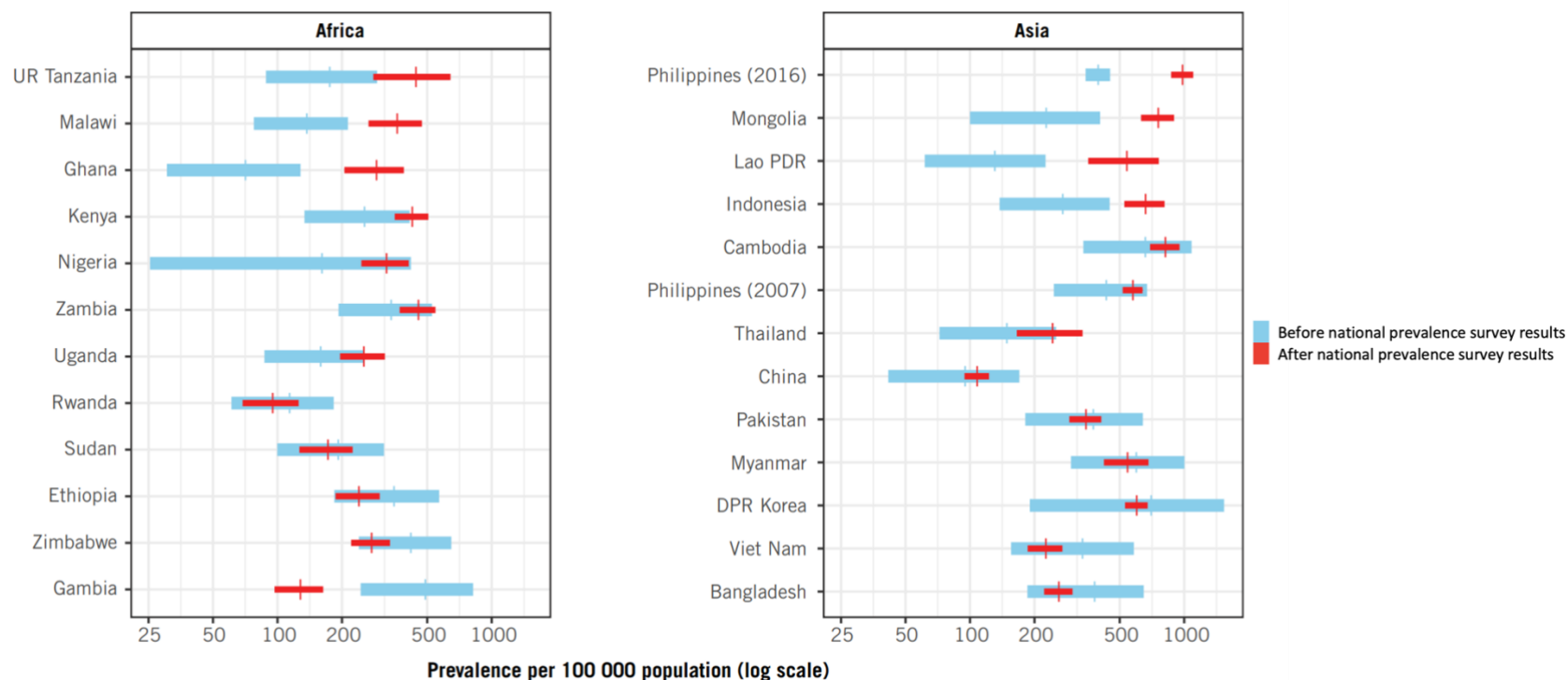
As many care cascades begin with an estimate of the TB burden in a country or region as the baseline from which subsequent losses occur, suboptimal data on the burden of TB at the population level is often a major challenge for estimating care cascades. For example, methods used in WHO estimates of TB incidence are heterogeneous³⁵ and have limitations, especially when extrapolated from a country's case notifications, which may underestimate true TB incidence.

Although they are expensive and time-consuming, national prevalence surveys help estimate the extent of missed cases and inform more accurate estimates of TB burden. A WHO analysis of TB prevalence surveys in 24 countries showed that these surveys often result in upward revisions of national prevalence estimates (**Figure 2**).³⁶ This suggests that care cascades often under-estimate losses, as they may be based on under-estimates of prevalence and, therefore, TB incidence, as estimates of incidence are often informed by prevalence estimates. For example, in South Africa, the first national TB prevalence survey, conducted in 2018, found a prevalence of all forms of TB of 737 cases (95% confidence interval [CI] 580-890) per 100,000 people,³⁷ as compared with a lower estimate of 696 cases (95%CI 390-1088) per 100,000 people reported in the 2015 WHO Global TB Report, which was the last time the WHO reported estimated TB prevalence (as opposed to incidence) for high-incidence countries.³⁸ Similarly, in India, a national prevalence survey conducted in 2019-2021 showed a prevalence of all forms of TB of 312 cases (95%CI 286-337) per 100,000 people,³⁹ as compared to the much lower

estimate of 195 cases (95%CI 131-271) per 100,000 people reported in the 2015 WHO Global TB Report.³⁸ In Peru, funding challenges in the national health system⁴⁰ hinder the implementation of national prevalence surveys despite the NTP's strong interest, highlighting funding as a barrier to wider implementation.

Even when data from nationally-representative TB prevalence surveys are available, apportioning TB burden to achieve accurate subnational-level estimates—to facilitate the construction of locally-relevant care cascades—remains challenging. Given sometimes wide disparities in the local burden of TB and important TB risk factors such as HIV or undernutrition, disaggregated data are critical. Data disaggregation is important not only geographically, but also along demographic and clinical strata, to allow strata-specific cascades to be constructed (e.g., for pediatric TB, DR-TB, incarcerated populations). Consequently, bottlenecks along the cascade for specific groups could be more easily identified, and NTPs could target resources to priority groups. Lastly, particularly in the context of public health shocks such as the COVID-19 pandemic, repeated prevalence surveys are needed to produce cascades that can inform programmatic decisions.

Figure 2: Estimates of TB prevalence (all ages and all forms of TB) in 24 countries before and after results of national TB prevalence surveys (implemented between 2007-2016) became available



Source: National tuberculosis prevalence surveys 2007-2016. Geneva: World Health Organization; 2021, creative commons license CC BY-NC-SA 3.0 IGO.³⁶

Countries are listed in decreasing order according to before-after difference in estimated prevalence.

DPR Korea, Democratic People's Republic of Korea; Lao PDR, Lao People's Democratic Republic; UR Tanzania, United Republic of Tanzania.

2. Lack of electronic data capture systems:

Lack of electronic data capture is a common challenge across many NTPs that affects the estimation of multiple steps of the care cascade. Some NTPs are utilizing systems for data digitization, including TIER.Net in South Africa,⁴¹ Nikshay in India,³² and SIGTB (Sistema de información gerencial de tuberculosis) in Peru.⁴² Nonetheless, barriers to implementing electronic data capture persist (e.g., internet speed and availability), especially in rural health centres. Reliance on paper-based data entry therefore continues to delay data collection, increase the risk of data loss, and preclude standardization of data entry. These factors hinder the timely tracking of people with TB with unique identifiers throughout their care pathway, particularly for people who transfer to other facilities, or whose contact information is illegible, incorrect, or missing, which contributes to pre-treatment loss to follow-up.^{43,44} As a result, outcomes for these people – including deaths before treatment initiation^{43,45} – are unlikely to be captured in the NTP database. In both South Africa and Zambia, the difficulty of tracking transfers has been identified as a major driver of under-notification.^{14,15}

In addition to data linkage across facilities, linkage among different databases—such as linkage of NTP data to general laboratory and vital statistics databases—is also critical. Electronic data capture would also enable analyses of disaggregated subnational data. Lastly, digitized data systems would also facilitate data quality assurance. This is critical, as recent analyses highlight the variable quality of routine TB program data,⁴⁶ underlining that improvements are needed for these data to serve as a reliable basis for estimating care cascades.

Although constraints in finances and digital infrastructure pose significant challenges to the feasibility of implementing electronic data systems, the COVID-19 pandemic and other public health emergencies have underlined the value – and current shortcomings – of robust national health data systems and governance, while leading to valuable improvements, including data digitization, in many settings.^{47,48} For example, in Uganda, an electronic health logistics data management platform launched during the Ebola epidemic was successfully leveraged for the COVID-19 response, providing timely data for program planning.⁴⁹ Investments in strengthening

digital infrastructure as a whole, therefore, have the potential to facilitate the shift to electronic data systems in specific programs such as NTPs.

3. Under-reporting of people with TB navigating fragmented and privatized health systems:

Under-notification is another barrier to estimating accurate care cascades. This occurs for several reasons, including the lack of unique identifiers to track people with TB throughout care, but is further complicated by the fragmented health systems people must navigate to access TB care. Unfortunately, a large proportion of people never access TB care in the first place, particularly in rural communities, as noted in a recent study of tribal populations across 17 states in India.⁵⁰ Even when people do seek care, they may not be appropriately referred for testing, as has been noted in standardized patient studies in India,⁵¹ China,⁵² Nigeria⁵³ and South Africa.⁵⁴ Furthermore, in some settings, particularly countries with large migrant populations, it is common for people with TB to seek care and be diagnosed in larger urban centers and then be lost to follow-up during referral back to rural TB centers to start treatment.^{43,55,56}

Under-notification can also occur due to non-NTP sites (academic hospitals, private sector providers, etc.) not serving as TB reporting units, as is the case in some settings (including in Zambia,⁵⁷ Madagascar, South Africa, and Nigeria⁵⁸), where people diagnosed with TB in hospitals are often not registered in the NTP. Under-notification is a particular concern in countries where the private sector plays a significant role in TB care.⁵⁹ In India, for example, while recent initiatives have substantially increased private sector notification, many people with TB in the private sector are still not being notified consistently, despite notification being mandatory.⁶⁰

Even when people with TB are notified from the private sector, treatment and post-treatment outcomes may not be consistently reported for these people, making it challenging to accurately estimate later care cascade stages. This underscores that more work is needed to engage private providers, as suggested by the WHO's roadmap for public-private mix (PPM), a

key recommendation of which is better tracking of the number of people with TB managed in the private sector, along with information on their referrals, notifications, and treatment outcomes.⁶¹ Notably, the Indian TB care cascade¹⁰ accounted for the public sector only. Not accounting for people with TB in the private sector is not a significant limitation in settings such as Zambia, where a small proportion of people with TB seek care in the private sector, and most are accounted for in the national cascade through notification to the NTP. In other settings with large private sectors however, cascades limited to the public sector cannot fully represent outcomes of TB care delivery.

Even in countries in which the private sector plays a small role in TB care, public sector under-notification remains significant, as shown in a recent data quality assessment in Zambia.⁵⁷ Difficulties with capturing TB deaths that occur before presenting for care also contribute to under-notification. In Peru for example, where all people with TB are treated in the public sector⁶² (and private sector care-seeking is not considered to be a major factor in under-notification), deaths from TB prior to registration in the NTP remain difficult to capture, due to limitations in death registry data. Similar challenges have been noted in Zambia, where post-mortem studies offer a strategy for estimating the extent of missed TB cases, with one study reporting incidental autopsy findings of TB in 1.2% of all sudden unexpected deaths in the community.⁶³ Data from post-mortem studies could therefore be incorporated into TB burden estimates.

Furthermore, systematic under-notification of people with TB who are more likely to have poor treatment outcomes jeopardizes routine programmatic data quality, particularly in settings where programs experience pressure to reach milestones. This creates incentives to avoid registering high-risk people with TB,^{64,65} which can introduce selection bias in treatment success rates. In Zambia, a nationally representative data quality audit was recently conducted to determine the number of TB people with TB who were diagnosed but not notified. This audit found that 33% of people with TB were unnotified (not reported in treatment registers).⁵⁷

Given the various mechanisms by which under-notification occurs, qualitative research may be used to improve our understanding of the reasons for under-notification and to identify opportunities for earlier registration of people with TB. A qualitative study in Peru has shown that imposed program targets (to carry out a certain number of TB tests per month) incentivized TB testing in individuals not suspected of having TB, delaying detection of actual cases.⁶⁶

4. Heterogeneity of diagnostic tests for TB

The heterogeneity of diagnostic tests used for diverse forms of TB, and their varying sensitivity and specificity, further complicates estimation of care cascades. Most tests in the TB diagnostic algorithm have suboptimal sensitivity, particularly compared to HIV testing, for example. Given that most HIV tests are highly sensitive and specific, rigorously estimating HIV prevalence using sentinel surveillance or population-based surveys has been possible, in turn facilitating more accurate estimation of HIV care cascades.⁶⁷

Recent studies, including care cascades, have used the known performance characteristics of TB diagnostic tests (sputum smear microscopy, GeneXpert) to estimate the proportion of people with test-negative pulmonary TB who may be missed by TB programs, with a Guatemalan study estimating that routine use of GeneXpert as a follow-up to smear microscopy would result in a 41% increase in TB notifications through identification of smear-negative cases.⁶⁸ However, prospective studies of pathways to care for people with extrapulmonary TB and children with TB are also needed to estimate follow-up throughout completion of the diagnostic workup, thereby facilitating estimation of diagnostic losses in these groups. This will require rigorous local care cascade studies and methodological innovation.

In addition, as countries may use a variety of TB diagnostic modalities (sputum microscopy, molecular tests, chest X-ray, etc.), characterizing diagnostic test performance under local NTP conditions may enable more accurate care cascade estimation, as would estimates of the proportion of people receiving specific modalities for upfront testing in different settings.

Lastly, counting all clinically diagnosed individuals as true TB cases poses a further challenge for care cascade analyses, as a proportion of these may not have TB (i.e., false positive misdiagnoses). This is particularly challenging in settings where clinical diagnoses make up a large proportion of all diagnoses, which is common in settings where sputum smear microscopy is relied upon, but is also observed in settings where access to rapid nucleic acid amplification tests (e.g., Xpert MTB/RIF) is readily available. For example, in many high TB burden countries, including North Korea, Mozambique, Myanmar, Papua New Guinea, the Philippines, Tanzania, and Zambia, more than 50% of pulmonary TB notifications are exclusively clinically or radiologically diagnosed, and in several additional high TB burden countries, exclusive clinical or radiological diagnoses exceed 40% of notifications.²¹ Case detection rates may therefore be overestimated in these settings, limiting the accuracy of care cascades.

5. Lack of routine post-treatment follow-up

There is growing awareness of the importance of post-TB lung disease,⁶⁹ and the need to assess long-term outcomes for people treated for TB. Most TB recurrence (91%) occurs in the first year following treatment,⁷⁰ especially in low HIV prevalence settings,⁷¹ providing a strong rationale for following people with TB for at least one year after treatment completion. Given high TB recurrence rates under programmatic conditions in many settings,^{26,72,73} routine post-treatment follow-up would not only estimate durable cure, providing a highly motivating outcome metric for TB programs, but it would also serve as an efficient form of active case finding, facilitating increased and early identification of TB recurrence, and continuity of care. This is particularly important given that previously treated people with TB have substantially poorer treatment outcomes than people with new TB.⁷⁴ However, despite its clear utility, one-year recurrence-free survival is not measured routinely in most TB programs, with episodes of recurrence detected only if the person presents to the health system again. Routine post-treatment follow-up would also be opportune for the continued engagement of people in the health system to provide care for post-TB lung disease and other co-morbidities, such as HIV and diabetes.⁶⁹ The current lack of post-treatment follow-up is therefore a major missed opportunity for TB

programs to improve care. Consequently, the proportion of people achieving one-year recurrence-free survival without post-TB lung disease should be seen as the final endpoint of the care cascade, and should be reportable to the WHO, along with estimates for previous care cascade steps.

Table 2. Challenges, data needs, and potential solutions for estimating each step in the TB care cascade

Step	Challenges	Solutions
Step 1: Estimated TB burden	Difficulty of estimating population-level TB burden - Lack of timely/routine national prevalence surveys to accurately estimate population-level disease burden, especially disaggregated by region and demographic strata - Regularity of prevalence surveys would facilitate estimation of well-characterised cascades - Limitations of methods used to derive WHO TB burden estimates - Limited accuracy especially if based on extrapolation of notifications, as this fails to account for people seeking care via non-NTP pathways, and TB deaths before presenting for care - High uncertainty (wide confidence intervals) in these estimates further hinders their utility as the basis of estimation of subsequent cascade steps - Spillover cases from previous years pose a challenge, as cascade analyses imply following a cohort through milestones in care	- Conduct disaggregated prevalence surveys at periodic intervals - Develop operational research and modelling capacity to facilitate subnational burden estimates, building on capacity developed in countries through ongoing initiatives such as the Global Burden of Disease Study⁷⁵ - Implement post-mortem studies more widely, and utilize the resulting data to inform TB burden estimates (to capture TB deaths prior to notification) - Implement the WHO roadmap on PPM, so that disease burden and outcomes in the private sector can be better estimated
	Lack of electronic TB databases and data linkage - Triangulation from multiple data sources is challenging (and means that estimated cascades rarely actually follow the same cohort throughout subsequent steps, i.e., each step is not a direct subset of the prior step) - Data linkage e.g., between vital statistics databases and NTP data is lacking - Processing of paper-based datasets is time-consuming and competes with NTP worker's ability to interpret and act on data	
	Lack of timeliness of data capture Often retrospective, not sufficiently timely to be useful for TB program management	
Step 2: Proportion accessing TB testing	Lack of clarity regarding what this step is attempting to estimate - Several potential gaps of interest: Those who did not /could not seek care, those who sought care but were not tested, those who were tested but did not receive their results / diagnosis, and those with false negative test results - Recommendations in some settings for the collection of smears on consecutive days create socioeconomic barriers to access to testing	- Use standardized questionnaires to help capture symptoms / presumptive cases and whether they sought care but were not diagnosed - Improve data capture at early stages - Conduct more frequent prevalence surveys (to help differentiate

Step	Challenges	Solutions
	Data capture, systems, and management - Many programs register people with TB at treatment initiation (and some at diagnosis), but not at testing – systems used to capture routine NTP data therefore, do not align with the data requirements of cascades - People presenting at general health centres (not TB-specific clinics) may not be referred for testing - Data capture at the presumptive TB stage is challenging, especially for those treated empirically, and those with paucibacillary disease or extrapulmonary TB - In Zambia, for example, although presumptive TB registers exist at all facilities, their quality is variable, especially compared to the national notification register Heterogeneity of diagnostic tests for TB: - Varying sensitivity and specificity, particularly in specific populations (e.g., GeneXpert MTB/RIF sensitivity in people living with HIV: 79% (95%CI: 70–86%),⁷⁶ and 62% (95%CI: 51–73) in children)⁷⁷ - Helpful to have sensitivity estimates for GeneXpert under local NTP conditions, and in specific populations such as those mentioned above - Helpful to know the proportion of people receiving specific tests in local testing algorithms	between those symptomatic but not seeking care vs. those seeking care but not being tested) Improve data quality of facility-level presumptive TB registries via NTP-led standardized guidance and training for facilities on data capture
Step 3: Proportion diagnosed with TB	Limitations of routine program data quality - e.g., not registering cases that are more likely to have a poor outcome - Consideration of clinically diagnosed TB as true TB, which may significantly overestimate case detection, particularly in settings where a large proportion of people are clinically diagnosed Timing of data capture - Pre-treatment loss to follow-up is difficult to measure (requires triangulation with laboratory data) as most NTPs register people at treatment initiation - Retrospective data entry from paper records Inability to track transfers to other centres before treatment initiation - Lack of unique IDs - Illegibility of contact information for people with presumptive TB - Lack of electronic data capture systems Lack of data linkage - e.g., lack of linkage of treatment data with laboratory data, or linkage over geographic areas	- Digitize data capture: Although this would in part facilitate addressing these challenges (data quality, linkage, timeliness), the barriers to implementing electronic data systems are significant, and are highlighted in section 2 above. - Conduct program quality monitoring and evaluation: It should be noted that data quality concerns apply to both, paper-based and electronic data capture systems. This underlines that other quality improvement efforts are also needed to improve paper-based and electronic records, including, for example, performance feedback.

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Step	Challenges	Solutions
Step 4: Proportion initiating TB treatment & Step 5: Proportion completing treatment	Under-notification and data quality limitations • People with TB who are more likely to have a poor outcome may not be registered • Under-notification due to transfers ◦ The use of paper-based systems and lack of unique identifiers to track transfers worsens this • People diagnosed at non-NTP sites are often not registered Lack of stratified data: • Although stratified reporting by sex and age group is now required by the WHO, stratification by other sociodemographic factors relevant to local contexts is needed for construction of sub-cascades that examine important differences in care-seeking and outcomes across strata	• Recognize the importance of medical colleges and hospitals as reporting units • Conduct data quality assessments and qualitative studies to understand the reasons for under-notification / missed cases and opportunities to enroll people earlier • Examine sub-cascades, e.g., MDR-TB, pediatric TB, and others, to gain a more granular understanding of stratum-specific cascade bottlenecks
Step 6: Proportion reaching one-year recurrence-free survival	Lack of post-treatment follow-up of people who completed TB treatment for at least one year • Despite a clear rationale for one-year recurrence-free survival as a measure of durable cure, especially given that most relapses occur within the first year after treatment, this is not captured in routine program data • In programs where discharge (at the end of treatment) is the endpoint of follow-up in TB registries, additional follow-up is solely passive • Although one-year follow-up is included in some NTP guidelines (e.g., in India), implementation remains a challenge • Even if one-year follow-up is done for recurrence and survival, this is unlikely to capture post-TB lung disease	• Establish robust data systems and follow-up capacity, allowing the reliable assessment of the one-year endpoint • Integrate post-treatment follow-up (and monitoring for post-TB lung disease) into adherence studies

3.6 Conclusion and calls to action

To rectify TB care cascade data gaps, NTP data systems and reporting practices must be improved, including through digitization of data capture, data linkage, and addressing under-notification. If applied routinely for the purpose of identifying bottlenecks in TB programs, care cascades can then serve as valuable QI tools to point towards the most needed interventions. Once robust care cascade analyses are available, acting upon them to improve TB outcomes at a population level will be even more critical.

To fully tap into the potential of care cascade analyses as a strategy for accelerating TB elimination, we present five calls to action (**Box 1**). First, we call on global agencies and funders to recognize the value of TB care cascades, so that investments can be made to support NTPs in the routine estimation of national and sub-national care cascades to inform program monitoring and improvement. A diverse international working group should be convened to develop recommendations regarding the routine use of care cascades by NTPs, including establishment of mandatory reporting standards, as well as standardization of methods for estimating cascade steps, to allow comparability across settings and time. Eventually, estimates for key steps in the TB care cascade should be reportable to the WHO, along with a description of the methods used to derive these estimates.

We further recommend that global bodies and funders support periodic, nationally-representative, prospective care cascade studies, which can be paired with community TB prevalence surveys. Such studies are being successfully implemented for HIV, where population-based surveys are identifying where to target resources to make progress most effectively. For example, the Population-based HIV Impact Assessment (launched in 2014) conducts nationally-representative surveys in 14 countries to determine HIV prevalence and estimates of the care cascade to the endpoint of viral load suppression.⁷⁹ While these surveys found high viral load suppression in individuals who were aware of their HIV status, the most difficult gap to close has been the high proportion of individuals—particularly men and young people—who are still unaware of their status. This has highlighted that HIV awareness

programs should prioritize these groups.⁶⁷ The surveys have also been used to identify gaps in care, such as treatment coverage gaps among children,⁸⁰ and long-term outcomes such as HIV-free survival among children born to mothers with HIV.⁸¹ For TB, accurate country-level care cascades could be similarly estimated through nationally-representative sampling of TB facilities, followed by prospective follow-up. If paired with population-based TB prevalence surveys, this could facilitate periodic rigorous estimates of the entire care cascade to inform a country's TB response.

With the necessary support from global agencies, we also call for the care cascade model to be applied to the *regular* and *transparent* tracking of progress towards the TB elimination goals to which countries have committed. This includes using care cascades to facilitate TB program monitoring and evaluation (including private sector TB care, in countries with large private health sectors), to provide an accurate foundation for evidence-based programmatic improvements, and to hold policymakers accountable for making the investments required to reach TB elimination targets. To this end, we hope the WHO will include national TB care cascades in the annual Global TB reports.

As a long-term yet critical call to action, NTPs should also work towards developing capacity (e.g., high-quality electronic data capture systems with real-time data entry and wide geographic coverage) for routine measurement of the care cascade, including at the local level. Given that outcomes are heterogenous within countries, local data will most directly drive improved outcomes for people with TB by identifying local bottlenecks and allowing precise resource allocation. It should be noted, however, that processes for establishing robust digital data capture will differ by setting, depending on the extent of infrastructure already available. In some settings, overall investment in general digital infrastructure will be required before specific TB-related systems can be adopted, and the implementation of electronic data systems should be accompanied by appropriate data governance policies.⁸² Data digitization is an overarching and critical challenge, that, if addressed, would significantly improve data availability and quality for the estimation of care cascades.

Our final call to action asks that progress be made towards integrating post-TB care into NTP guidelines and practices, including routinely monitoring people for at least one year after treatment completion. Beyond active follow-up for recurrence and survival, there must also be additional efforts to monitor and provide care for post-TB lung disease and morbidity⁸³ and to include measures of post-TB lung disease as part of the final outcome of the care cascade. This will advance multiple goals, including improving care for people with TB, serving as a form of active case-finding (through increased and earlier identification of recurrence), and providing a measure of durable cure, which is a better indicator of TB program performance.

Together, these calls to action offer a way forward for effectively utilizing care cascades as tools for identifying gaps in TB care and facilitating evidence-based improvements to TB programs globally.

Box 1. Calls to action to address TB care cascade data gaps and effectively utilize cascade analyses in working toward TB elimination

Call to Action 1: Recognition of the value of care cascades by global agencies and funders, and the creation of an international working group on TB care cascades

So that NTPs can be appropriately supported in the routine estimation of TB care cascades, the value of the TB care cascade model – and its potential to improve TB care, if appropriately acted upon – must be recognized by global agencies and funders. First steps towards this include:

- Global bodies convening an international working group to develop recommendations regarding the routine use of care cascades in national TB programs, including establishing mandatory reporting standards, and the standardization of methods/approaches used to estimate TB care cascades, to facilitate comparability.
 - Estimates of all steps (1-6) in the TB care cascade, along with the methods used to derive them, should be reportable to the WHO
- The WHO presenting care cascades in annual TB reports, as key indicators of progress towards TB elimination
- Major funders such as The Global Fund and USAID advocating for TB care cascades as a measure of system performance, and allocating resources to global capacity-building in this regard
 - This will generate capacity, resources and support for their routine application in NTPs.

Call to Action 2: The funding and conduct of national TB care cascade studies and TB prevalence surveys

In the short-term, global bodies and funders should support periodic, nationally-representative, prospective care cascade studies, as well as TB prevalence surveys (similar to population-based survey initiatives being done for HIV⁷⁹)

Call to Action 3: The routine application of care cascades to track TB elimination

National TB programs, with guidance from the WHO, should apply care cascades to the regular and transparent tracking of progress towards TB elimination goals, including to:

- Facilitate TB program monitoring and evaluation (e.g., via Joint Monitoring Missions and other evaluations of NTPs)
- Facilitate evidence-based planning for program improvements
- Improve visibility of TB management in the private sector
 - NTPs in countries in which a large proportion of people seek TB care in the private sector will need to step up efforts towards private provider engagement in order to construct meaningful cascades and consequently be able to act on robust findings
- Hold policymakers accountable to making the investments required to reach TB elimination targets

Call to Action 4: The development of capacity for data digitization and routine care cascade measurement

In the long term, national TB programs should work towards developing capacity for routine measurement of the care cascade, including at the local level. This includes developing capacity for:

- High-quality electronic data capture
- Real-time data entry
- Wide geographic coverage
- Data quality assessments

Call to Action 5: The integration of post-treatment monitoring into NTP guidelines

Progress should be made towards integrating post-TB care into NTP guidelines, practices, and reporting, including routinely monitoring people for at least one year after treatment completion.

3.7 Contributors:

Study conceptualisation: RS and LF. Data curation and analysis/visualisation: LF and RS. Study supervision: RS and MP. Writing of original draft: LF and RS. Review and editing: MP, CO, JK, OAA, SGL, NR, SS, KN, ADK, MM, CUG, GCC, PN, LF and RS. Access and verification of all data reported in the study: LF and RS. All authors agreed with the decision to submit for publication.

3.8 Conflicts of interest:

MP serves on the Scientific Advisory Committee of the Foundation of Innovative New Diagnostics (FIND), a non-profit global alliance for diagnostics. MP is also an advisor to the Bill & Melinda Gates Foundation. He has no financial or industry conflicts. CUG has received research support from the International Development Research Centre (Canada) and the Canadian Institutes of Health Research, the National Institutes of Health, FIND, and Abbott for projects unrelated to this work. CUG has also received honoraria from Molbio for presentations unrelated to this work. The other authors declared no conflicts of interest.

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CHAPTER 4: MANUSCRIPT 2:

TB care cascades and predictors of cascade completion prior to and during the COVID-19 pandemic in Lima province, Peru

4.1 Preface

Having outlined challenges for the accurate estimation of care cascades in the previous chapter, in this paper, using Peruvian National TB Program data, we estimate the first active TB care cascade in Peru, focusing on Lima province, the country's most populous province, which accounts for 48.5% of the national DS-TB burden and 65.4% of the national DR-TB burden. To understand the impact of the COVID-19 pandemic on bottlenecks in TB care delivery, we construct separate cascades for cohorts who received their care prior to, partially during, and entirely during the COVID-19 pandemic. Rather than focusing on a single indicator of disruption (e.g., decreases in case notifications, etc.), the cascade model allows identification of gaps in care throughout the care cascade, and whether COVID-19-related disruptions have exacerbated these gaps. We also assess predictors of care cascade completion among a cohort of n=1,513 patients receiving TB care at public primary care clinics in a high TB burden district of Lima province.

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TB care cascades and predictors of cascade completion prior to and during the COVID-19 pandemic in Lima province, Peru

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4.2 Abstract:

Background: Tuberculosis (TB) is an urgent public health concern in Peru, and the COVID-19 pandemic has significantly disrupted TB care in the country. However, the impact of the pandemic on specific steps in the cascade of care for TB in Peru has not yet been explored.

Methods: We constructed the drug-susceptible (DS) and drug-resistant (DR) TB care cascades prior to and during COVID-19 in Lima province (Aim 1), an area responsible for 48.5% of the national DS-TB burden and 65.4% of the national DR-TB burden. We also identified predictors of cascade completion among a sample of people receiving TB care prior to and during COVID-19 in San Juan de Lurigancho (SJL), a high TB burden district of Lima province (Aim 2). For Aim 1, cascades were constructed separately for cohorts receiving TB care prior to, partially during and entirely during COVID-19, based on standard TB treatment durations for DS and DR-TB, and considering 16 Mar 2020, the date the national emergency due to COVID-19 was declared in Peru as the start of COVID-19 pandemic. Steps in the TB care cascade were estimated based on published methods (step 1: the estimated number of people with TB in the population, step 2: the proportion of people accessing TB testing, step 3: the proportion diagnosed with TB, step 4: the proportion initiating TB treatment, and step 5: the proportion successfully completing treatment). Steps 4 and 5 were based on Peruvian national TB program data from 1 Jan 2018 to 16 Mar 2021 (up to one year into the COVID-19 pandemic), and prior steps are back-calculated using parameters available in the literature (e.g., on the sensitivity of TB tests under local conditions) or estimated from a sample of people receiving TB care in SJL (see Aim 2). For Aim 2, clinical and demographic data were collected from TB treatment registers of a sample of 1,513 people diagnosed with TB from Jan 2017 to Nov 2021 and receiving care at 25 primary clinics in SJL. Predictors of cascade completion in this sample were explored using logistic regression.

Results: Although the DR-TB cascade was exploratory given lower numbers of patients, the DS-TB cascade showed that 92.8% (95%CI: 86.3-101.1%), 92.5% (95%CI: 86.0-100.8%) and 58.9% (54.8-64.2%) of those estimated to have DS-TB accessed TB testing (cascade step 2) in the pre-,

partially during, and fully during COVID-19 groups, respectively. For the cohort receiving care prior to and partially during COVID-19, the largest gap in the cascade (relative to the prior step) was between those initiating treatment (step 4) and those completing treatment (step 5), whilst in the fully during COVID-19 cohort, the largest gap is between the estimated number of people with DS-TB in the population (step 1) and those accessing TB testing (step 2). Examining predictors of cascade completion among the SJL sample (Aim 2) showed that receiving TB care entirely during COVID-19 was associated with a lower likelihood of cascade completion (OR: 0.51, 95%CI: 0.29-0.88).

Conclusions: Keeping in mind the challenges and limitations associated with accurately estimating TB care cascades, our findings suggest that case detection was the most severely impacted aspect of care delivery for TB during the COVID-19 pandemic. National TB programs could use care cascades to identify specific bottlenecks in the TB care pathway and inform priorities for recovery from pandemic-related disruptions.

4.3 Background:

Tuberculosis (TB) is an urgent public health concern in Peru, which had an estimated incidence of 44,000 (34,000-54,000) cases of all forms of TB in 2021, corresponding to an incidence rate of 130 (102-161) cases per 100,000 population.¹ Peru is also one of 30 high-burden countries for drug-resistant TB as defined by the World Health Organisation (WHO).² With frequent political crises in recent years and the associated high turnover of Ministry of Health leadership posing challenges for the country's health system,³ the COVID-19 pandemic has represented a significant additional strain. Although important gains have been made in TB prevention and control in Peru, including the scale-up of molecular diagnostics and the increased screening for co-morbidities among people with TB,³ the pandemic has significantly disrupted TB services in the country, as it has globally, with health systems around the world being over-burdened, patients facing increased barriers to accessing care, TB staff being diverted to COVID-19 work⁴ and TB case notifications declining significantly.^{5,6}

Globally, it is estimated that 1.4 million fewer people accessed TB care in 2020 compared to 2019, and that TB deaths increased for the first time since 2005.⁷ In Peru specifically, having been hard-hit by the COVID-19 pandemic (with over 4.5 million COVID-19 cases and over 220,000 deaths as of June 2023),⁸ disruptions to TB services have also been significant. For example, Peru experienced the 13th largest shortfall in TB case notifications between 2019 and 2020 among all countries.⁷ A modelling study found that passive (demand-driven) TB case detection was the most severely disrupted aspect of TB care delivery in Peru during the pandemic, falling by 64%.⁹ Beyond the drop in case notifications, other disruptions to TB care in Peru during the COVID-19 pandemic include delays in care-seeking,¹⁰ and disruptions to treatment monitoring, such as directly observed therapy (DOT), in response to which the NTP implemented alternative DOT strategies, including via video, telephone, or home visits.¹¹

TB care cascades, a representation of the proportion of all people with TB reaching particular milestones in care (accessing testing, receiving a diagnosis, initiating treatment, and completing treatment) offer a useful approach to identifying bottlenecks in care delivery for TB, and

contribute valuable information to TB program planning and priorities. Based on published methods,¹² the TB care cascade model has been applied to estimate national or subnational cascades in various countries,¹³⁻¹⁷ but has not yet been applied in Peru. The value of TB care cascades (as well as the challenges in estimating them) are discussed in detail in previous work by the authors.¹⁸ In the context of COVID-19-associated disruptions to TB programs, however, it is particularly informative to estimate the TB care cascade in Peru, prior to and during the COVID-19 pandemic. While it has been established that TB notifications decreased in Peru during COVID-19,^{7,9} estimating losses throughout the care cascade will highlight gaps in care delivery at all care pathway milestones (beyond notification). We therefore estimated the pre- and during-COVID-19 drug-susceptible (DS) and drug-resistant (DR) TB care cascades for Lima province, a high TB burden province of Peru, and also identified predictors of cascade completion in a sample of people receiving TB care prior to and during the COVID-19 pandemic in San Juan de Lurigancho (SJL), a district of Lima province.

4.4 Methods:

Research ethics:

Research ethics approval was obtained from research ethics boards at Universidad Peruana Cayetano Heredia (Lima, Peru) (UPCH IRB SIDISI: 206189) and McGill University (Montreal, Canada) (McGill IRB ID: A09-M51-21A). In addition, access to the Peruvian national TB program (NTP) database (Sistema de información gerencial de tuberculosis, SIGTB)¹⁹ was granted by the Peruvian NTP (for Aim 1), and permission to access TB treatment charts was granted from health centres in SJL (for Aim 2). This study is registered in Peru's health research registry (Registro de proyectos de investigación en salud, PRISA)²⁰ at the Peruvian National Institute of Health (EI00000002446).

Engagement of communities affected by TB:

To ensure this work is relevant to and respectful of the experiences of communities affected by TB, a summary of the research protocol was shared with a panel of five TB survivors and advocates for discussion and incorporation of their feedback into the work.

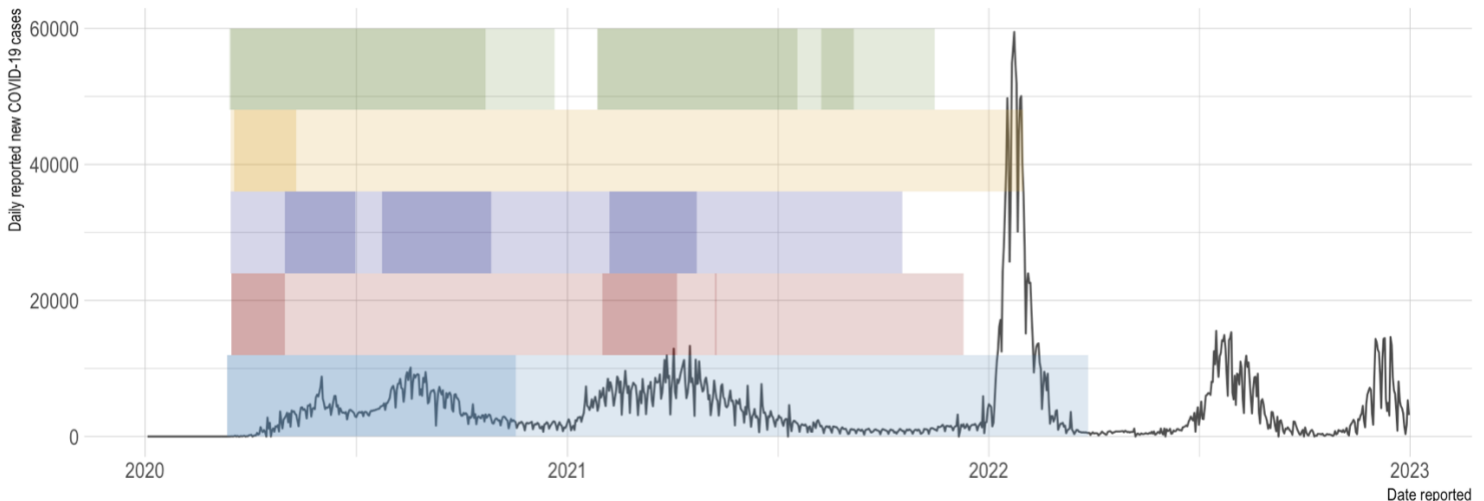
Study setting:

Aim 1 focuses on Lima province, the most populous province of Peru, with a population of 10,004,141 (30.0% of Peru's total population) in 2022.²¹ **Figure S1 (Supplement 1)** shows a map of Lima province within Peru. TB care in the province, as in the rest of the country, is provided entirely through the public health sector. According to NTP guidelines,²² the diagnostic algorithm for TB in Peru consisted of sputum smear microscopy carried out at baseline, and drug-susceptibility testing (DST) via GeneXpert, GenoType, or Microscopic-Observation Drug-Susceptibility Assay²³ (MODS), depending on the availability of tests in each region. GeneXpert testing was scaled up in Peru in 2018, and as of 2022 is available at 38 laboratories in the country.²⁴ Repeat sputum smear microscopy is carried out for treatment monitoring, monthly among people with DR-TB, and at two and six months for those with DS-TB (or monthly if positive at two months). Sputum culture is done monthly for DR-TB patients and at the end of treatment for DS-TB patients, or at two months (end of intensive phase) if smear positive at two months (and monthly thereafter if culture positive).

In response to the decrease in TB case detection during COVID-19, the NTP implemented active case finding campaigns (including mass mobile chest X-ray screening) in multiple districts of Lima province, supported by Socios en Salud (Partners in Health).²⁵ COVID-19 cases as well as COVID-19-related restrictions (movement restrictions, school/workplace closures, etc.) in Peru are shown in **Figure 1**, to provide context on COVID-19-related disruptions in this population during the study time period.

Aim 2 is based on a sample of people receiving TB care in San Juan de Lurigancho (SJL), one of 43 districts in the province of Lima. With a population of 1,225,092, SJL is the most populous district in the country.²¹ TB care in the district is provided through NTP offices at 33 primary clinics.

Figure 1. Daily new COVID-19 cases reported in Peru,²⁶ and COVID-19-related restrictions (Jan 2020 – Dec 2022)²⁷



COVID-19-related restrictions/policies

Local travel restrictions

- Travel between regions not recommended
- Travel between regions restricted

Stay-at-home orders

- Stay-at-home order with exceptions (e.g. exercise, groceries)
- Stay-at-home order with minimal exceptions (e.g. once a week / one person at a time)

Transport closures

- Significantly reduced routes/volumes/means of transport, or recommended closure
- Closed

Workplace closures

- Closure of some sectors
- Closure of all sectors (except essential services)

School closures

- Closure at some levels/categories (e.g. public/private or grade-level differences)
- Closure at all levels/categories

Work closure policies not available for 2021-12-10 to 2022-09-30

Transport closure policies and local travel restrictions not available for 2021-11-15 to 2022-06-30

COVID-19 cases are from the WHO COVID-19 database.²⁶

COVID-19 measures/policies are from the Oxford COVID-19 Government Response Tracker.²⁷

This figure is presented in another unpublished thesis manuscript by the first author, "Tuberculosis case notifications and outcomes in Peruvian prisons prior to and during the COVID-19 pandemic: A national-level interrupted time series analysis", Faust et al.

Definition of pre- and during COVID-19 cohorts:

For both aims, the start of the COVID-19 pandemic is defined as the date the national emergency due to COVID-19 was declared in Peru (16 Mar 2020). To take into account whether individuals' TB care occurred prior to or during the pandemic, in both study aims, treatment time is considered in the categorisation of the pre/during COVID-19 cohorts into three categories: TB care occurring prior to COVID-19, partially during COVID-19, or entirely during COVID-19. The specific cut-offs defining these cohorts however differ by aim and are described below.

For Aim 1 (constructing the DS- and DR-TB care cascades), categorization of the pre- and during COVID-19 cohorts is based on the standard treatment lengths for DS- and DR-TB in Peru (6 and 18 months, respectively). As such, people with DS-TB diagnosed 6 months or more prior to 16 Mar 2020 (i.e., prior to 16 Sep 2019) are defined as the pre-COVID-19 cohort, as all of their TB treatment is expected to have occurred prior to the pandemic. Similarly, those diagnosed between 16 Sep 2019 and 15 Mar 2020 are defined as having received their TB care partially during COVID-19, and those diagnosed 16 Mar 2020 onwards as receiving their TB care entirely during COVID-19. For further details on aim 1 COVID-19 cohort definitions for DS- and DR-TB, see **Table S1 (Supplement 1)**. Given that the idea of the care cascade approach is to follow a defined cohort across milestones of care, a single, standard treatment length cut-off is used for each cascade (6 months for DS-TB and 18 months for DR-TB) rather than individualized cut-offs adapted to each person's treatment length (as is done in Aim 2, explained below).

For Aim 2, identifying predictors of cascade completion among people receiving TB care in SJL, the pre-, partially during, and fully during COVID-19 cohorts are defined similarly to Aim 1, but adapted to the length of each individual's treatment regimen, rather than the standard treatment length. The lengths of treatment regimens among people in the study sample (according to NTP guidelines) and the associated COVID-19 period definitions for Aim 2 are shown in **Table S2 (Supplement 2)**.

Study population, data sources (Aim 1), and data collection (Aim 2):

The estimation of the TB care cascades for Lima province (Aim 1) is based on all TB cases notified in SIGTB¹⁹ from 1 Jan 2018 to 15 Mar 2021 (DS-TB cascade), and 1 Jan 2018 to 1 Aug 2020 (DR-TB cascade) (see **Tables S1 (supplement 1)** for dates by COVID-19 cohort), as well as on WHO TB burden estimates for Peru,²⁸ and other parameters such as published estimates of the sensitivity of tests in the diagnostic algorithm for TB under local conditions.^{23,29} Specific sources for parameters informing the estimation of each step in the cascade are shown in **Table 1**. Limitations associated with the use of a routine programmatic database such as SIGTB are described in the discussion section.

For Aim 2, data were collected by a study nurse from TB treatment charts at 25 (75.8%) of the 33 clinics providing TB care in SJL district. Although no clinic specifically refused to provide access to TB registries, data could not be collected from 8 (24.2%) of the clinics due to clinic staff not being available when the study nurse arrived to collect data, and these clinics were therefore excluded. At the 25 included clinics, all treatment registers accessible to the study nurse for people diagnosed from Jan 2017 to Nov 2021 were included (n=1,513). Initial data collection occurred between Sep 2021 and Feb 2022, with subsequent treatment status updates occurring until Nov 2022.

Analysis:

The care cascades for people with DS- and DR-TB treated prior to, partially during and fully during COVID-19 in Lima province (Aim 1) were estimated based on established methods for TB care cascade construction,¹² and included the following steps 1) the estimated burden of TB in Lima province, 2) the proportion of people who accessed TB testing, 3) the proportion of people who were diagnosed with TB, 4) the proportion initiating TB treatment, and 5) the proportion successfully completing treatment. It should be noted that step 2 represents people who truly had TB who accessed testing (not people with symptoms who accessed testing). The challenges in estimating this step are described in prior work.¹⁸ As only steps 4 and 5 are captured in SIGTB, as in most routine NTP databases, other steps are based on available

estimates (e.g., WHO TB burden estimates for Peru,²⁸ for step 1) or back-calculated from prior steps based on parameters available in the literature. Estimates for each step and their sources are outlined in **Table 1**. Full calculations for each step are provided in **Supplement 1**.

For step 5 in the cascades (the proportion successfully completing treatment), treatment success was defined as either a status of cured or treatment complete recorded in SIGTB. For those without a final treatment outcome reported, further information in the database was consulted and a treatment outcome was assigned according to updated WHO treatment outcome definitions,³⁰ if the relevant information was available (otherwise, the outcome was left as missing). For example, for the DS-TB cascade, the development of drug-resistance, or permanent treatment suspensions or changes were considered failures of first-line treatment. For the DR-TB cascade, permanent changes to initial DR-TB treatment due to increased resistance were also considered unsuccessful treatment outcomes. Patients reported in the database to have received an erroneous diagnosis of TB were excluded from both cascades. Final cascade steps are presented as a percentage of the estimated burden of TB (step 1), to allow clearer comparison of gaps across differently sized cohorts (pre-COVID-19, during COVID-19).

Table 1. Steps and data sources for the estimation (a) of the DS- and DR-TB care cascades in Lima province, Peru, prior to and during the COVID-19 pandemic.

DS-TB cascade		DR-TB cascade	
Step	Estimation approach and data sources	Step	Estimation approach and data sources
Step 1: the estimated burden of DS-TB in Lima province	Based on WHO estimates of the burden of all forms of TB in Peru²⁸ plus 50% of previously undetected cases,¹² (b) apportioned to the cohorts receiving TB care prior to, partially during, and fully during COVID-19, (c) then apportioned to DS-TB based on the proportion of DS-TB notifications vs. overall TB notifications in SIGTB,¹⁹ and finally, apportioned to Lima province based on the proportion of all DS-TB notifications in SIGTB that are from Lima province. Error bars are based on uncertainty intervals in WHO estimates of TB burden in Peru.	Step 1: the estimated burden of DR-TB in Lima province	Based on WHO estimates of the burden of all forms of TB in Peru,²⁸ plus 50% of previously undetected cases,¹² (b) apportioned to the cohorts receiving TB care prior to, partially during, and fully during COVID-19, (c) then apportioned to DR-TB based on the proportion of DR-TB notifications vs. overall TB notifications in SIGTB,¹⁹ and finally, apportioned to Lima province based on the proportion of all DR-TB notifications in SIGTB that are from Lima province. Error bars are based on uncertainty intervals in WHO estimates of TB burden in Peru.
Step 2: the proportion of people with DS-TB accessing TB testing	Back-calculated from step 3 (see below), step 2 is the number of people diagnosed with DS-TB (step 3) plus the number of people who truly had TB and accessed testing but were missed (were not diagnosed with TB although they truly had TB), due to the imperfect sensitivity of tests in the diagnostic algorithm for TB. The number of people missed is based on the proportion of people receiving each test in the diagnostic algorithm for TB (based on a sample of patients receiving TB care in San Juan de Lurigancho district of Lima province, see aim 2), and the sensitivity of each of these tests under local conditions (from the literature).^{23,29} Lastly, the number missed is then corrected for those treated empirically (DS pulmonary TB patients initiated on treatment without bacteriological confirmation, and DS extrapulmonary TB patients initiated on treatment without histopathological confirmation, according to SIGTB data). Error bars are based on 95%CI for the sensitivity of each test.	Step 2: the proportion of people with DR-TB accessing TB testing	Back-calculated from step 3 (see below), step 2 is the number of people diagnosed with DR-TB (step 3) plus the number of people who truly had TB and accessed testing but were missed (were not diagnosed with TB although they truly had TB), due to the imperfect sensitivity of tests in the diagnostic algorithm for TB (including imperfect sensitivity for rifampin resistance). The number of people missed is based on the proportion of people receiving each test in the diagnostic algorithm for TB (based on a sample of patients receiving TB care in San Juan de Lurigancho district of Lima province, see aim 2), and the sensitivity of each of these tests under local conditions (from the literature).^{23,29} Lastly, the number missed is then corrected for those treated empirically (DR pulmonary TB patients initiated on treatment without bacteriological confirmation, and DR extrapulmonary TB patients initiated on treatment without histopathological confirmation, according to SIGTB data). Error bars are based on 95%CI for the sensitivity of each test.
Step 3: the proportion of people with DS-TB diagnosed (d)	Back-calculated from step 4 (see below), taking into account pre-treatment loss to follow-up (those who are diagnosed with TB but do not initiate treatment). This is based on aggregate annual data on the number of people diagnosed with TB vs. the number initiating treatment, as reported by the Peruvian CDC and NTP. ²⁴ Weighted averages of the annual aggregate proportions of those diagnosed that initiated treatment were	Step 3: the proportion of people with DR-TB diagnosed (d)	Back-calculated from step 4 (see below), taking into account pre-treatment loss to follow-up (those who are diagnosed with TB but do not initiate treatment). This is based on aggregate annual data on the number of people diagnosed with TB vs. the number initiating treatment, as reported by the Peruvian CDC and NTP. ²⁴ Weighted averages of the annual aggregate proportions of those diagnosed that initiated treatment were used to estimate

	used to estimate cohort-specific proportions (pre- / partially during / during COVID-19) based on the contribution of years to each cohort.		cohort-specific proportions (pre- / partially during / during COVID-19) based on the contribution of years to each cohort.
Step 4: the proportion of people with DS-TB initiating treatment (d)	The number of people with DS-TB in Lima province who had a treatment start date recorded in SIGTB, by cohort (TB care pre-, partially during, fully during COVID-19).	Step 4: the proportion of people with DR-TB initiating treatment (d)	The number of people with DR-TB in Lima province who had a treatment start date recorded in SIGTB, by cohort (TB care pre-, partially during, fully during COVID-19)
Step 5: the proportion of people with DS-TB successfully completing treatment (d)	The number of people with DS-TB in Lima province who had a successful treatment outcome (cured or treatment complete) recorded in SIGTB, by cohort (TB care pre-, partially during, fully during COVID-19)	Step 5: the proportion of people with DR-TB successfully completing treatment (d)	The number of people with DR-TB in Lima province who had a successful treatment outcome (cured or treatment complete) recorded in SIGTB, by cohort (TB care pre-, partially during, fully during COVID-19)

CDC = Peruvian national centre for epidemiology, prevention and control of diseases (Centro Nacional de Epidemiología, Prevención y Control de Enfermedades)

*(a) See **Supplement 1** for detailed calculations of each step for each cohort*

*(b) See **Supplement 1** for prior period considered in estimation of undetected cases (based on time periods of each COVID-19 cohort)*

*(c) See **Table S1 (Supplement 1)** for dates defining each cohort*

(d) No confidence intervals for these steps, as they are based on exact values from NTP data.

Predictors of cascade completion (successful treatment completion) among people receiving TB care prior to and during the COVID-19 pandemic in SJL district (Aim 2) were explored using logistic regression (**Equation S1, Supplement 2**). Covariates adjusted for in the model (extracted from patient charts) included: poverty (based on type of material individual's house was made of housing materials [rudimentary materials, e.g., thatched vs. non-rudimentary, e.g. brick] and the availability of basic services [electricity, piped water, sewage system] in the home as a proxy for socioeconomic status), sex, age, type of case (new vs. retreatment), drug-susceptibility (DR-TB/DS-TB), HIV status, diabetes status, smoking (never/past/currently), alcohol consumption (none/occasional/abuse), drug use (none/past/currently), treatment adherence (total number of days with missed doses recorded in treatment chart), and whether TB care was received pre-, partially during, or entirely during the COVID-19 pandemic, according to definitions described in **Table S2 (Supplement 2)**. In addition, as health centres not being open after working hours may contribute to treatment adherence barriers, and missing

or illegible patient contact information has been found to be associated with loss to follow-up,^{31,32} these were also included as covariates. Completeness of patient contact information was defined as either address or phone number complete and legible vs. incomplete, illegible or missing, and clinic opening hours were categorised as open vs. closed after 5pm. Penalised splines were used to model non-linear relationships between continuous predictors (age and treatment adherence) and the outcome.

People with missing outcome data (those who were transferred (n=77, 5.1%) or who were still on treatment (n=45, 3.0%)) were excluded from the analysis. Covariates with missing data included diabetes status (n=1, 0.1%), EPTB (n=1, 0.1%), legibility of contact information (n=3, 0.2%), previous TB (n=3, 0.2%), HIV (n=5, 0.4%), adherence (n=5, 0.4%), drug use (n=22, 1.6%), alcohol use (n=23, 1.7%), smoking (n=24, 1.7%). As missing data on covariates were very low (overall missingness in total dataset: 0.3%, and percent missingness for covariates ranging from 0.1% to 1.7%), missing covariate data were not imputed.

A sensitivity analysis was conducted redefining the COVID-19 variable as the time (number of weeks) since the start of the COVID-19 pandemic state of emergency in Peru (16 Mar 2020) at the time of each person's TB diagnosis, rather than the COVID-19 categories used in the main analysis. In addition, as the housing materials / the availability of basic services in the home are an imperfect indicator of socioeconomic status, a further sensitivity analysis was conducted using an alternative indicator for socioeconomic status; neighbourhood-level income categories (average per capita monthly income by neighbourhood, according to National Institute of Statistics and Informatics [INEI] estimates)³³ based on the neighbourhood in which each patients' TB clinic is located. This is expected to be a relevant (although imperfect) indicator of socioeconomic status given that people with TB in Peru must be treated at the clinic in their neighbourhood (and are referred there if presenting to a different clinic for care).

Power calculations:

Constructing the pre- and during-COVID-19 TB care cascades (Aim 1): Being based on all TB notifications in Lima province, the sample size for this objective is fixed by design. However, based on a treatment success rate of 83% for all forms of TB in 2019 (pre-COVID-19), according to WHO estimates for Peru,¹ and 26,317 people with DS-TB in Lima province receiving their TB care prior to COVID-19, we expect to estimate the final step (treatment completion) of the pre-COVID-19 cascade with a margin of error of 0.45%. Assuming a drop to 73% treatment completion for the entirely during-COVID-19 cascade, we expect to estimate this with a margin of error of 0.86% (based on 10,314 people with DS-TB in Lima province receiving TB care entirely during COVID-19), which we consider sufficiently precise for estimates to be of value to TB programs. Given the lower incidence and longer treatment times for DR-TB, the DR-TB cascade is exploratory and expected to have lower precision.

Identifying predictors of cascade completion (Aim 2): Considering a drop in treatment completion proportions of those who received TB care pre-COVID-19 vs. entirely during COVID-19 from 83% to 73% to be of importance to TB programs, a sample size of at least $n=270$ in both the pre- and during-COVID-19 groups would allow detection of this 10% difference with 80% power, making our sample sizes of $n=644$ in the pre-COVID-19 group and $n=498$ in the fully during COVID-19 group sufficient to detect this difference. In addition, logistic models are sufficiently powered when meeting the 5 events per variable (EPV) criterion,³⁴ so at 73% treatment completion, the model will be powered to accommodate the 22 predictors (**Eq. S1**).

4.5 Results:

Aim 1: Lima province DS- and DR-TB care cascades

DS-TB care cascade:

Between 1 Jan 2018 and 16 Mar 2021, 91,518 people with DS-TB in Peru were notified in SIGTB. Of these, 148 were excluded from the cascade due to an erroneous diagnosis of TB (noted in the SIGTB database), leaving 91,370 DS-TB notifications in Peru in the above period. Of the national DS-TB notifications, 44,351 (48.5%) were in Lima province. Based on the COVID-19

cohort definitions and date cut-offs in **Table S1 (Supplement 1)**, 26,317, people with DS-TB in Lima province received their TB care prior to the COVID-19 pandemic, 7,720 partially during COVID-19, and 10,314 fully during COVID-19. Characteristics of people with DS-TB in Lima province notified in SIGTB in the study period are shown in **Table 2**.

The DS-TB care cascade for Lima province is shown in **Figure 2**. Apportioning WHO estimates for the burden of all forms of TB in Peru to DS-TB in Lima province, the estimated number of people with DS-TB in Lima province (step 1 in the DS-TB care cascade) receiving TB care prior to, partially during, and fully during the COVID-19 pandemic was 33,463 (95%CI: 23,109-45,409), 9,841 (95%CI: 6,724-13,305) and 20,327 (95%CI: 14,065-27,180), respectively (refer to **Table 1** for a summary of the approach to estimating cascade steps, and **Supplement 1** for detailed calculations). Of these, 92.8% (95%CI: 86.3-101.1%), 92.5% (95%CI: 86.0-100.8%) and 58.9% (54.8-64.2%) accessed TB testing (cascade step 2) among the pre-, partially during and fully during COVID-19 cohorts, respectively, and 80.4%, 80.7% and 51.4% were diagnosed with TB (cascade step 3). The numbers of people initiating TB treatment (step 4) represent 78.6%, 78.4% and 50.7% of the estimated DS-TB burden (step 1) in the pre-, partially during and fully during COVID-19 TB care periods, respectively. Finally, 60.3%, 60.3% and 36.1% of those estimated to have DS-TB in Lima province in the pre-, partially during and fully during COVID-19 cohorts had a successful TB treatment outcome, thereby completing the TB care cascade. The proportion of people completing the cascade differed significantly between the COVID-19 cohorts (Chi-squared test p value <0.001). For the cohort receiving care prior to and partially during COVID-19, the largest gap in the cascade (relative to the prior step) is between those initiating treatment (step 4) and those completing treatment (step 5), whilst in the fully during COVID-19 cohort, the largest gap is between the estimated number of people with DS-TB in the population (step 1) and those accessing TB testing (step 2).

Of those initiating treatment in each cohort (pre-, partially during and fully during COVID-19), 1.5%, 2.1% and 7.7% did not have a treatment outcome recorded, respectively. In the best-case scenario, assuming that all those without a treatment outcome recorded had a successful

outcome (completed the TB care cascade), the difference in proportions of cascade completion among those receiving TB care prior to, partially during and fully during COVID-19 did not remain significant (Chi-squared test p value 0.360).

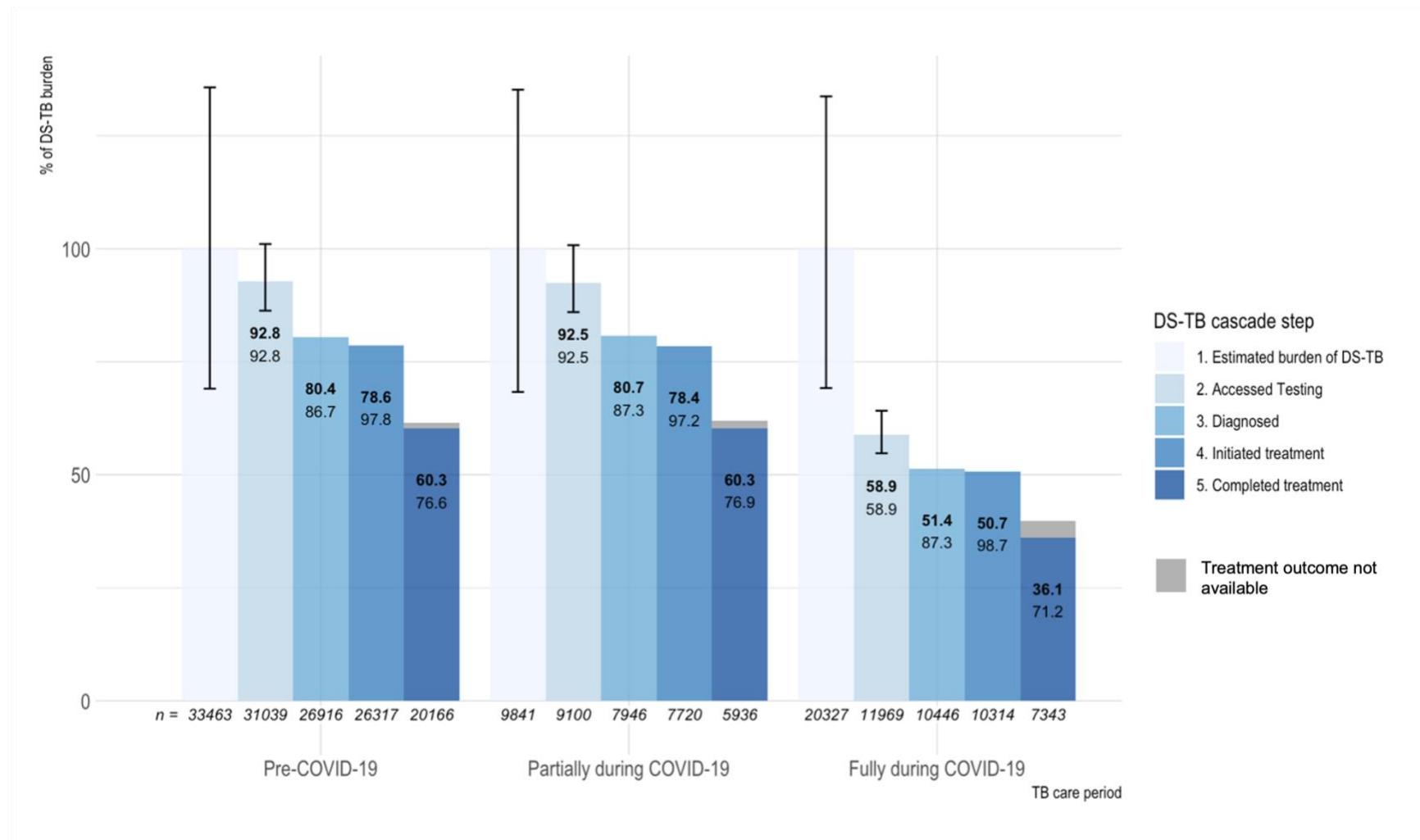
Table 2. Characteristics of individuals diagnosed with DS-TB in Lima province, pre- and during COVID-19 (Jan 2018 - Mar 2021)

	Pre-COVID-19 TB care (a)	TB care partially during COVID-19 (a)	TB care fully during COVID-19 (a)
Total	N = 26,317	N = 7,720	N = 10,314
Sex, male	16,839 (64.0%)	4,910 (63.6%)	6,460 (62.6%)
Age (years) (Mean (SD))	35.4 (18.5)	36.0 (18.7)	35.9 (17.7)
Type of case			
New	23,095 (87.8%)	6,836 (88.5%)	8,999 (87.3%)
Previous treatment stopped or failed	790 (3.0%)	187 (2.4%)	273 (2.6%)
Relapse	2,432 (9.2%)	697 (9.0%)	1,042 (10.1%)
Extrapulmonary TB	5,215 (19.8%)	1,536 (19.9%)	1,783 (17.3%)
HIV positive	1,306 (5.4%)	367 (5.3%)	438 (4.9%)
Diabetes	1,724 (7.4%)	577 (7.8%)	845 (9.0%)

Variables with missing data: EPTB n=5 (0.01%), HIV n=4,210 (9.5%), Diabetes n=4,123 (9.3%)

(a) See **Table S1 (Supplement 1)** for COVID-19 period definitions.

Figure 2. The DS-TB care cascade among those receiving TB care prior to, partially during, and fully during the COVID-19 pandemic in Lima province, Peru



Labels: bold = % of step 1, plain text = % of prior step, n = number of people at each step. Error bars: based on uncertainty in WHO TB burden estimates (step 1), and 95%CI for sensitivity of tests (step 2). See **Table 1** for estimation approach and data sources, and **Supplement 1** for detailed calculations of each step.

DR-TB care cascade:

Between 1 Jan 2018 and 1 Aug 2020, 3,603 people with DR-TB in Peru were notified in SIGTB. Of these, two were excluded from the cascade due to an erroneous diagnosis of TB. 2,355 (65.4%) of the national DR-TB case notifications were in Lima province. Based on the COVID-19 cohort definitions and date cut-offs in **Table S1 (Supplement 1)**, 696, 1,446, and 213 people with DR-TB in Lima province received their TB care pre-, partially during, and fully during the COVID-19 pandemic, respectively. Their characteristics are described in **Table 3**.

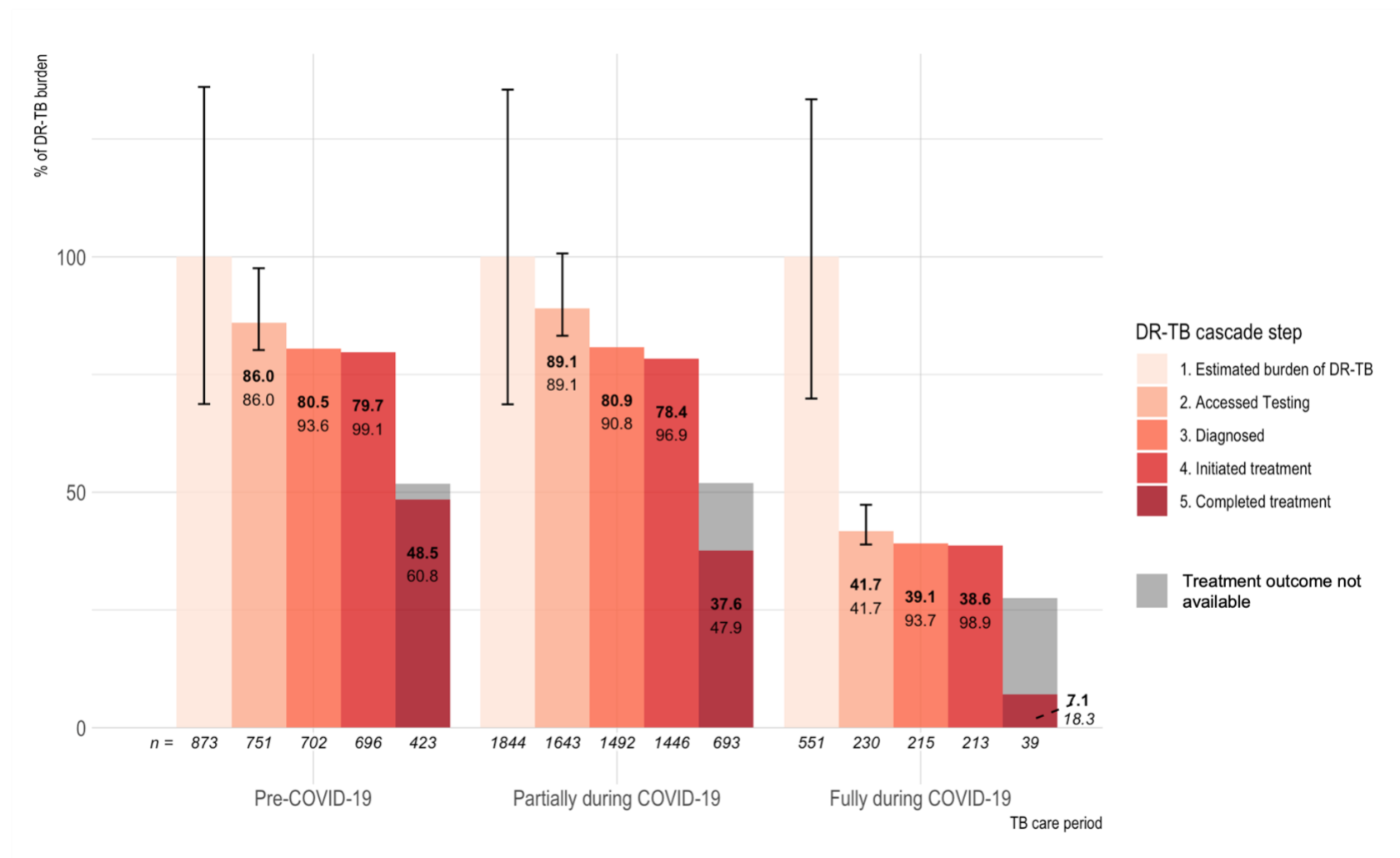
The DR-TB care cascade for Lima province for those receiving TB care prior to, partially during and fully during COVID-19 is shown in **Figure 3**. Given the low absolute numbers of DR-TB cases and the long treatment times for DR-TB, the DR-TB care cascade is exploratory, but, similarly to DS-TB, the largest gap in the pre- and partially during COVID-19 cascades was the gap between the proportion of people initiating and successfully completing treatment, whilst the gap between those estimated to have DR-TB in the population vs. those accessing testing was largest in the fully during COVID-19 cascade. Estimation approaches for each step in the cascade are summarised in **Table 1**, and detailed calculations are provided in **Supplement 1**.

Table 3. Characteristics of individuals diagnosed with DR-TB in Lima province, pre- and during COVID-19 (Jan 2018 - Aug 2020)

	Pre-COVID-19 TB care (a)	TB care partially during COVID-19 (a)	TB care fully during COVID-19 (a)
Total	N = 696	N = 1,446	N = 213
Sex, male	516 (74.1%)	1,013 (70.1%)	161 (75.6%)
Age (years)	32.6 (15.5)	33.4 (15.3)	33.0 (15.3)
Type of case			
New	498 (71.6%)	1,049 (73.1%)	144 (67.6%)
Previous treatment stopped or failed	99 (14.2%)	243 (16.9%)	46 (21.6%)
Relapse	99 (14.2%)	144 (10.0%)	23 (10.8%)
Extrapulmonary TB	14 (2.0%)	38 (2.6%)	4 (1.9%)
HIV positive	37 (5.6%)	75 (5.5%)	9 (4.4%)
Diabetes	38 (5.6%)	125 (8.8%)	17 (8.1%)

Variables with missing data: Age n=1 (0.04%), Type of case n=10 (0.4%), HIV n = 122 (5.2%), Diabetes n=34 (1.4%)
*(a) See **Table S1 (Supplement 1)** for COVID-19 period definitions.*

Figure 3. The DR-TB care cascade among those receiving TB care prior to, partially during, and fully during the COVID-19 pandemic in Lima province, Peru



Labels: bold = % of step 1, plain text = % of prior step, n = number of people at each step. Error bars: based on uncertainty in WHO TB burden estimates (step 1), and 95%CI for sensitivity of tests (step 2). See **Table 1** for estimation approach and data sources, and **Supplement 1** for detailed calculations of each step.

Aim 2: Predictors of TB care cascade completion in San Juan de Lurigancho district

The characteristics of clinics included (n=25, 75.8%) and those from which data could not be collected (n=8, 24.2%) are compared in **Table 4** (and did not differ significantly on most key characteristics). Of the 33 primary care sites providing TB care in the district, 23 are health centres (centros de salud) and 10 are health posts (puestos de salud). Health centres are generally larger than health posts, and have more staff and specialized services available. Of the 25 clinics included, 7 (28.0%) were health posts and 18 (72.0%) were health centres, and of the 8 clinics not included, 3 (37.5%) were health posts and 5 (62.5%) were health centres.

The clinics included and not included were also comparable on other characteristics, including the average catchment area size, the average number of patients presenting at the clinics with respiratory symptoms per month and the average number of people diagnosed with TB per month (see **Table 4**). In the majority of clinics (n=15, 60.0% of the 25 clinics included, and n=7, 87.5% of the clinics not included), sputum smear microscopy was done directly at the clinic (on-site microscopy facilities were available), while a minority of clinics also had capacity for on-site culture (n=9, 36.0% of the included clinics and none of the not included clinics). Availability of on-site smear microscopy or culture also did not differ between included and not included clinics. However, a characteristic that differed across included and not included clinics was the frequency with which sputum samples were sent for analysis, with most included clinics sending samples for analysis daily (n=18, 72.0%), whilst only one not included clinic (12.5%) sent samples daily (most sending samples only three times per week instead). This suggests that diagnostic delays for people presenting at the clinics included in the sample may be somewhat shorter than at clinics not included in the sample, which may bias findings given that shorter treatment delays increase the likelihood of successful treatment outcomes.

Regarding disruptions to TB services during COVID-19 at the clinics, included and not included clinics were also comparable. For example, only 3 of the 25 included clinics (12.0%) and 2 of the 8 not included clinics (25.0%) ever closed during the COVID-19 pandemic. Lastly, some clinics adapted to the COVID-19 pandemic by making changes to the provision of directly observed

therapy (DOT). Prior to the pandemic, patients presented to the clinics daily to receive DOT, but during the pandemic, to reduce COVID-19 transmission risk, some or all patients (or specific groups, such as patients with co-morbidities at high risk of COVID-19) at some clinics received a supply of TB medications to take home. The proportions of clinics with adapted DOT policies were also comparable across included and not included clinics.

Table 4. *Characteristics of the 33 primary care clinics serving people with TB in San Juan de Lurigancho district (Lima province, Peru)*

Clinic characteristics	In study sample	Not in study sample (a)
Total number of clinics (n, % of total)	25 (75.8%)	8 (24.2%)
Type of clinic: (b)		
Health posts (n, % of sub-group)	7 (28.0%)	3 (37.5%)
Health centres (n, % of sub-group)	18 (72.0%)	5 (62.5%)
Catchment area size (Mean, SD) (c)	35,067 (13,660)	26,317 (11,258)
Individuals presenting with respiratory symptoms per month (Mean, SD)	115 (102)	63 (50)
Individuals positive for TB per month (Mean, SD)	30 (16)	23 (11)
Sputum samples collected at clinic (n clinics, % of sub-group)	24 (96.0%)	7 (87.5%)
Sputum smear microscopy done at clinic (n clinics, % of sub-group) (d)	15 (60.0%)	7 (87.5%)
Culture done at clinic (n clinics, % of sub-group) (d)	9 (36.0%)	0 (0.0%)
Frequency with which sputum samples are sent for analysis	- Daily: 18 (72.0%) 3 days per week: 7 (28.0%) - Dependent on quantity: 0 (0.0%)	- Daily: 1 (12.5%) 3 days per week: 5 (62.5%) - Dependent on quantity: 2 (25.0%)
Clinic ever closed during COVID-19 pandemic (n clinics ever closed, % of sub-group) (e)	3 (12.0%)	2 (25.0%)
Effect of COVID-19 pandemic on DOT provision at this clinic (n clinics with each policy, % of sub-group)	- Continued as normal: 13 (52.0%) - People with TB received a supply of medication to take home: 7 (28.0%) - Some received a supply of medications to take home, others continued DOT in clinic: 3 (12.0%) - DOT continued as normal, but people with comorbidities	- Continued as normal: 4 (50.0%) - People with TB received a supply of medication to take home: 3 (37.5%) - Some received a supply of medications to take home, others continued DOT in clinic: 1 (12.5%) - DOT continued as normal, but people with comorbidities received a supply of medications to take home: 0 (0.0%)

	received a supply of medications to take home: 2 (8.0%)	

- (a) Although no clinic explicitly refused to be included in the study, data could not be collected from some clinics due to clinic staff not being available when the study nurse arrived to collect the data, and the study nurse working more regularly in some centres than in others.
- (b) All locations providing TB care in this district are primary care clinics, however, they are classified as either health posts or health centres. This classification corresponds to differing levels of service availability at health posts vs. health centres, with health centres generally being larger, having more doctors and nurses available, and offering more specialized services.
- (c) Catchment area size not available for n=6 included clinics and n=2 not included clinics
- (d) Otherwise sent for analysis at a laboratory or higher-level centre / hospital.
- (e) For the five clinics that experienced closures during COVID-19, n=1 was closed for two weeks, n=3 were closed for four weeks, and n=1 was closed for 8 weeks.

Of the initial sample (n=1,513), 1,240 (82.0%) reached the final step in the TB care cascade (successful treatment completion), 115 (7.6%) were lost to follow-up, 77 (5.1%) were transferred, 36 (2.4%) died, and 45 (3.0%) remained on treatment. People whose treatment outcome is unavailable (those who were transferred or still on treatment) were excluded from subsequent analyses.

Of the 77 people (5.1%) who were transferred, a minority of transfers were due to hospitalization (n=6, 0.4%) or incarceration (n=2, 0.1%), and the remaining were transfers to other TB clinics (n=69, 4.6%), for example if the patient moved residence. People with TB who were transferred are therefore not expected to differ significantly from those with available data. Regarding those still on treatment, given the long treatment times for DR-TB, the subset of people with DR-TB treated *entirely* during the COVID-19 pandemic had a larger proportion of people still on treatment (n=36/170, 21.1%) compared to among those with DS-TB (n=7/1,071, 0.7%). Similarly, two people with DR-TB (1.2%) but none with DS-TB treated *partially* during COVID-19 were still on treatment. As these are right-censored and not missing, we do not expect the characteristics of these individuals to differ from others with DR-TB treated during

the COVID-19 pandemic. A comparison of characteristics of those excluded (due to transfer or ongoing treatment) vs. included is provided in **Table S3 (Supplement 2)**.

Characteristics of the final sample (n=1,391) are shown in **Table 5**, stratified by people receiving TB care prior to, partially during and fully during the COVID-19 pandemic (see COVID-19 cohort definitions in **Table S2, supplement 2**). People in the final sample had a mean age of 32.2 years (SD: 16.3) and 61.1% were male. In total, 644 people received their TB care prior to the COVID-19 pandemic, 249 partially during COVID-19, and 498 fully during COVID-19.

Table 5. Characteristics of 1,391 people with TB receiving care in San Juan de Lurigancho pre- and during the COVID-19 pandemic

	DS-TB			DR-TB		
	Pre-COVID-19	Partially during COVID-19	Fully during COVID-19	Pre-COVID-19	Partially during COVID-19	Fully during COVID-19
Total	N = 491	N = 149	N = 382	N = 153	N = 100	N = 116
Sex, male	315 (64.2%)	89 (59.7%)	217 (56.8%)	100 (65.4%)	63 (63.0%)	66 (56.9%)
Age (years) [mean (SD)]	31.0 (16.5)	33.4 (18.6)	32.0 (15.2)	32.1 (15.2)	33.1 (15.1)	35.4 (17.8)
HIV	15 (3.1%)	4 (2.7%)	17 (4.5%)	19 (12.4%)	9 (9.0%)	4 (3.4%)
Diabetes	13 (2.6%)	7 (4.7%)	22 (5.8%)	11 (7.2%)	11 (11.0%)	9 (7.8%)
Level of care of TB clinic: Health post (vs. Health centre) (a)	67 (13.6%)	31 (20.8%)	96 (25.1%)	10 (6.5%)	6 (6.0%)	15 (12.9%)
Previously diagnosed with TB	30 (6.1%)	5 (3.4%)	37 (9.7%)	23 (15.0%)	7 (7.0%)	5 (4.4%)
Extrapulmonary TB	63 (12.9%)	49 (32.9%)	54 (14.1%)	9 (5.9%)	4 (4.0%)	11 (9.5%)
Adherence (Number of days with missed doses) [mean (SD)]	8.2 (17.4)	2.5 (7.9)	6.2 (15.3)	32.5 (43.6)	25.4 (38.8)	22.4 (38.0)
Basic sanitation unavailable / Rudimentary housing (b)	4 (0.8%)	1 (0.7%)	6 (1.6%)	2 (1.3%)	0 (0.0%)	1 (0.9%)
Telephone number or address incomplete, illegible, or not indicated	39 (8.0%)	11 (7.4%)	30 (7.9%)	25 (16.3%)	14 (14.0%)	17 (14.7%)

Missing covariate data: HIV (n=5), Diabetes (n=1), Previous TB (n=3), EPTB (n=1), Adherence (n=5), Completeness of contact information (n=3).

(a) The distinction between health posts and health centres indicates the differing level of services available at the two types of clinics, with health centres generally having more staff and equipment, and offering more specialized services compared to health posts (health centres are also usually larger, serving a higher volume of patients).

(b) Proxy for socioeconomic status indicating if any basic services (water, light, or sewage system) are missing in the home, or the home is built of rudimentary material.

Results of the logistic regression analysis identifying predictors of TB care cascade completion are shown in **Table 6**. Spline functions for continuous predictors (age and adherence [number of days with missed doses]) are shown in **Figure 4**. People with TB who were HIV positive were less likely to have a successful TB treatment outcome (OR: 0.34, 95%CI: 0.17-0.69), as were people who had previously been treated for TB (OR: 0.35, 95%CI: 0.19-0.65), and people with DR-TB (OR: 0.54, 95%CI: 0.34-0.88). The likelihood of cascade completion differed significantly between people receiving TB care prior to vs. during the COVID-19 pandemic, with people who received TB care during COVID-19 being only about half as likely to reach the end of the TB care cascade (successfully completing treatment) (OR: 0.51, 95%CI: 0.29-0.88 and OR: 0.49, 95%CI: 0.26-0.92 for those treated fully during and partially during COVID-19, respectively, compared to prior to COVID-19). Although the likelihood of cascade completion differed significantly by COVID-19 cohorts, COVID-19-related disruptions at the clinic level (clinic closures and changes in DOT administration during the pandemic) were not significantly associated with cascade completion (DOT method altered during COVID-19: OR: 1.99, 95%CI: 0.98-4.03, clinic ever closed during COVID-19: OR: 0.77, 95%CI: 0.31-1.92). Holding other covariates constant, the relationship between age and the probability of treatment completion (**Figure 4**) remained fairly linear until decreasing after approximately age 70, and the probability of treatment completion decreased as treatment adherence decreased (i.e., the number of days with missed doses increased).

Table 6. Predictors of TB care cascade completion (treatment success) among people receiving TB care prior to and during the COVID-19 pandemic in San Juan de Lurigancho district (Lima province, Peru)

Predictor (a)	OR	95%CI	
Health post (Ref = health centre) (b)	0.68	0.38	1.20
Contact information incomplete (Ref = contact information complete) (c))	0.67	0.36	1.25
Sex, male (Ref = female)	0.77	0.49	1.21
HIV positive (Ref = HIV negative)	0.34	0.17	0.69
Diabetic (Ref = non-diabetic)	0.60	0.26	1.40
Smoking (Ref = never smoked)			
Smoked in the past	1.16	0.36	3.73
Smokes currently	0.64	0.11	3.77
Alcohol use (Ref = never drinks alcohol)			
Occasional alcohol consumption	1.17	0.54	2.55
Alcohol abuse	0.66	0.20	2.23
Drug use (Ref = never used drugs)			
Used drugs in the past	0.48	0.09	2.62
Currently uses drugs	0.50	0.10	2.36
Previously diagnosed with TB (Ref = new diagnosis of TB)	0.35	0.19	0.65
DR-TB (Ref = DS-TB)	0.54	0.34	0.88
Basic services unavailable / rudimentary housing (d) (Ref = all basic services available and non-rudimentary housing)	0.79	0.09	7.12
Clinic closed after 5pm (Ref = clinic open after 5pm)	0.63	0.39	1.02
Extrapulmonary TB (Ref = pulmonary TB)	0.75	0.39	1.42
COVID-19 period of TB care (Ref = pre-COVID-19)			
TB care fully during COVID-19	0.51	0.29	0.88
TB care partially during COVID-19	0.49	0.26	0.92
DOT method altered during COVID-19 (e) (Ref = regular DOT maintained during COVID-19)	1.99	0.98	4.03
Clinic ever closed during COVID-19 (f) (Ref = never closed)	0.77	0.31	1.92

Ref = reference category

(a) For continuous predictors (age and adherence [number of days with missed doses]), see **Figure 4** for spline functions.

(b) The distinction between health posts and health centres indicates the differing level of services available at the two types of clinics, with health centres generally having more staff and equipment, and offering more specialized services compared to health posts (health centres are also usually larger, serving a higher volume of patients).

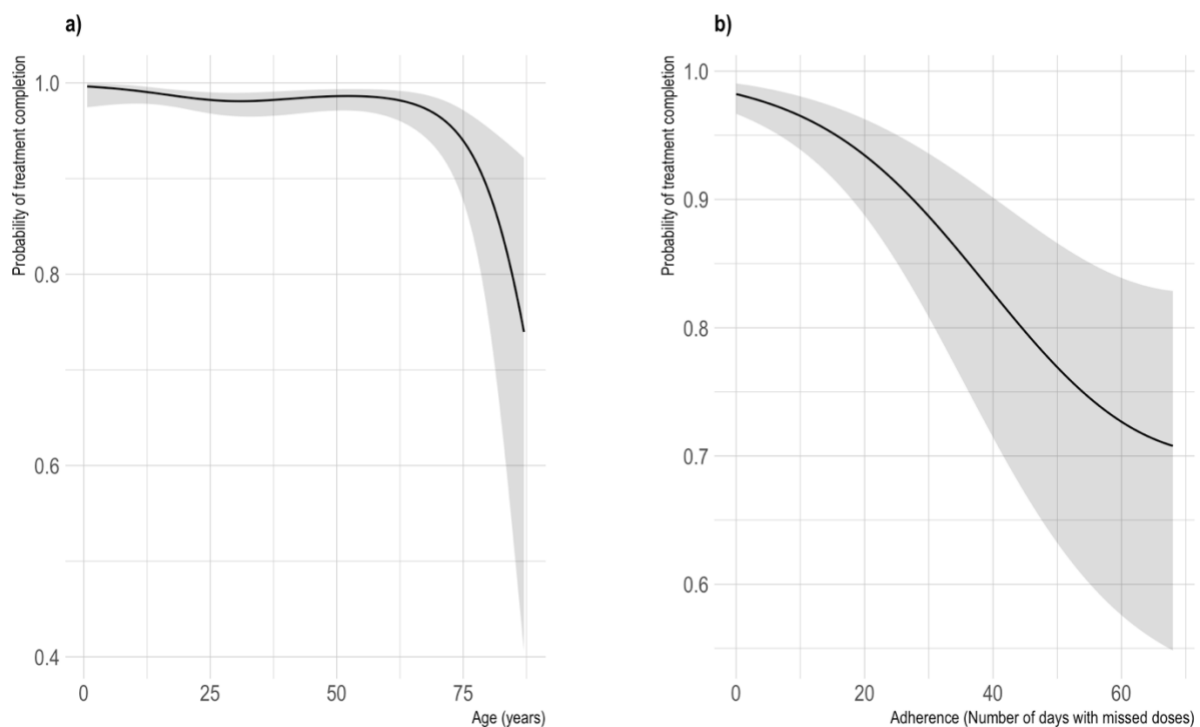
(c) Address or phone number incomplete, ineligible or not provided

(d) Proxy for socioeconomic status. Coded 1 if any basic services (water, light, or sewage system) missing in the home, or home built of rudimentary material. Ref = 0.

(e) All or some people with TB received a supply of medications to take home during COVID-19 (instead of receiving DOT at clinic). Ref = DOT continued in clinics, the same as before COVID-19.

(f) Three of the clinics in this sample were closed during COVID-19, one for a period of 2 weeks and the other two for a period of 1 month. All other clinics remained open during COVID-19.

Figure 4. Non-linear relationships of age (a) and adherence (number of days with missed doses) (b) vs. treatment completion



Penalised spline functions (df=4) for age (a) and adherence (number of days with missed doses) (b). Shaded area = 95%CI. Plots show predicted values of probability of treatment completion across values of age (a) and adherence (b), holding all other covariates constant (at their most common values for categorical variables, at the median value for adherence (in (a)), and at the mean age (in (b))). Plots therefore do not represent treatment completion probabilities in the overall population, but rather represent, for example in (a), treatment completion probabilities at different ages for a new case of drug-susceptible, pulmonary TB in a HIV-negative, non-diabetic, non-smoking male with no alcohol or drug consumption, who missed one day of TB treatment, whose home had access to basic services (proxy for socioeconomic status), who presented for TB care at a health centre that was open in the

evenings, and who received TB care prior to the COVID-19 pandemic. As the distribution of adherence (number of days with missed doses) was highly skewed, plot b shows adherence up to the 95th percentile (68 days with missed doses) rather than the maximum (292 days with missed doses), so that the relationship with treatment completion at the most common values of adherence can be seen more clearly.

Results of the sensitivity analysis redefining the COVID-19 variable as time (weeks) since the start of the COVID-19 pandemic (taken as the start of the declaration of the national emergency due to COVID-19 in Peru, i.e., 16 Mar 2020) at the time of each person's TB diagnosis are shown in **Table S4 (Supplement 2)**. As the relationship between time since COVID-19 and probability of treatment completion was non-linear, it was modelled flexibly using penalized splines, as were the other continuous predictors (age and adherence). Spline functions are shown in **Figure S2**. The spline function for the time since COVID-19 indicator suggests stable cascade completion probabilities throughout the first year of the pandemic. However, as the level of COVID-19-related disruptions varied over time, and the occurrence of disruptions at the time of diagnosis may not reflect downstream disruptions, time since the start of COVID-19 at the time of a person's TB diagnoses may not clearly represent the impact of disruptions over the course of an individual's TB care. The definition of COVID-19 used in the main analysis is therefore considered more interpretable, as it takes into account whether individuals with varying TB treatment times had their TB care occur prior to or during COVID-19. Predictors significantly associated with cascade completion in the main analysis (HIV status, previous treatment for TB, DR-TB) remained significant in this sensitivity analysis. COVID-19-related disruptions to TB services at clinics (clinic closures and changes in DOT provision) remained non-significant.

In the sensitivity analysis exploring a different proxy of socioeconomic status, replacing the housing materials and availability of basic services indicator with neighbourhood-level per capita income categories, neighbourhood-level income was not found to be a significant predictor of cascade completion (ORs for treatment completion, compared to middle income: lower middle income: 0.92, 95%CI: 0.45-1.86, low income: 1.50, 95%CI: 0.82-2.72). Although HIV status, previous treatment for TB, and DR-TB were significant predictors of cascade completion in the main analysis and remained so in the sensitivity analysis, interestingly,

whether TB care occurred prior to vs. during COVID-19, although significantly associated with cascade completion in the main analysis, was not significantly associated with cascade completion in this sensitivity analysis (OR: 0.57, 95%CI: 0.32-1.01 and OR: 0.56, 95%CI: 0.29-1.07 for TB care occurring fully and partially during COVID-19, respectively, compared to pre-COVID-19). Full results of this analysis are shown in **Table S5 (Supplement 2)**. Spline functions for continuous predictors are shown in **Figure S3**.

4.6 Discussion:

In this paper, benefitting from access to national-level TB program data, we estimated the first active TB care cascade for Peru, in a high-burden province responsible for almost half (48.5%) of the DS-TB cases and almost two-thirds of DR-TB cases in the country, providing useful information for TB programs. Stratifying these cascades by cohorts who would have received their TB care prior to, partially during and entirely during the COVID-19 pandemic, we find that prior to the pandemic, the largest loss along the DS- and DR-TB care cascades for Lima province occurred between treatment initiation and treatment completion, whilst for the entirely-during COVID-19 cohort, the largest loss in the cascade occurred prior to accessing TB testing. This indicates that the greatest barrier to TB care during the pandemic was case detection, rather than subsequent steps in the cascade such as pre-treatment loss to follow-up or loss to follow-up during treatment. This aligns with findings of a modelling study of TB case notifications in Peru during COVID-19, which estimated that passive diagnosis (case detection in people presenting to TB clinics) was the most detrimentally affected TB service during the pandemic⁹ (likely due to clinic closures at the beginning of the pandemic in Peru, preventing patients from accessing TB testing).

Further, to better understand predictors of cascade completion, collecting data on a sample of patients treated for TB in SJL district of Lima province allowed us to examine important covariates that are not available in the SIGTB database (e.g., clinic opening hours, clinic closures during COVID-19, completeness of patient contact information, number of missed doses, etc).

Our findings for this aim indicate significantly reduced cascade completion among those treated entirely during COVID-19 compared to prior to COVID-19 (OR: 0.51, 95%CI: 0.29-0.88).

However, our findings are subject to important limitations. Firstly, regarding Aim 1 (the TB care cascades for Lima province) there are various challenges and data gaps inherent in estimating TB care cascades based on routine national TB program data. These have been discussed in detail by the authors in prior work,¹⁸ but include limitations in the quality and granularity of programmatic data, as well as the lack of electronic data systems. In settings where a large number of people with TB present for care in the private sector, under-notification of cases from the private sector to the NTP is a further significant limitation of the routine data approach to TB care cascade estimation,¹⁸ however, this is expected to be minimal in the Peruvian context, as TB care is provided through the public sector in Peru.

A further limitation however is the lack of prevalence surveys to provide accurate estimates of the burden of TB in the population (step 1 in the cascade). In the case of Peru specifically, without recent prevalence surveys to inform national or subnational estimates of TB burden, the first step in the cascades presented here are based on WHO TB burden estimates for Peru,²⁸ the methods of which are heterogeneous and, for countries where prevalence surveys are lacking, rely on extrapolation from case notifications combined with expert opinion on undernotification.³⁵ As outlined in previous work,¹⁸ we therefore recommend investment in the conduct of prevalence surveys to better understand the population-level burden of TB and allow more accurate estimation of TB care cascades, strengthening their utility for subsequent evidence-based TB program planning.

In addition, the heterogeneity of tests used for TB diagnosis and their imperfect sensitivity pose challenges for estimating the second step in the cascade (the proportion accessing testing), especially in cases where data on diagnostic performance of tests under local conditions are unavailable. In the cascades presented here, we used estimates from studies conducted among a sample of people in the region of interest (Lima, Peru),^{23,29} although one study included

samples from multiple countries and did not stratify diagnostic performance results by location for smear microscopy.²⁹

Although subsequent steps in the cascade are less challenging to estimate, particularly steps 4 and 5 which are based on data routinely reported to TB programs, there remain limitations in the estimation of these steps with respect to routine programmatic data quality and completeness. As studies in other settings highlight, undernotification of TB cases is a well-established problem in programmatic data.³⁶ Even prior to COVID-19-related drops in case detection, global TB case notifications accounted for only 71.0% of the estimated global TB burden in 2019 and this dropped to 58.6% in 2020.^{7,37} In Peru specifically, although the proportion of TB cases notified pre-COVID-19 (in 2019), as a proportion of estimated burden, was higher than the global notification proportion (81.4%),²⁸ suggesting less undernotification than in other routine databases, this is a possible source of bias in the estimation of later cascade steps (e.g., the proportion successfully completing treatment), given that differential undernotification by treatment outcome is possible, for example if patients who are likely to have less favourable treatment outcomes are less likely to be notified. In addition, in 2020 (first year of COVID-19), the number of cases notified in Peru represented only 60.9% of the estimated burden.²⁸ Given the higher undernotification during COVID-19 compared to pre-COVID-19, this suggests estimates of cascade completion could be biased towards the null, if those with unfavourable outcomes are less likely to be notified.

Investigating the completeness of SIGTB in the Peruvian department of Cajamarca, a study found 74.4% of estimated TB cases in the department in 2018 were notified in SIGTB.³⁸ However, given that Cajamarca is a lower-incidence region compared to Lima province (2021 TB incidence in Cajamarca: 13.3 cases / 100,000 people) it is likely that undernotification in SIGTB in Cajamarca is not representative of higher-incidence areas such as Lima province, where resources and diagnostic capacity are concentrated.²⁴

In addition to the challenges in estimating TB care cascade steps, a challenge in our current work aiming to construct pre- and during COVID-19 TB cascades was appropriately defining the COVID-19 cohorts. Given that the care cascade approach attempts to follow a cohort throughout stages in care, a standard cut-off to define the periods of TB care (pre-, partially during and fully during COVID-19) was required (i.e., diagnosis 6 and 18 months prior to the start of the pandemic for the pre-COVID-19 cohort, based on standard DS-TB and DR-TB treatment times, respectively). As treatment lengths may vary beyond the standard treatment time, this categorization is imperfect, however, the definition used is expected to be conservative (as an individual classified as part of the pre-COVID-19 cohort that had a longer than standard treatment regimen would have had some disrupted care). Observed effects are therefore a warning to TB programs that the impact of COVID-19 has likely been even more disruptive. Furthermore, in Aim 2 (identifying predictors of cascade completion among a sample of people with TB in SJL), we use a more precise definition of the COVID-19 period cohorts, adapted to each individual's treatment length.

The above definition of COVID-19 cohorts also means that, by definition, patients in the during-COVID-19 cohorts were more likely to still be on treatment than those in the pre-COVID-19 cohort, and as a result treatment outcomes were unavailable at the time of analysis for a higher proportion of the during COVID-19 cohorts, making findings regarding the proportions in each cohort reaching the final step in the cascade difficult to interpret. Although our findings relating to earlier steps in the cascade are still informative for the TB program, further analyses with updated outcome data, when they are available, would strengthen conclusions.

A further limitation for Aim 1 is the generalizability of the cascade. We chose to estimate a provincial cascade for Lima province, rather than a national cascade for Peru, given that health systems capacity in Peru is highly concentrated in urban areas,³ and TB diagnostic capacity, specifically, is highly concentrated in the capital region of Lima province.²⁴ Therefore, it is likely that case detection and diagnostic algorithms in Lima province may not be representative of processes in the rest of the country, especially in more remote regions. As a result, certain

parameters that informed the cascade estimates, such as test sensitivity values from the literature (which were based on studies among people in Lima), or the proportion of people receiving each TB test (which was based on our sample of people in SJL district, Lima) would not be reliably extrapolated to national estimates for a Peru-wide cascade.

For Aim 2, one limitation of our findings is that data could only be collected from 75.8% of the clinics in SJL district. This may have introduced selection bias, if, for example, clinics at which staff were not available to allow data collection by the study nurse may also have been dealing with higher patient volumes or staff shortages, in turn possibly resulting in patients experiencing less favourable treatment outcomes. However, we found the included and not included clinics to be comparable on key characteristics, reducing potential for this bias. A further limitation, however, is the fact that clinic-level variables, such as whether DOT administration was altered during COVID-19, did not allow investigation of whether DOT changes at the individual-level were associated with the likelihood of cascade completion.

Moreover, the proxy for socioeconomic status used in the main analysis (based on type of housing and the availability of basic services in the home) is insufficiently granular. Although a sensitivity analysis was conducted using an alternative proxy for socioeconomic status (average neighbourhood-level income), this is also limited given that it may not adequately represent individual-level differences in income. Notably, although receiving TB care pre- vs. during COVID-19 was a significant predictor of cascade completion in the main analysis, this was no longer the case in the sensitivity analysis replacing the socioeconomic status indicator in the main analysis with neighbourhood-level income. This suggests that differences in socioeconomic status may explain some of the association between COVID-19-related disruptions to TB services and treatment outcomes, although the fact that both indicators of socioeconomic status (in the main analysis and sensitivity analysis) are imperfect proxies limits the ability to draw conclusions regarding its association with TB outcomes, as well as the potential role of higher socioeconomic status in shielding against the detrimental effects of COVID-19 disruptions on TB outcomes.

An additional limitation was the lack of outcome data on those transferred or still on treatment. This was particularly high among the DR-TB group receiving TB care entirely during COVID-19, given longer treatment times for DR-TB, and more recent diagnosis in the during-COVID cohort (by definition). Comparison of baseline characteristics among those with treatment outcomes available vs. unavailable in the group receiving TB entirely during COVID-19 however showed comparability on a variety of characteristics (sex, age, HIV status, previous TB diagnosis, extrapulmonary TB, adherence, etc., except for on diabetes prevalence, which was higher in those without available treatment outcome data). We therefore do not expect the outcomes of right-censored individuals to differ significantly from those with available outcome data.

Further, although our definition of those receiving TB care pre, partially during and fully during COVID-19 is more precise than in the previous aim (as it is adapted to each individual's expected treatment length), this categorization remains imperfect given that it does not capture variation in the extent of disruptions in specific periods over the course of the pandemic.

Conclusively, keeping in mind their limitations, our findings suggest that, in addition to ensuring that people presenting for TB testing are tested and diagnosed in a timely manner, increased active case finding efforts to close the gap in case detection left by the COVID-19 pandemic may be an effective strategy for TB programs to recover from COVID-19-related setbacks. Strategies for intervening upon losses at later stages in the cascade (such as between treatment initiation and completion) however are less clear. For example, given that Aim 2 findings suggest that patients receiving TB care during COVID-19 were less likely to complete the care cascade, but that factors such as changes in DOT administration during COVID-19 were not significantly associated with cascade completion (1.99, 95%CI: 0.98-4.03), the specific – and heterogeneous – mechanisms by which the pandemic has impacted TB outcomes require further elucidation.

4.7 Contributors:

Study conceptualisation: CUG, MP, LF. Data curation: NUS, GCC, LF. Data analysis/visualisation: LF, SH. Study supervision: CUG, MP. Writing of original draft: LF. Review and editing: LF, GCC, LVC, JRV, HHC, MCR, SH, RS, MP, CUG. Access and verification of all data reported in the study: LF. All authors agreed with the decision to submit for publication.

4.8 Conflicts of Interest:

MP serves as an advisor to several non-profit organizations, including Bill & Melinda Gates Foundation, WHO, Stop TB Partnership and FIND. He has no financial or industry conflicts. CUG has received research support from the International Development Research Centre (Canada) and the Canadian Institutes of Health Research, the National Institutes of Health, FIND, and Abbott for projects unrelated to this work. CUG has also received honoraria from Molbio and Abbott for presentations unrelated to this work. The other authors declared no conflicts of interest.

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4.12 Supplement:

Supplement 1: DS- and DR-TB care cascades for Lima province, Peru, prior to and during the COVID-19 pandemic

Figure S1. The province of Lima (red), within the department of Lima (dark grey), Peru.



Table S1. COVID-19 cohort definitions for constructing the DS- and DR-TB care cascades for people receiving TB care prior to, partially during, and fully during the COVID-19 pandemic

Cascade:	TB care pre-COVID-19	TB care partially during COVID-19	TB care fully during COVID-19
DS-TB (a)	Diagnosed 1 Jan 2018 - 15 Sep 2019 (≥ 6 months prior to start of COVID-19 restrictions)	Diagnosed 16 Sep 2019 - 15 Mar 2020	Diagnosed 16 Mar 2020 - 16 Mar 2021 (c)
DR-TB (b)	Diagnosed 1 Jan 2018 - 15 Sep 2018 (≥ 18 months prior to start of COVID-19 restrictions)	Diagnosed 16 Sep 2018 - 15 Mar 2020	Diagnosed 16 Mar 2020 - 1 Aug 2020 (d)

- (a) Based on standard DS-TB treatment length (6 months) according to Peruvian NTP guidelines.²²
- (b) Based on standard DR-TB treatment length (18 months) according to Peruvian NTP guidelines.²²
- (c) To represent disruptions within the first year of the COVID-19 pandemic.
- (d) Earlier cut-off used in the DR-TB cohort to accommodate longer treatment time for DR-TB.

Calculations for the estimation of the DS-TB and DR-TB cascades in Lima province, Peru, prior to and during the COVID-19 pandemic:

For brevity, parameters required to reproduce estimates and results at end of main calculation sections are provided (rather than line-by-line results). Although estimates in analysis were unrounded until final step, results shown here at each calculation stage are rounded to the nearest one person (for cascade step estimates) or to three decimal places (for proportions).

DS-TB cascade:

COVID-19 period cohorts for DS-TB cascade

TB care pre-COVID-19: those diagnosed 1 Jan 2018 to 15 Sep 2019

TB care partially during COVID-19: those diagnosed 16 Sep 2019 to 15 Mar 2020

TB care fully during COVID-19: those diagnosed 16 Mar 2020 to 16 Mar 2021

Step 1: the estimated burden of DS-TB in Lima province

WHO estimates of TB burden (all forms of TB) for Peru,²⁸ apportioned to pre-covid, partially during COVID-19 and fully during COVID-19 periods (as defined above). According to established methods for TB care cascade construction,¹² 50% of the undetected cases from the prior year are usually added to step 1, in addition to the burden in the year in question. As the pre- and during COVID-19 cohorts span differing time periods, the prior burden is considered to be the burden in the period directly preceding and of the same length as the one in question.

WHO burden estimates ('e') for Peru (all forms of TB), by year:

e2016 = 37000

e2017 = 37000

e2018 = 38000

e2019 = 39000

e2020 = 39000

e2021 = 44000

Lower (lci) bounds of uncertainty intervals for WHO burden estimates:

lci2016 = 29000

lci2017 = 29000

lci2018 = 29000

lci2019 = 30000

lci2020 = 30000

lci2021 = 34000

upper (uci) bounds of uncertainty intervals for WHO burden estimates:

uci2016 = 47000

uci2017 = 47000

uci2018 = 48000

uci2019 = 49000

uci2020 = 49000

uci2021 = 54000

WHO burden estimates apportioned to pre-COVID ('pre'), partially during COVID ('partial') and fully during COVID ('full') cohorts:

Pre-COVID-19: 12 months of 2018 burden + 8.5 months of 2019 burden:

WHOest_alltb_pre_201819 = $e2018 + ((8.5/12) * (e2019))$

Partially during COVID-19: 3.5 months of 2019 burden + 2.5 months of 2020 burden:

WHOest_alltb_partial_201920 = $((3.5/12) * (e2019)) + ((2.5/12) * (e2020))$

Fully during COVID-19: 9.5 months of 2020 burden + 2.5 months of 2021 burden:

$$\text{WHOest\_alltb\_full\_202021} = ((9.5/12)*(e2020)) + ((2.5/12)*(e2021))$$

Uncertainty intervals for the above estimates, based on uncertainty in WHO TB burden estimates for Peru:

Upper bounds:

$$\text{WHOest\_alltb\_pre\_201819uci} = \text{uci2018} + ((8.5/12)*(\text{uci2019}))$$

$$\text{WHOest\_alltb\_partial\_201920uci} = ((3.5/12)*(\text{uci2019})) + ((2.5/12)*(\text{uci2020}))$$

$$\text{WHOest\_alltb\_full\_202021uci} = ((9.5/12)*(\text{uci2020})) + ((2.5/12)*(\text{uci2021}))$$

Lower bounds:

$$\text{WHOest\_alltb\_pre\_201819lci} = \text{lci2018} + ((8.5/12)*(\text{lci2019}))$$

$$\text{WHOest\_alltb\_partial\_201920lci} = ((3.5/12)*(\text{lci2019})) + ((2.5/12)*(\text{lci2020}))$$

$$\text{WHOest\_alltb\_full\_202021lci} = ((9.5/12)*(\text{lci2020})) + ((2.5/12)*(\text{lci2021}))$$

Plus 50% of undetected cases from prior months (each prior period is the period directly preceding the cohort period, proportional to the number of months in each cohort):

Prior burden for Pre-COVID cohort: the 20.5 months preceding 1 Jan 2018: 8.5 months of 2016 burden + 12 months of 2017 burden

$$\text{prior\_burden\_pre} = ((8.5/12)*e2016) + e2017$$

Prior burden for partially-during COVID cohort: the 6 months preceding 16 Sep 2019: 6 months of 2019 burden

$$\text{prior\_burden\_partial} = (6/12)*e2019$$

Prior burden for fully-during COVID cohort: the 12 months preceding 16 Mar 2020: 9.5 months of 2019 burden + 2.5 months of 2020 burden

$$\text{prior\_burden\_full} = ((9.5/12)*e2019) + ((2.5/12)*e2020)$$

Uncertainty intervals for prior burden estimates, based on uncertainty intervals in WHO burden estimates:

$\text{prior\_burden\_pre\_uci} = ((8.5/12) * \text{uci2016}) + \text{uci2017}$

$\text{prior\_burden\_partial\_uci} = (6/12) * \text{uci2019}$

$\text{prior\_burden\_full\_uci} = ((9.5/12) * \text{uci2019}) + ((2.5/12) * \text{uci2020})$

$\text{prior\_burden\_pre\_lci} = ((8.5/12) * \text{lci2016}) + \text{lci2017}$

$\text{prior\_burden\_partial\_lci} = (6/12) * \text{lci2019}$

$\text{prior\_burden\_full\_lci} = ((9.5/12) * \text{lci2019}) + ((2.5/12) * \text{lci2020})$

Undetected cases in prior periods based on prior burden minus detected cases:

Detected cases, by year (based on notifications reported in the WHO global TB database):

$\text{det2016} = 29733$

$\text{det2017} = 29840$

$\text{det2018} = 31421$

$\text{det2019} = 31764$

$\text{det2020} = 23755$

Cases detected in the prior period

$\text{prior\_detected\_pre} = ((8.5/12) * \text{det2016}) + \text{det2017}$

$\text{prior\_detected\_partial} = (6/12) * \text{det2019}$

$\text{prior\_detected\_full} = ((9.5/12) * \text{det2019}) + ((2.5/12) * \text{det2020})$

50% of undetected cases in prior period (burden in prior period minus cases detected in prior period):

$\text{prior\_undetected\_pre\_50} = (\text{prior\_burden\_pre} - \text{prior\_detected\_pre}) * 0.5$

$\text{prior\_undetected\_partial\_50} = (\text{prior\_burden\_partial} - \text{prior\_detected\_partial}) * 0.5$

$\text{prior\_undetected\_full\_50} = (\text{prior\_burden\_full} - \text{prior\_detected\_full}) * 0.5$

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

$\text{prior\_undetected\_pre\_50\_uci} = (\text{prior\_burden\_pre\_uci} - \text{prior\_detected\_pre}) * 0.5$

$\text{prior\_undetected\_partial\_50\_uci} = (\text{prior\_burden\_partial\_uci} - \text{prior\_detected\_partial}) * 0.5$

$\text{prior\_undetected\_full\_50\_uci} = (\text{prior\_burden\_full\_uci} - \text{prior\_detected\_full}) * 0.5$

$\text{prior\_undetected\_pre\_50\_lci} = (\text{prior\_burden\_pre\_lci} - \text{prior\_detected\_pre}) * 0.5$

$\text{prior\_undetected\_partial\_50\_lci} = (\text{prior\_burden\_partial\_lci} - \text{prior\_detected\_partial}) * 0.5$

$\text{prior\_undetected\_full\_50\_lci} = (\text{prior\_burden\_full\_lci} - \text{prior\_detected\_full}) * 0.5$

Final estimated burden in the pre-, partially during and during COVID cohorts (burden in period plus 50% of undetected cases in prior period):

$\text{WHOest\_alltb\_pre} = \text{WHOest\_alltb\_pre\_201819} + \text{prior\_undetected\_pre\_50} = \mathbf{71779}$

$\text{WHOest\_alltb\_partial} = \text{WHOest\_alltb\_partial\_201920} + \text{prior\_undetected\_partial\_50} = \mathbf{21309}$

$\text{WHOest\_alltb\_full} = \text{WHOest\_alltb\_full\_202021} + \text{prior\_undetected\_full\_50} = \mathbf{44494}$

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

$\text{WHOest\_alltb\_pre\_uci} = \text{WHOest\_alltb\_pre\_201819uci} + \text{prior\_undetected\_pre\_50\_uci} = \mathbf{97404}$

$\text{WHOest\_alltb\_partial\_uci} = \text{WHOest\_alltb\_partial\_201920uci} + \text{prior\_undetected\_partial\_50\_uci} = \mathbf{28809}$

$\text{WHOest\_alltb\_full\_uci} = \text{WHOest\_alltb\_full\_202021uci} + \text{prior\_undetected\_full\_50\_uci} = \mathbf{59494}$

$\text{WHOest\_alltb\_pre\_lci} = \text{WHOest\_alltb\_pre\_201819lci} + \text{prior\_undetected\_pre\_50\_lci} = \mathbf{49570}$

$\text{WHOest\_alltb\_partial\_lci} = \text{WHOest\_alltb\_partial\_201920lci} + \text{prior\_undetected\_partial\_50\_lci} = \mathbf{14559}$

$\text{WHOest\_alltb\_full\_lci} = \text{WHOest\_alltb\_full\_202021lci} + \text{prior\_undetected\_full\_50\_lci} = \mathbf{30786}$

Apportioning the burden of all forms of TB to DS-TB:

The burden estimate for all forms of TB apportioned to DS-TB based on the proportion of DR- vs. DS-TB case notifications in the Peruvian NTP database (SIGTB) in the same time periods (pre-COVID-19, partially during COVID-19, fully during COVID-19):

Where dstb_notif_pre = Pre-COVID-19 cohort DS-TB case notifications in Peru, drtb_notif_pre = Pre-COVID-19 cohort DR-TB case notifications in Peru, etc.:

DS-TB notifications

dstb_notif_pre = 53946

dstb_notif_partial = 15952

dstb_notif_during = 21472

DR-TB notifications

drtb_notif_pre = 2505

drtb_notif_partial = 764

drtb_notif_during = 1104

Estimated DS-TB burden, pre-COVID-19 period:

WHOest_dstb_pre = WHOest_alltb_pre * (dstb_notif_pre/(dstb_notif_pre+drtb_notif_pre)) =
68594

Estimated DS-TB burden, partially during COVID-19 period:

WHOest_dstb_partial = WHOest_alltb_partial *
(dstb_notif_partial/(dstb_notif_partial+drtb_notif_partial)) = **20335**

Estimated DS-TB burden, fully during COVID-19 period:

WHOest_dstb_during = WHOest_alltb_full *

(dstb_notif_during/(dstb_notif_during+drtb_notif_during)) = **42318**

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

WHOest_dstb_pre_lci = WHOest_alltb_pre_lci *

(dstb_notif_pre/(dstb_notif_pre+drtb_notif_pre)) = **47371**

WHOest_dstb_partial_lci = WHOest_alltb_partial_lci *

(dstb_notif_partial/(dstb_notif_partial+drtb_notif_partial)) = **13894**

WHOest_dstb_during_lci = WHOest_alltb_full_lci *

(dstb_notif_during/(dstb_notif_during+drtb_notif_during)) = **29280**

WHOest_dstb_pre_uci = WHOest_alltb_pre_uci *

(dstb_notif_pre/(dstb_notif_pre+drtb_notif_pre)) = **93081**

WHOest_dstb_partial_uci = WHOest_alltb_partial_uci *

(dstb_notif_partial/(dstb_notif_partial+drtb_notif_partial)) = **27492**

WHOest_dstb_during_uci = WHOest_alltb_full_uci *

(dstb_notif_during/(dstb_notif_during+drtb_notif_during)) = **56585**

Apportioning the national estimated DS-TB burden to Lima province

For cascade step 1 (the estimated DS-TB burden in Lima province, for each COVID-19 period), apportion WHO DS-TB burden estimates to Lima province for each COVID-19 period, based on the proportion of national DS-TB notifications (dstb_notif, see above) that are from Lima (dstb_notif_lima):

DS-TB notifications in Lima province:

dstb_notif_lima_pre = 26317

dstb_notif_lima_partial = 7720

dstb_notif_lima_during = 10314

DS-TB burden apportioned to Lima province:

Step 1, pre-COVID-19 period:

$$\text{step1\_ds\_pre} = \text{WHOest\_dstb\_pre} * (\text{dstb\_notif\_lima\_pre}/\text{dstb\_notif\_pre}) = \mathbf{33463}$$

Step 1, partially during COVID-19 period:

$$\text{step1\_ds\_partial} = \text{WHOest\_dstb\_partial} * (\text{dstb\_notif\_lima\_partial}/\text{dstb\_notif\_partial}) = \mathbf{9841}$$

Step 1, fully during COVID-19 period:

$$\text{step1\_ds\_during} = \text{WHOest\_dstb\_during} * (\text{dstb\_notif\_lima\_during}/\text{dstb\_notif\_during}) = \mathbf{20327}$$

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

$$\text{step1\_ds\_pre\_uci} = \text{WHOest\_dstb\_pre\_uci} * (\text{dstb\_notif\_lima\_pre}/\text{dstb\_notif\_pre}) = \mathbf{45409}$$

$$\text{step1\_ds\_partial\_uci} = \text{WHOest\_dstb\_partial\_uci} * (\text{dstb\_notif\_lima\_partial}/\text{dstb\_notif\_partial}) \\ = \mathbf{13305}$$

$$\text{step1\_ds\_during\_uci} = \text{WHOest\_dstb\_during\_uci} * (\text{dstb\_notif\_lima\_during}/\text{dstb\_notif\_during}) \\ = \mathbf{27180}$$

$$\text{step1\_ds\_pre\_lci} = \text{WHOest\_dstb\_pre\_lci} * (\text{dstb\_notif\_lima\_pre}/\text{dstb\_notif\_pre}) = \mathbf{23109}$$

$$\text{step1\_ds\_partial\_lci} = \text{WHOest\_dstb\_partial\_lci} * (\text{dstb\_notif\_lima\_partial}/\text{dstb\_notif\_partial}) = \\ \mathbf{6724}$$

$$\text{step1\_ds\_during\_lci} = \text{WHOest\_dstb\_during\_lci} * (\text{dstb\_notif\_lima\_during}/\text{dstb\_notif\_during}) = \\ \mathbf{14065}$$

Step 4: the proportion of people with DS-TB initiating TB treatment

(Note, step 4 is shown before steps 2 and 3, as steps 2 and 3 are back-calculated from their subsequent steps, see below).

As all patients reported in SIGTB in the study period had a TB treatment start date recorded, step 4 is equal to the number of DS-TB patients in SIGTB in each COVID-19 period:

step4_ds_pre = dstb_notif_lima_pre = **26317**
step4_ds_partial = dstb_notif_lima_partial = **7720**
step4_ds_during = dstb_notif_lima_during = **10314**

Step 3: the proportion of people with DS-TB diagnosed (back-calculated from step 4)

This step is back-calculated from step 4, taking into account pre-treatment loss to follow-up (those who are diagnosed with TB but do not initiate treatment). The proportion of cases diagnosed that initiated treatment is based on treatment initiation data from the Peruvian NTP and aggregate annual diagnosis data from the Peruvian National Centre for the Epidemiology, Prevention and Control of Diseases.²⁴ Given that the pre-, partial and during COVID-19 cohorts span different years, weighted averages of the annual value for the proportion of those diagnosed initiating treatment were used, according to the contribution of specific years to each cohort.

Proportion of those diagnosed initiating treatment, by year.

propinit_2018 = 0.991
propinit_2019 = 0.959
propinit_2020 = 0.989
propinit_2021 = 0.981

Weighted average of treatment initiation proportion, based on contribution of years to each cohort (see cohort definitions and dates on first page):

propinit_ds_pre = (propinit_2018+((8.5/12)*propinit_2019))/(1+(8.5/12))
propinit_ds_partial = (((3.5/12)*propinit_2019)+((2.5/12)*propinit_2020))/((2.5/12)+(3.5/12))
propinit_ds_during = (((9.5/12)*propinit_2020)+((2.5/12)*propinit_2021))/((9.5/12)+(2.5/12))

Step 3, back-calculated from Step 4 based on the proportion of those diagnosed initiating treatment:

$\text{step3\_ds\_pre} = \text{step4\_ds\_pre} / \text{propinit\_ds\_pre} = \mathbf{26916}$

$\text{step3\_ds\_partial} = \text{step4\_ds\_partial} / \text{propinit\_ds\_partial} = \mathbf{7946}$

$\text{step3\_ds\_during} = \text{step4\_ds\_during} / \text{propinit\_ds\_during} = \mathbf{10446}$

Step 2: the proportion of people with DS-TB accessing TB testing (back-calculated from Step 3)

Given the imperfect sensitivity of tests in the diagnostic algorithm for TB, this step is based on the proportion of people diagnosed (step 3), and the proportion of people who truly had TB that were missed (false negatives) due to imperfect test sensitivity. The proportion of people missed is calculated based on the proportion of people receiving each test, and the sensitivity of these tests under local conditions, correcting for those who were treated empirically (pulmonary TB patients initiated on treatment without microbiological confirmation, and extrapulmonary TB patients initiated on treatment without histopathological confirmation).

The proportion of people receiving each test is based on a sample of DS-TB patients (n=1,071) receiving TB care in San Juan de Lurigancho (SJL) district of Lima province (see aim 2 in main paper), of which 2.5% received MODS, 14.8% received GeneXpert (but not MODS), and 82.6% received sputum smear microscopy only (neither MODS nor GeneXpert) as the initial diagnostic test.

The sensitivity of tests is based on values available in the literature. A multicentre study (n=6,648) including n=1,185 TB patients in Lima, Peru found the sensitivity of GeneXpert specific to subgroup of patients from Lima to be 96.6% (95%CI: 92.8-98.4%).²⁹ The sensitivity of sputum smear microscopy in the study (whilst this estimate included patients in Lima, it is not specific to Lima, as Lima-specific values for this test were not provided) was 68.6% (95%CI: 63.5-73.3%). A study evaluating MODS in Lima, Peru (n=1,980) found its sensitivity in patients suspected of TB to be 97.3% (95%CI: 96.8-97.9).²³

Proportion receiving each test:

prop_mods_ds = 0.025

prop_genexpert_ds = 0.148

prop_smear_ds = 0.826

Sensitivity of tests:

Sensitivity and 95% confidence interval (95%CI) of MODS in patients suspected of TB in Lima, Peru²³:

sens_mods = 0.973

lci_mods = 0.968

uci_mods = 0.979

Sensitivity and 95%CI of GeneXpert in patients in Lima, Peru (based on Lima subset of the source study²⁹ only).

sens_genexpert = 0.966

lci_xpert = 0.928

uci_xpert = 0.984

Sensitivity and 95%CI of smear microscopy in a sample including patients from Lima, Peru²⁹ (Lima-only estimates not available for this test):

sens_smear = 0.686

lci_smear = 0.635

uci_smear = 0.733

Number of patients diagnosed by each method (based on Step 3 and test sensitivities), in each cohort:

dx_mods_pre = prop_mods_ds*step3_ds_pre

dx_genexpert_pre = prop_genexpert_ds*step3_ds_pre

dx_smear_pre = prop_smear_ds*step3_ds_pre

$dx\_mods\_partial = prop\_mods\_ds * step3\_ds\_partial$
 $dx\_genexpert\_partial = prop\_genexpert\_ds * step3\_ds\_partial$
 $dx\_smear\_partial = prop\_smear\_ds * step3\_ds\_partial$
 $dx\_mods\_dur = prop\_mods\_ds * step3\_ds\_during$
 $dx\_genexpert\_dur = prop\_genexpert\_ds * step3\_ds\_during$
 $dx\_smear\_dur = prop\_smear\_ds * step3\_ds\_during$

Number of patients (who truly had TB) that were missed by each test

$missed\_mods\_pre = dx\_mods\_pre / sens\_mods - dx\_mods\_pre$
 $missed\_genexpert\_pre = dx\_genexpert\_pre / sens\_genexpert - dx\_genexpert\_pre$
 $missed\_smear\_pre = dx\_smear\_pre / sens\_smear - dx\_smear\_pre$
 $missed\_mods\_partial = dx\_mods\_partial / sens\_mods - dx\_mods\_partial$
 $missed\_genexpert\_partial = dx\_genexpert\_partial / sens\_genexpert - dx\_genexpert\_partial$
 $missed\_smear\_partial = dx\_smear\_partial / sens\_smear - dx\_smear\_partial$
 $missed\_mods\_dur = dx\_mods\_dur / sens\_mods - dx\_mods\_dur$
 $missed\_genexpert\_dur = dx\_genexpert\_dur / sens\_genexpert - dx\_genexpert\_dur$
 $missed\_smear\_dur = dx\_smear\_dur / sens\_smear - dx\_smear\_dur$

95% CIs for the number of patients missed, based on 95% CIs for test sensitivities:

Lower bound:

$missed\_mods\_pre\_lci = dx\_mods\_pre / lci\_mods - dx\_mods\_pre$
 $missed\_genexpert\_pre\_lci = dx\_genexpert\_pre / lci\_xpert - dx\_genexpert\_pre$
 $missed\_smear\_pre\_lci = dx\_smear\_pre / lci\_smear - dx\_smear\_pre$
 $missed\_mods\_partial\_lci = dx\_mods\_partial / lci\_mods - dx\_mods\_partial$
 $missed\_genexpert\_partial\_lci = dx\_genexpert\_partial / lci\_xpert - dx\_genexpert\_partial$
 $missed\_smear\_partial\_lci = dx\_smear\_partial / lci\_smear - dx\_smear\_partial$
 $missed\_mods\_dur\_lci = dx\_mods\_dur / lci\_mods - dx\_mods\_dur$
 $missed\_genexpert\_dur\_lci = dx\_genexpert\_dur / lci\_xpert - dx\_genexpert\_dur$
 $missed\_smear\_dur\_lci = dx\_smear\_dur / lci\_smear - dx\_smear\_dur$

Upper bound:

$\text{missed\_mods\_pre\_uci} = \text{dx\_mods\_pre} / \text{uci\_mods} - \text{dx\_mods\_pre}$

$\text{missed\_genexpert\_pre\_uci} = \text{dx\_genexpert\_pre} / \text{uci\_xpert} - \text{dx\_genexpert\_pre}$

$\text{missed\_smear\_pre\_uci} = \text{dx\_smear\_pre} / \text{uci\_smear} - \text{dx\_smear\_pre}$

$\text{missed\_mods\_partial\_uci} = \text{dx\_mods\_partial} / \text{uci\_mods} - \text{dx\_mods\_partial}$

$\text{missed\_genexpert\_partial\_uci} = \text{dx\_genexpert\_partial} / \text{uci\_xpert} - \text{dx\_genexpert\_partial}$

$\text{missed\_smear\_partial\_uci} = \text{dx\_smear\_partial} / \text{uci\_smear} - \text{dx\_smear\_partial}$

$\text{missed\_mods\_dur\_uci} = \text{dx\_mods\_dur} / \text{uci\_mods} - \text{dx\_mods\_dur}$

$\text{missed\_genexpert\_dur\_uci} = \text{dx\_genexpert\_dur} / \text{uci\_xpert} - \text{dx\_genexpert\_dur}$

$\text{missed\_smear\_dur\_uci} = \text{dx\_smear\_dur} / \text{uci\_smear} - \text{dx\_smear\_dur}$

Accounting for patients empirically diagnosed:

Pulmonary TB (PTB) cases who were initiated on treatment without microbiological confirmation (smear negative / not done and culture negative / not done), based on SIGTB data, in each cohort:

$\text{empiric\_ptb\_ds\_pre} = 4289$

$\text{empiric\_ptb\_ds\_partial} = 1339$

$\text{empiric\_ptb\_ds\_during} = 1837$

Extrapulmonary TB (EPTB) cases who were initiated on treatment without histopathological confirmation (negative or not done):

$\text{empiric\_eptb\_ds\_pre} = 1928$

$\text{empiric\_eptb\_ds\_partial} = 560$

$\text{empiric\_eptb\_ds\_during} = 653$

Final step 2 estimates (back-calculated from those diagnosed (step 3), adding those missed, correcting for those empirically treated):

$$\begin{aligned}\text{step2\_ds\_pre} &= \text{step3\_ds\_pre} + \text{missed\_genexpert\_pre} + \text{missed\_smear\_pre} + \\ &\text{missed\_mods\_pre} - (\text{empiric\_ptb\_ds\_pre} + \text{empiric\_eptb\_ds\_pre}) = \mathbf{31039} \\ \text{step2\_ds\_partial} &= \text{step3\_ds\_partial} + \text{missed\_genexpert\_partial} + \text{missed\_smear\_partial} + \\ &\text{missed\_mods\_partial} - (\text{empiric\_ptb\_ds\_partial} + \text{empiric\_eptb\_ds\_partial}) = \mathbf{9100} \\ \text{step2\_ds\_dur} &= \text{step3\_ds\_during} + \text{missed\_genexpert\_dur} + \text{missed\_smear\_dur} + \\ &\text{missed\_mods\_dur} - (\text{empiric\_ptb\_ds\_during} + \text{empiric\_eptb\_ds\_during}) = \mathbf{11969}\end{aligned}$$

95%CIs for final step 2 estimates (based on 95%CIs for the sensitivity of tests):

Lower bound:

$$\begin{aligned}\text{step2\_ds\_pre\_lci} &= \text{step3\_ds\_pre} + \text{missed\_genexpert\_pre\_uci} + \text{missed\_smear\_pre\_uci} + \\ &\text{missed\_mods\_pre\_uci} - (\text{empiric\_ptb\_ds\_pre} + \text{empiric\_eptb\_ds\_pre}) = \mathbf{28880} \\ \text{step2\_ds\_partial\_lci} &= \text{step3\_ds\_partial} + \text{missed\_genexpert\_partial\_uci} + \\ &\text{missed\_smear\_partial\_uci} + \text{missed\_mods\_partial\_uci} - (\text{empiric\_ptb\_ds\_partial} + \\ &\text{empiric\_eptb\_ds\_partial}) = \mathbf{8463} \\ \text{step2\_ds\_dur\_lci} &= \text{step3\_ds\_during} + \text{missed\_genexpert\_dur\_uci} + \text{missed\_smear\_dur\_uci} + \\ &\text{missed\_mods\_dur\_uci} - (\text{empiric\_ptb\_ds\_during} + \text{empiric\_eptb\_ds\_during}) = \mathbf{11131}\end{aligned}$$

Upper bound:

$$\begin{aligned}\text{step2\_ds\_pre\_uci} &= \text{step3\_ds\_pre} + \text{missed\_genexpert\_pre\_lci} + \text{missed\_smear\_pre\_lci} + \\ &\text{missed\_mods\_pre\_lci} - (\text{empiric\_ptb\_ds\_pre} + \text{empiric\_eptb\_ds\_pre}) = \mathbf{33815} \\ \text{step2\_ds\_partial\_uci} &= \text{step3\_ds\_partial} + \text{missed\_genexpert\_partial\_lci} + \\ &\text{missed\_smear\_partial\_lci} + \text{missed\_mods\_partial\_lci} - (\text{empiric\_ptb\_ds\_partial} + \\ &\text{empiric\_eptb\_ds\_partial}) = \mathbf{9919} \\ \text{step2\_ds\_dur\_uci} &= \text{step3\_ds\_during} + \text{missed\_genexpert\_dur\_lci} + \text{missed\_smear\_dur\_lci} + \\ &\text{missed\_mods\_dur\_lci} - (\text{empiric\_ptb\_ds\_during} + \text{empiric\_eptb\_ds\_during}) = \mathbf{13046}\end{aligned}$$

Step 5: the proportion of people with DS-TB successfully completing treatment

DS-TB patients with a successful treatment outcome (cured or treatment complete) recorded in SIGTB, by cohort:

step5_ds_pre = **20166**
step5_ds_partial = **5936**
step5_ds_during = **7343**

Calculations for final DS-TB cascade plot

Express steps as percentage of burden (step 1), so that differing cohort sizes (pre-, partially during and during COVID-19) can be more easily compared:

Pre-COVID-19 cascade:

step1_ds_pre_percent = 100
step2_ds_pre_percent = step2_ds_pre/step1_ds_pre*100
step3_ds_pre_percent = step3_ds_pre/step1_ds_pre*100
step4_ds_pre_percent = step4_ds_pre/step1_ds_pre*100
step5_ds_pre_percent = step5_ds_pre/step1_ds_pre*100

Error bars:

step1_ds_pre_percent_lci = step1_ds_pre_lci/step1_ds_pre*100
step2_ds_pre_percent_lci = step2_ds_pre_lci/step1_ds_pre*100
step1_ds_pre_percent_uci = step1_ds_pre_uci/step1_ds_pre*100
step2_ds_pre_percent_uci = step2_ds_pre_uci/step1_ds_pre*100

Partially during COVID-19 cascade:

step1_ds_partial_percent = 100
step2_ds_partial_percent = step2_ds_partial/step1_ds_partial*100

$\text{step3\_ds\_partial\_percent} = \text{step3\_ds\_partial} / \text{step1\_ds\_partial} * 100$

$\text{step4\_ds\_partial\_percent} = \text{step4\_ds\_partial} / \text{step1\_ds\_partial} * 100$

$\text{step5\_ds\_partial\_percent} = \text{step5\_ds\_partial} / \text{step1\_ds\_partial} * 100$

Error bars

$\text{step1\_ds\_partial\_percent\_lci} = \text{step1\_ds\_partial\_lci} / \text{step1\_ds\_partial} * 100$

$\text{step2\_ds\_partial\_percent\_lci} = \text{step2\_ds\_partial\_lci} / \text{step1\_ds\_partial} * 100$

$\text{step1\_ds\_partial\_percent\_uci} = \text{step1\_ds\_partial\_uci} / \text{step1\_ds\_partial} * 100$

$\text{step2\_ds\_partial\_percent\_uci} = \text{step2\_ds\_partial\_uci} / \text{step1\_ds\_partial} * 100$

Fully during COVID-19 cascade:

$\text{step1\_ds\_during\_percent} = 100$

$\text{step2\_ds\_during\_percent} = \text{step2\_ds\_dur} / \text{step1\_ds\_during} * 100$

$\text{step3\_ds\_during\_percent} = \text{step3\_ds\_during} / \text{step1\_ds\_during} * 100$

$\text{step4\_ds\_during\_percent} = \text{step4\_ds\_during} / \text{step1\_ds\_during} * 100$

$\text{step5\_ds\_during\_percent} = \text{step5\_ds\_during} / \text{step1\_ds\_during} * 100$

Error bars

$\text{step1\_ds\_during\_percent\_lci} = \text{step1\_ds\_during\_lci} / \text{step1\_ds\_during} * 100$

$\text{step2\_ds\_during\_percent\_lci} = \text{step2\_ds\_dur\_lci} / \text{step1\_ds\_during} * 100$

$\text{step1\_ds\_during\_percent\_uci} = \text{step1\_ds\_during\_uci} / \text{step1\_ds\_during} * 100$

$\text{step2\_ds\_during\_percent\_uci} = \text{step2\_ds\_dur\_uci} / \text{step1\_ds\_during} * 100$

DR-TB Cascade:

COVID-19 period cohorts for DR-TB cascade

TB care pre-COVID-19: those diagnosed 1 Jan 2018 to 15 Sep 2018

TB care partially during COVID-19: those diagnosed 16 Sep 2018 to 15 Mar 2020

TB care fully during COVID-19: those diagnosed 16 Mar 2020 to 1 Aug 2020

Step 1: the estimated burden of DR-TB in Lima province

WHO estimates of TB burden (all forms of TB)²⁸ for Peru, apportioned to pre-covid, partially during COVID-19 and fully during COVID-19 periods (as defined above, “COVID-19 period cohorts for DR-TB cascade”). According to established methods for TB care cascade construction,¹² 50% of the undetected cases from the prior year are usually added to step 1, in addition to the burden in the year in question. As the pre- and during COVID-19 cohorts span differing time periods, the prior burden is considered to be the burden in the period directly preceding and of the same length as the one in question.

WHO burden estimates (‘e’) for Peru (all forms of TB), by year:

e2016 = 37000

e2017 = 37000

e2018 = 38000

e2019 = 39000

e2020 = 39000

e2021 = 44000

Lower (lci) bounds of uncertainty intervals for WHO burden estimates:

lci2016 = 29000

lci2017 = 29000

lci2018 = 29000

lci2019 = 30000

lci2020 = 30000

lci2021 = 34000

upper (uci) bounds of uncertainty intervals for WHO burden estimates:

uci2016 = 47000

uci2017 = 47000

uci2018 = 48000

uci2019 = 49000

uci2020 = 49000

uci2021 = 54000

WHO burden estimates apportioned to pre-COVID ('pre'), partially during COVID ('partial') and fully during COVID ('full') cohorts (note DR-TB-specific cohort definitions differ from DS-TB cascade cohort definitions, see dates at start of each section).

Pre-COVID-19: 8.5 months of 2018 burden

WHOest_alltb_pre2_2018 = $(8.5/12) * e_{2018}$

Partially during COVID-19: 3.5 months of 2018 burden + 12 months of 2019 burden + 2.5 months of 2020 burden

WHOest_alltb_partial2_20181920 = $((3.5/12) * (e_{2018})) + e_{2019} + ((2.5/12) * (e_{2020}))$

Fully during COVID-19: 4.5 months of 2020 burden

WHOest_alltb_full2_2020 = $(4.5/12) * e_{2020}$

Uncertainty intervals for the above estimates, based on uncertainty in WHO TB burden estimates for Peru:

Upper bounds:

WHOest_alltb_pre_uci2_2018 = $(8.5/12) * uci_{2018}$

WHOest_alltb_partial_uci2_20181920 = $((3.5/12) * (uci_{2018})) + uci_{2019} + ((2.5/12) * (uci_{2020}))$

WHOest_alltb_full_uci2_2020 = $(4.5/12) * uci_{2020}$

Lower bounds:

WHOest_alltb_pre_lci2_2018 = $(8.5/12) * lci_{2018}$

WHOest_alltb_partial_lci2_20181920 = $((3.5/12) * (lci_{2018})) + lci_{2019} + ((2.5/12) * (lci_{2020}))$

WHOest_alltb_full_lci2_2020 = $(4.5/12) * lci_{2020}$

Plus 50% of undetected cases from prior months (each prior period is the period directly preceding the cohort period, proportional to the number of months in each cohort):

Prior burden for Pre-COVID cohort: the 8.5 months preceding 1 Jan 2018: 8.5 months of 2017 burden

$$\text{prior\_burden\_pre2} = (8.5/12)*e2017$$

Prior burden for partially-during COVID cohort: the 18 months preceding 16 Sep 2018: 9.5 months of 2017 burden + 8.5 months of 2018 burden

$$\text{prior\_burden\_partial2} = ((9.5/12)*e2017) + ((8.5/12)*e2018)$$

Prior burden for fully-during COVID cohort: the 4.5 months preceding 16 Mar 2020: 2 months of 2019 burden + 2.5 months of 2020 burden

$$\text{prior\_burden\_full2} = ((2/12)*e2019)+((2.5/12)*e2020)$$

Uncertainty intervals for prior burden estimates, based on uncertainty intervals in WHO burden estimates:

$$\text{prior\_burden\_pre\_uci2} = (8.5/12)*uci2017$$

$$\text{prior\_burden\_partial\_uci2} = ((9.5/12)*uci2017) + ((8.5/12)*uci2018)$$

$$\text{prior\_burden\_full\_uci2} = ((2/12)*uci2019)+((2.5/12)*uci2020)$$

$$\text{prior\_burden\_pre\_lci2} = (8.5/12)*lci2017$$

$$\text{prior\_burden\_partial\_lci2} = ((9.5/12)*lci2017) + ((8.5/12)*lci2018)$$

$$\text{prior\_burden\_full\_lci2} = ((2/12)*lci2019)+((2.5/12)*lci2020)$$

Undetected cases in prior periods based on prior burden minus detected cases:

Detected cases, by year (based on notifications reported in the WHO global TB database):

$$\text{det2016} = 29733$$

$$\text{det2017} = 29840$$

det2018 = 31421

det2019 = 31764

det2020 = 23755

Cases detected in the prior period

prior_detected_pre2 = (8.5/12)*det2017

prior_detected_partial2 = ((9.5/12)*det2017) + ((8.5/12)*det2018)

prior_detected_full2 = ((2/12)*det2019)+((2.5/12)*det2020)

50% of undetected cases in prior period (burden in prior period minus cases detected in prior period):

prior_undetected_pre2_50 = (prior_burden_pre2 - prior_detected_pre2)*0.5

prior_undetected_partial2_50 = (prior_burden_partial2 - prior_detected_partial2)*0.5

prior_undetected_full2_50 = (prior_burden_full2 - prior_detected_full2)*0.5

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

prior_undetected_pre2_50_uci = (prior_burden_pre_uci2 - prior_detected_pre2)*0.5

prior_undetected_partial2_50_uci = (prior_burden_partial_uci2 - prior_detected_partial2)*0.5

prior_undetected_full2_50_uci = (prior_burden_full_uci2 - prior_detected_full2)*0.5

prior_undetected_pre2_50_lci = (prior_burden_pre_lci2 - prior_detected_pre2)*0.5

prior_undetected_partial2_50_lci = (prior_burden_partial_lci2 - prior_detected_partial2)*0.5

prior_undetected_full2_50_lci = (prior_burden_full_lci2 - prior_detected_full2)*0.5

Final estimated burden in the pre-, partially during and during COVID cohorts (burden in period plus 50% of undetected cases in prior period):

WHOest_alltb_pre2 = WHOest_alltb_pre2_2018 + prior_undetected_pre2_50 = **29453**

WHOest_alltb_partial2 = WHOest_alltb_partial2_20181920 + prior_undetected_partial2_50 = **63373**

WHOest_alltb_full2 = WHOest_alltb_full2_2020 + prior_undetected_full2_50 = **16816**

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

Upper bound:

WHOest_alltb_pre_uci2 = WHOest_alltb_pre_uci2_2018 + prior_undetected_pre2_50_uci = **40078**

WHOest_alltb_partial_uci2 = WHOest_alltb_partial_uci2_20181920 +
prior_undetected_partial2_50_uci = **85873**

WHOest_alltb_full_uci2 = WHOest_alltb_full_uci2_2020 + prior_undetected_full2_50_uci = **22441**

Lower bound:

WHOest_alltb_pre_lci2 = WHOest_alltb_pre_lci2_2018 + prior_undetected_pre2_50_lci = **20244**

WHOest_alltb_partial_lci2 = WHOest_alltb_partial_lci2_20181920 +
prior_undetected_partial2_50_lci = **43518**

WHOest_alltb_full_lci2 = WHOest_alltb_full_lci2_2020 + prior_undetected_full2_50_lci = **11754**

Apportioning the burden of all forms of TB to DR-TB:

The burden estimate for all forms of TB apportioned to DR-TB based on the proportion of DR- vs. DS-TB case notifications in the Peruvian NTP database (SIGTB) in the same time periods (pre-COVID-19, partially during COVID-19, fully during COVID-19):

Where dstb_notif_pre = Pre-COVID-19 cohort DS-TB case notifications in Peru, drtb_notif_pre = Pre-COVID-19 cohort DR-TB case notifications in Peru, etc (note, cohort definitions are specific to DR-TB cascade as defined at start of DR-TB section, i.e. not the same as cohort definitions for DS-TB cascade outlined earlier).

DS-TB notifications:

dstb_notif_pre2 = 22385

dstb_notif_partial2 = 47513

dstb_notif_during2 = 6165

DR-TB notifications:

drtb_notif_pre2 = 1100

drtb_notif_partial2 = 2169

drtb_notif_during2 = 334

Estimated DR-TB burden, pre-COVID-19 period:

WHOest_drtb_pre2 = WHOest_alltb_pre2 *

$(drtb\_notif\_pre2 / (dstb\_notif\_pre2 + drtb\_notif\_pre2)) = \mathbf{1380}$

Estimated DR-TB burden, partially during COVID-19 period:

WHOest_drtb_partial2 = WHOest_alltb_partial2 *

$(drtb\_notif\_partial2 / (dstb\_notif\_partial2 + drtb\_notif\_partial2)) = \mathbf{2767}$

Estimated DR-TB burden, fully during COVID-19 period:

WHOest_drtb_during2 = WHOest_alltb_full2 *

$(drtb\_notif\_during2 / (dstb\_notif\_during2 + drtb\_notif\_during2)) = \mathbf{864}$

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

WHOest_drtb_pre_lci2 = WHOest_alltb_pre_lci2 *

$(drtb\_notif\_pre2 / (dstb\_notif\_pre2 + drtb\_notif\_pre2)) = \mathbf{948}$

WHOest_drtb_partial_lci2 = WHOest_alltb_partial_lci2 *

$(drtb\_notif\_partial2 / (dstb\_notif\_partial2 + drtb\_notif\_partial2)) = \mathbf{1900}$

WHOest_drtb_during_lci2 = WHOest_alltb_full_lci2 *

$(drtb\_notif\_during2 / (dstb\_notif\_during2 + drtb\_notif\_during2)) = \mathbf{604}$

WHOest_drtb_pre_uci2 = WHOest_alltb_pre_uci2 *

$(drtb\_notif\_pre2 / (dstb\_notif\_pre2 + drtb\_notif\_pre2)) = \mathbf{1877}$

$\text{WHOest\_drtb\_partial\_uci2} = \text{WHOest\_alltb\_partial\_uci2} * (\text{drtb\_notif\_partial2} / (\text{dstb\_notif\_partial2} + \text{drtb\_notif\_partial2})) = \mathbf{3749}$
 $\text{WHOest\_drtb\_during\_uci2} = \text{WHOest\_alltb\_full\_uci2} * (\text{drtb\_notif\_during2} / (\text{dstb\_notif\_during2} + \text{drtb\_notif\_during2})) = \mathbf{1153}$

Apportioning the national estimated DR-TB burden to Lima province

For cascade step 1 (the estimated DR-TB burden in Lima province, for each COVID-19 period), apportion WHO DR-TB burden estimates to Lima province for each COVID-19 period, based on the proportion of national DR-TB notifications (drtb_notif, see above) that are from Lima (drtb_notif_lima):

DR-TB notifications in Lima province:

$\text{drtb\_notif\_lima\_pre2} = 696$
 $\text{drtb\_notif\_lima\_partial2} = 1446$
 $\text{drtb\_notif\_lima\_during2} = 213$

DR-TB burden apportioned to Lima province:

Step 1, pre-COVID-19 period:

$\text{step1\_dr\_pre2} = \text{WHOest\_drtb\_pre2} * (\text{drtb\_notif\_lima\_pre2} / \text{drtb\_notif\_pre2}) = \mathbf{873}$

Step 1, partially during COVID-19 period:

$\text{step1\_dr\_partial2} = \text{WHOest\_drtb\_partial2} * (\text{drtb\_notif\_lima\_partial2} / \text{drtb\_notif\_partial2}) = \mathbf{1844}$

Step 1, fully during COVID-19 period:

$\text{step1\_dr\_during2} = \text{WHOest\_drtb\_during2} * (\text{drtb\_notif\_lima\_during2} / \text{drtb\_notif\_during2}) = \mathbf{551}$

Uncertainty intervals (based on uncertainty intervals for WHO burden estimates):

$\text{step1\_dr\_pre\_uci2} = \text{WHOest\_drtb\_pre\_uci2} * (\text{drtb\_notif\_lima\_pre2}/\text{drtb\_notif\_pre2}) = \mathbf{1188}$

$\text{step1\_dr\_partial\_uci2} = \text{WHOest\_drtb\_partial\_uci2} *$

$(\text{drtb\_notif\_lima\_partial2}/\text{drtb\_notif\_partial2}) = \mathbf{2499}$

$\text{step1\_dr\_during\_uci2} = \text{WHOest\_drtb\_during\_uci2} *$

$(\text{drtb\_notif\_lima\_during2}/\text{drtb\_notif\_during2}) = \mathbf{735}$

$\text{step1\_dr\_pre\_lci2} = \text{WHOest\_drtb\_pre\_lci2} * (\text{drtb\_notif\_lima\_pre2}/\text{drtb\_notif\_pre2}) = \mathbf{600}$

$\text{step1\_dr\_partial\_lci2} = \text{WHOest\_drtb\_partial\_lci2} *$

$(\text{drtb\_notif\_lima\_partial2}/\text{drtb\_notif\_partial2}) = \mathbf{1267}$

$\text{step1\_dr\_during\_lci2} = \text{WHOest\_drtb\_during\_lci2} *$

$(\text{drtb\_notif\_lima\_during2}/\text{drtb\_notif\_during2}) = \mathbf{385}$

Step 4: the proportion of people with DR-TB initiating TB treatment

(Note, step 4 is shown before steps 2 and 3, as steps 2 and 3 are back-calculated from their subsequent steps, see below).

As all patients reported in SIGTB in the study period had a TB treatment start date recorded, step 4 is equal to the number of DR-TB patients in SIGTB in each COVID-19 period:

$\text{step4\_dr\_pre2} = \mathbf{696}$

$\text{step4\_dr\_partial2} = \mathbf{1446}$

$\text{step4\_dr\_during2} = \mathbf{213}$

Step 3: the proportion of people with DR-TB diagnosed

This step is back-calculated from step 4, taking into account pre-treatment loss to follow-up (those who are diagnosed with TB but do not initiate treatment). The proportion of cases diagnosed that initiated treatment is based on treatment initiation data from the Peruvian NTP

and aggregate annual diagnosis data from the Peruvian National Centre for the Epidemiology, Prevention and Control of Diseases.²⁴ Given that the pre-, partial and during COVID-19 cohorts span different years, weighted averages of the annual value for the proportion of those diagnosed initiating treatment were used, according to the contribution of specific years to each cohort.

Proportion of those diagnosed initiating treatment, by year.

propinit_2018 = 0.991

propinit_2019 = 0.959

propinit_2020 = 0.989

propinit_2021 = 0.981

Weighted average of treatment initiation proportion, based on contribution of years to each cohort (see cohort definitions and dates for DR-TB cascade at the start of the DR-TB section):

propinit_dr_pre = propinit_2018

propinit_dr_partial = (((3.5/12)*propinit_2018)+propinit_2019+
((2.5/12)*propinit_2020))/((3.5/12)+1+(2.5/12))

propinit_dr_during = propinit_2020

Step 3, back-calculated from Step 4 based on the proportion of those diagnosed initiating treatment:

step3_dr_pre2 = step4_dr_pre2/propinit_dr_pre = **702**

step3_dr_partial2 = step4_dr_partial2/propinit_dr_partial = **1492**

step3_dr_during2 = step4_dr_during2/propinit_dr_during = **215**

Step 2: the proportion of people with DR-TB accessing TB testing

Given the imperfect sensitivity of tests in the diagnostic algorithm for TB, this step is based on the proportion of people diagnosed (step 3), and the proportion of people who truly had TB

that were missed (false negatives) due to imperfect test sensitivity. The proportion of people missed is calculated based on the proportion of people receiving each test, and the sensitivity of these tests under local conditions, correcting for those who were treated empirically (pulmonary TB patients initiated on treatment without microbiological confirmation, and extrapulmonary TB patients initiated on treatment without histopathological confirmation).

The proportion of people receiving each test is based on a sample of DR-TB patients (n=442) receiving TB care in San Juan de Lurigancho (SJL) district of Lima province (see aim 2 in main paper), of which 4.3% received MODS, 30.8% received GeneXpert (but not MODS), and 64.9% received sputum smear microscopy only (neither MODS nor GeneXpert) as the initial diagnostic test.

The sensitivity of tests is based on values available in the literature. A multicentre study (n=6,648) including n=1,185 TB patients in Lima, Peru found the sensitivity of GeneXpert for the detection of Rifampicin resistance in the subgroup of patients from Lima who were Rifampin-resistant (n=23) to be 95.7% (95%CI: 79.0-99.2%).²⁹ The sensitivity of sputum smear microscopy in the study (whilst this estimate included patients in Lima, it is not specific to Lima, as Lima-specific values for this test were not provided) was 68.6% (95%CI: 63.5-73.3%). A study evaluating MODS in Lima, Peru (n=1,980) found its sensitivity in patients at high risk of TB or MDR-TB to be 98.9% (95%CI: 97.9-99.9%).²³

Proportion receiving each test:

prop_mods_dr = 0.043

prop_genexpert_dr = 0.308

prop_smear_dr = 0.649

Sensitivity of tests:

Sensitivity and 95% confidence interval (95%CI) of MODS for patients at high risk of TB or MDR-TB in Lima, Peru²³:

sens_mods = 0.989

lci_mods = 0.979

uci_mods = 0.999

Sensitivity and 95%CI of GeneXpert for detection of Rifampicin resistance in patients in Lima, Peru (based on Lima subset of the source study²⁹ only).

sens_genexpert = 0.957

lci_xpert = 0.790

uci_xpert = 0.992

Sensitivity and 95%CI of smear microscopy in a sample including patients from Lima, Peru²⁹ (Lima-only estimates not available for this test):

sens_smear = 0.686

lci_smear = 0.635

uci_smear = 0.733

Number of patients diagnosed by each method (based on Step 3 and test sensitivities), in each cohort:

dx_mods_pre2 = prop_mods_dr*step3_dr_pre2

dx_genexpert_pre2 = prop_genexpert_dr*step3_dr_pre2

dx_smear_pre2 = prop_smear_dr*step3_dr_pre2

dx_mods_partial2 = prop_mods_dr*step3_dr_partial2

dx_genexpert_partial2 = prop_genexpert_dr*step3_dr_partial2

dx_smear_partial2 = prop_smear_dr*step3_dr_partial2

dx_mods_dur2 = prop_mods_dr*step3_dr_during2

dx_genexpert_dur2 = prop_genexpert_dr*step3_dr_during2

dx_smear_dur2 = prop_smear_dr*step3_dr_during2

Number of patients (who truly had TB) that were missed by each test

$\text{missed\_mods\_pre2} = \text{dx\_mods\_pre2} / \text{sens\_mods} - \text{dx\_mods\_pre2}$

$\text{missed\_genexpert\_pre2} = \text{dx\_genexpert\_pre2} / \text{sens\_genexpert} - \text{dx\_genexpert\_pre2}$

$\text{missed\_smear\_pre2} = \text{dx\_smear\_pre2} / \text{sens\_smear} - \text{dx\_smear\_pre2}$

$\text{missed\_mods\_partial2} = \text{dx\_mods\_partial2} / \text{sens\_mods} - \text{dx\_mods\_partial2}$

$\text{missed\_genexpert\_partial2} = \text{dx\_genexpert\_partial2} / \text{sens\_genexpert} - \text{dx\_genexpert\_partial2}$

$\text{missed\_smear\_partial2} = \text{dx\_smear\_partial2} / \text{sens\_smear} - \text{dx\_smear\_partial2}$

$\text{missed\_mods\_dur2} = \text{dx\_mods\_dur2} / \text{sens\_mods} - \text{dx\_mods\_dur2}$

$\text{missed\_genexpert\_dur2} = \text{dx\_genexpert\_dur2} / \text{sens\_genexpert} - \text{dx\_genexpert\_dur2}$

$\text{missed\_smear\_dur2} = \text{dx\_smear\_dur2} / \text{sens\_smear} - \text{dx\_smear\_dur2}$

95% CIs for the number of patients missed, based on 95% CIs for test sensitivities:

Lower bound:

$\text{missed\_mods\_pre\_lci2} = \text{dx\_mods\_pre2} / \text{lci\_mods} - \text{dx\_mods\_pre2}$

$\text{missed\_genexpert\_pre\_lci2} = \text{dx\_genexpert\_pre2} / \text{lci\_xpert} - \text{dx\_genexpert\_pre2}$

$\text{missed\_smear\_pre\_lci2} = \text{dx\_smear\_pre2} / \text{lci\_smear} - \text{dx\_smear\_pre2}$

$\text{missed\_mods\_partial\_lci2} = \text{dx\_mods\_partial2} / \text{lci\_mods} - \text{dx\_mods\_partial2}$

$\text{missed\_genexpert\_partial\_lci2} = \text{dx\_genexpert\_partial2} / \text{lci\_xpert} - \text{dx\_genexpert\_partial2}$

$\text{missed\_smear\_partial\_lci2} = \text{dx\_smear\_partial2} / \text{lci\_smear} - \text{dx\_smear\_partial2}$

$\text{missed\_mods\_dur\_lci2} = \text{dx\_mods\_dur2} / \text{lci\_mods} - \text{dx\_mods\_dur2}$

$\text{missed\_genexpert\_dur\_lci2} = \text{dx\_genexpert\_dur2} / \text{lci\_xpert} - \text{dx\_genexpert\_dur2}$

$\text{missed\_smear\_dur\_lci2} = \text{dx\_smear\_dur2} / \text{lci\_smear} - \text{dx\_smear\_dur2}$

Upper bound:

$\text{missed\_mods\_pre\_uci2} = \text{dx\_mods\_pre2} / \text{uci\_mods} - \text{dx\_mods\_pre2}$

$\text{missed\_genexpert\_pre\_uci2} = \text{dx\_genexpert\_pre2} / \text{uci\_xpert} - \text{dx\_genexpert\_pre2}$

$\text{missed\_smear\_pre\_uci2} = \text{dx\_smear\_pre2} / \text{uci\_smear} - \text{dx\_smear\_pre2}$

$\text{missed\_mods\_partial\_uci2} = \text{dx\_mods\_partial2} / \text{uci\_mods} - \text{dx\_mods\_partial2}$

$\text{missed\_genexpert\_partial\_uci2} = \text{dx\_genexpert\_partial2} / \text{uci\_xpert} - \text{dx\_genexpert\_partial2}$

$\text{missed\_smear\_partial\_uci2} = \text{dx\_smear\_partial2} / \text{uci\_smear} - \text{dx\_smear\_partial2}$
 $\text{missed\_mods\_dur\_uci2} = \text{dx\_mods\_dur2} / \text{uci\_mods} - \text{dx\_mods\_dur2}$
 $\text{missed\_genexpert\_dur\_uci2} = \text{dx\_genexpert\_dur2} / \text{uci\_xpert} - \text{dx\_genexpert\_dur2}$
 $\text{missed\_smear\_dur\_uci2} = \text{dx\_smear\_dur2} / \text{uci\_smear} - \text{dx\_smear\_dur2}$

Accounting for patients empirically diagnosed:

Pulmonary TB (PTB) cases who were initiated on treatment without microbiological confirmation (smear negative / not done and culture negative / not done), based on SIGTB data, in each cohort:

$\text{empiric\_ptb\_dr\_pre} = 165$
 $\text{empiric\_ptb\_dr\_partial} = 299$
 $\text{empiric\_ptb\_dr\_during} = 51$

Extrapulmonary TB (EPTB) cases who were initiated on treatment without histopathological confirmation (negative or not done). As information on histopathology was not available in the DR-TB SIGTB dataset, this is based on the proportion of DS-TB patients with EPTB empirically treated ($\text{prop\_empiric\_eptb\_ds}$), according to SIGTB data, multiplied by the number of DR-TB patients with EPTB (eptb_dr).

Number of DR-TB patients with EPTB, by cohort:

$\text{eptb\_dr\_pre} = 14$
 $\text{eptb\_dr\_partial} = 38$
 $\text{eptb\_dr\_during} = 4$

Proportion of DS-TB patients with EPTB empirically treated (as histopathology data not available for DR-TB patients):

$\text{prop\_empiric\_eptb\_ds\_pre} = 0.370$
 $\text{prop\_empiric\_eptb\_ds\_partial} = 0.365$

prop_empiric_eptb_ds_during = 0.366

Proportion of DR-TB patients with EPTB empirically treated (based on

empiric_eptb_dr_pre = eptb_dr_pre*prop_empiric_eptb_ds_pre = 5

empiric_eptb_dr_partial = eptb_dr_partial*prop_empiric_eptb_ds_partial = 14

empiric_eptb_dr_during = eptb_dr_during*prop_empiric_eptb_ds_during = 1

Final step 2 estimates (back-calculated from those diagnosed (step 3), adding those missed, correcting for those empirically treated):

step2_dr_pre2 = step3_dr_pre2 + missed_genexpert_pre2 + missed_smear_pre2 -

(empiric_ptb_dr_pre + empiric_eptb_dr_pre) = **751**

step2_dr_partial2 = step3_dr_partial2 + missed_genexpert_partial2 + missed_smear_partial2 -

(empiric_ptb_dr_partial + empiric_eptb_dr_partial) = **1643**

step2_dr_dur2 = step3_dr_during2 + missed_genexpert_dur2 + missed_smear_dur2 -

(empiric_ptb_dr_during + empiric_eptb_dr_during) = **230**

95%CI for final step 2 estimates (based on 95%CI for the sensitivity of tests):

Lower bound:

step2_dr_pre_lci2 = step3_dr_pre2 + missed_genexpert_pre_uci2 + missed_smear_pre_uci2 -

(empiric_ptb_dr_pre + empiric_eptb_dr_pre) = **700**

step2_dr_partial_lci2 = step3_dr_partial2 + missed_genexpert_partial_uci2 +

missed_smear_partial_uci2 - (empiric_ptb_dr_partial + empiric_eptb_dr_partial) = **1535**

step2_dr_dur_lci2 = step3_dr_during2 + missed_genexpert_dur_uci2 + missed_smear_dur_uci2

- (empiric_ptb_dr_during + empiric_eptb_dr_during) = **214**

Upper bound:

step2_dr_pre_uci2 = step3_dr_pre2 + missed_genexpert_pre_lci2 + missed_smear_pre_lci2 -

(empiric_ptb_dr_pre + empiric_eptb_dr_pre) = **852**

step2_dr_partial_uci2 = step3_dr_partial2 + missed_genexpert_partial_lci2 +

missed_smear_partial_lci2 - (empiric_ptb_dr_partial + empiric_eptb_dr_partial) = **1858**

step2_dr_dur_uci2 = step3_dr_during2 + missed_genexpert_dur_lci2 + missed_smear_dur_lci2
- (empiric_ptb_dr_during + empiric_eptb_dr_during) = **261**

Step 5: the proportion of people with DR-TB successfully completing treatment

DR-TB patients with a successful treatment outcome (cured or treatment complete) recorded in SIGTB, by cohort:

step5_dr_pre2 = **423**
step5_dr_partial2 = **693**
step5_dr_during2 = **39**

Calculations for final DR-TB cascade plot

Express steps as percentage of burden (step 1), so that differing cohort sizes (pre-, partially during and during COVID-19) can be more easily compared:

Pre-COVID-19 cohort:

step1_dr_pre_percent = 100
step2_dr_pre_percent = step2_dr_pre2/step1_dr_pre2*100
step3_dr_pre_percent = step3_dr_pre2/step1_dr_pre2*100
step4_dr_pre_percent = step4_dr_pre2/step1_dr_pre2*100
step5_dr_pre_percent = step5_dr_pre2/step1_dr_pre2*100

Error bars:

step1_dr_pre_percent_lci2 = step1_dr_pre_lci2/step1_dr_pre2*100
step2_dr_pre_percent_lci2 = step2_dr_pre_lci2/step1_dr_pre2*100
step1_dr_pre_percent_uci2 = step1_dr_pre_uci2/step1_dr_pre2*100
step2_dr_pre_percent_uci2 = step2_dr_pre_uci2/step1_dr_pre2*100

Partially during COVID-19 cohort:

$\text{step1\_dr\_partial\_percent} = 100$

$\text{step2\_dr\_partial\_percent} = \text{step2\_dr\_partial2} / \text{step1\_dr\_partial2} * 100$

$\text{step3\_dr\_partial\_percent} = \text{step3\_dr\_partial2} / \text{step1\_dr\_partial2} * 100$

$\text{step4\_dr\_partial\_percent} = \text{step4\_dr\_partial2} / \text{step1\_dr\_partial2} * 100$

$\text{step5\_dr\_partial\_percent} = \text{step5\_dr\_partial2} / \text{step1\_dr\_partial2} * 100$

Error bars:

$\text{step1\_dr\_partial\_percent\_lci2} = \text{step1\_dr\_partial\_lci2} / \text{step1\_dr\_partial2} * 100$

$\text{step2\_dr\_partial\_percent\_lci2} = \text{step2\_dr\_partial\_lci2} / \text{step1\_dr\_partial2} * 100$

$\text{step1\_dr\_partial\_percent\_uci2} = \text{step1\_dr\_partial\_uci2} / \text{step1\_dr\_partial2} * 100$

$\text{step2\_dr\_partial\_percent\_uci2} = \text{step2\_dr\_partial\_uci2} / \text{step1\_dr\_partial2} * 100$

Fully during covid cohort:

$\text{step1\_dr\_during\_percent} = 100$

$\text{step2\_dr\_during\_percent} = \text{step2\_dr\_dur2} / \text{step1\_dr\_during2} * 100$

$\text{step3\_dr\_during\_percent} = \text{step3\_dr\_during2} / \text{step1\_dr\_during2} * 100$

$\text{step4\_dr\_during\_percent} = \text{step4\_dr\_during2} / \text{step1\_dr\_during2} * 100$

$\text{step5\_dr\_during\_percent} = \text{step5\_dr\_during2} / \text{step1\_dr\_during2} * 100$

Error bars:

$\text{step1\_dr\_during\_percent\_lci2} = \text{step1\_dr\_during\_lci2} / \text{step1\_dr\_during2} * 100$

$\text{step2\_dr\_during\_percent\_lci2} = \text{step2\_dr\_dur\_lci2} / \text{step1\_dr\_during2} * 100$

$\text{step1\_dr\_during\_percent\_uci2} = \text{step1\_dr\_during\_uci2} / \text{step1\_dr\_during2} * 100$

$\text{step2\_dr\_during\_percent\_uci2} = \text{step2\_dr\_dur\_uci2} / \text{step1\_dr\_during2} * 100$

Supplement 2: Predictors of cascade completion among people diagnosed with TB in San Juan de Lurigancho district, Lima province, Peru, prior to and during the COVID-19 pandemic

Table S2. COVID-19 cohort definitions for assessing predictors of TB care cascade completion among people in San Juan de Lurigancho (Lima province, Peru) receiving TB care prior to, partially during, and fully during the COVID-19 pandemic

Regimen length (a)	TB care pre-COVID-19	TB care partially during COVID-19	TB care fully during COVID-19
6 months	Diagnosed 1 Jan 2017 - 15 Sep 2019 (≥ 6 months prior to start of COVID-19 restrictions)	Diagnosed 16 Sep 2019 - 15 Mar 2020	Diagnosed 16 Mar 2020 - 30 Nov 2021
9 months	Diagnosed 1 Jan 2017 - 15 June 2019 (≥ 9 months prior to start of COVID-19 restrictions)	Diagnosed 16 June 2019 - 15 Mar 2020	
12 months	Diagnosed 1 Jan 2017 - 15 Mar 2019 (≥ 12 months prior to start of COVID-19 restrictions)	Diagnosed 16 Mar 2019 - 15 Mar 2020	
18 months	Diagnosed 1 Jan 2017 - 15 Sep 2018 (≥ 18 months prior to start of COVID-19 restrictions)	Diagnosed 16 Sep 2018 - 15 Mar 2020	
24 months	Diagnosed 1 Jan 2017 - 15 Mar 2018 (≥ 24 months prior to start of COVID-19 restrictions)	Diagnosed 16 Mar 2018 - 15 Mar 2020	

(a) based on treatment standards outlined in Peruvian national TB program guidelines:²² Standard DS-TB regimen: 6 months. DS-TB in people living with HIV: 9 months. Extrapulmonary DS-TB: 12 months. Standard DR-TB regimen: 18 months. Extensively DR-TB (XDR-TB): 24 months. Other empirical DR-TB regimens: varying lengths dependent on resistance profile, according to program guidelines.

Equation S1: Logistic regression identifying predictors of TB treatment completion

$$\begin{aligned} \text{logit}(p(Y = 1|X)) = & \beta_0 + \beta_1 X_{\text{level}} + \beta_2 X_{\text{contact\_info}} + \beta_3 X_{\text{sex}} + \beta_4 X_{\text{HIV}} + \beta_5 X_{\text{diabetes}} + \\ & \beta_6 X_{\text{smoke\_current}} + \beta_7 X_{\text{smoke\_past}} + \beta_8 X_{\text{alcohol\_occ}} + \beta_9 X_{\text{alcohol\_abuse}} + \beta_{10} X_{\text{drugs\_current}} + \\ & \beta_{11} X_{\text{drugs\_past}} + \beta_{12} X_{\text{previousTB}} + \beta_{13} X_{\text{DRTB}} + \beta_{14} X_{\text{SES\_proxy}} + \beta_{15} X_{\text{closed\_evenings}} + \\ & \beta_{16} X_{\text{EPTB}} + \beta_{17} X_{\text{COVID\_full}} + \beta_{18} X_{\text{COVID\_partial}} + \beta_{19} X_{\text{dots\_COVID}} + \\ & \beta_{20} X_{\text{closed\_COVID}} + \text{spline}(X_{\text{adherence}}) + \text{spline}(X_{\text{age}}) \end{aligned}$$

Where: Y=1 = treatment complete, level = level of care of clinic (health centre vs. health post), contact_info = phone number and address incomplete / illegible / not provided (vs. complete and legible), smoke_current = currently smokes (vs. never), smoke_past = smoked in the past (vs. never), alcohol_occ = occasional alcohol consumption (vs. never), alcohol_abuse = alcohol abuse / heavy alcohol consumption (vs. never), drugs_current = current drug use (vs. never), drugs_past = past drug use (vs. never), previous TB = prior TB diagnosis (vs. new case), DR-TB = drug-resistant TB (vs. drug-susceptible), SES proxy = proxy for socioeconomic status, based on availability of basic services (light, water, sewage) in the home, and quality of housing materials (any basic services not available or rudimentary housing materials vs. all services available and non-rudimentary housing materials), closed_evenings = health post or health centre closed after 5pm, EPTB = extrapulmonary TB (vs. pulmonary), COVID_full = TB care fully during COVID-19 pandemic, COVID_partial = TB care partially during COVID-19 pandemic, dots_COVID = provision of directly observed therapy (DOTS) altered during COVID-19 (yes vs. no), closed_COVID = health centre or health post closed (for any duration) during COVID-19 (yes vs. no), adherence = number of days with missed doses.

Table S3. Comparison of characteristics among people with TB in San Juan de Lurigancho with available treatment outcome data and those with missing outcome data (due to transfer or remaining on treatment), by DR-TB status and period of TB care (pre / during COVID-19):

	DS-TB					
	Pre-COVID-19		Partially during COVID-19		Fully during COVID-19	
	Outcome available	Outcome missing (transferred or still on treatment)	Outcome available	Outcome missing (transferred or still on treatment)	Outcome available	Outcome missing (transferred or still on treatment)
Total	N = 491	N = 17	N=149	N=3	N = 382	N = 29
Sex, male	315 (64.2%)	13 (76.5%)	89 (59.7%)	3 (100.0%)	217 (56.8%)	21 (72.4%)
Age (years)	31.0 (16.5)	30.1 (12.3)	33.4 (18.6)	32.3 (19.7)	32.0 (15.2)	35.7 (16.1)
HIV positive	15 (3.1%)	0 (0.0%)	4 (2.7%)	0 (0.0%)	17 (4.5%)	1 (3.4%)
Diabetes	13 (2.6%)	0 (0.0%)	7 (4.7%)	0 (0.0%)	22 (5.8%)	2 (6.9%)
Level of care of TB clinic: Health post (vs health centre) (a)	67 (13.6%)	2 (11.8%)	31 (20.8%)	0 (0.0%)	96 (25.1%)	4 (13.8%)
Previously diagnosed with TB	30 (6.1%)	4 (25.0%)	5 (3.4%)	0 (0.0%)	37 (9.7%)	3 (10.7%)
Extrapulmonary TB	63 (12.9%)	1 (5.9%)	49 (32.9%)	1 (33.3%)	54 (14.1%)	6 (20.7%)
Adherence (Number of days with missed doses)	8.2 (17.4)	2.7 (7.8)	2.5 (7.9)	0.3 (0.6)	6.2 (15.3)	8.9 (20.2)

Basic sanitation unavailable / Rudimentary housing	4 (0.8%)	0 (0.0%)	1 (0.7%)	1 (33.3%)	6 (1.6%)	0 (0.0%)
Telephone number or address incomplete, illegible or not indicated	39 (8.0%)	2 (11.8%)	11 (7.4%)	1 (33.3%)	30 (7.9%)	1 (3.4%)
	DR-TB					
	Pre-COVID-19		Partially during COVID-19		Fully during COVID-19	
	Outcome available	Outcome missing (transferred or still on treatment)	Outcome available	Outcome missing (transferred or still on treatment)	Outcome available	Outcome missing (transferred or still on treatment)
Total	N = 153	N = 12	N = 100	N = 7	N = 116	N = 54
Sex, male	100 (65.4%)	10 (83.3%)	63 (63.0%)	6 (85.7%)	66 (56.9%)	30 (55.6%)
Age (years)	32.1 (15.2)	31.1 (16.6)	33.1 (15.1)	41.1 (14.8)	35.4 (17.8)	33.9 (17.6)
HIV positive	19 (12.4%)	0 (0.0%)	9 (9.0%)	0 (0.0%)	4 (3.4%)	3 (5.6%)
Diabetes	11 (7.2%)	1 (8.3%)	11 (11.0%)	2 (28.6%)	9 (7.8%)	11 (20.4%)
Level of care of TB clinic: Health post (vs health centre) (a)	10 (6.5%)	2 (16.7%)	6 (6.0%)	1 (14.3%)	15 (12.9%)	5 (9.3%)
Previously diagnosed with TB	23 (15.0%)	0 (0.0%)	7 (7.0%)	2 (28.6%)	5 (4.4%)	7 (13.0%)
Extrapulmonary TB	9 (5.9%)	0 (0.0%)	4 (4.0%)	1 (14.3%)	11 (9.5%)	1 (1.9%)
Adherence (Number of days with missed doses)	32.5 (43.6)	17.6 (20.1)	25.4 (38.8)	112.6 (166.1)	22.4 (38.0)	17.4 (28.3)
Basic sanitation unavailable / Rudimentary housing (b)	2 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Telephone number or address incomplete, illegible or not indicated	25 (16.3%)	1 (8.3%)	14 (14.0%)	1 (14.3%)	17 (14.7%)	11 (20.4%)

Missing covariate data: Diabetes (n=1), HIV (n=6), Previous TB (n=5, EPTB (n=1), Adherence (n=6), Contact information completeness (n=3)

(a) The distinction between health posts and health centres indicates the differing level of services available at the two types of clinics, with health centres generally having more staff and equipment, and offering more specialized services compared to health posts (health centres are also usually larger, serving a higher volume of patients).

(b) Proxy for socioeconomic status indicating if any basic services (water, light, or sewage system) are missing in the home, or the home is built of rudimentary material.

Equation S2: Logistic regression model for sensitivity analysis using continuous predictor for COVID-19 pandemic (weeks since start of the COVID-19 pandemic at the time of TB diagnosis)

$$\begin{aligned} \text{logit}(p(Y = 1|X)) = & \beta_0 + \beta_1 X_{\text{level}} + \beta_2 X_{\text{contact\_info}} + \beta_3 X_{\text{sex}} + \beta_4 X_{\text{HIV}} + \beta_5 X_{\text{diabetes}} + \\ & \beta_6 X_{\text{smoke\_current}} + \beta_7 X_{\text{smoke\_past}} + \beta_8 X_{\text{alcohol\_occ}} + \beta_9 X_{\text{alcohol\_abuse}} + \beta_{10} X_{\text{drugs\_current}} + \\ & \beta_{11} X_{\text{drugs\_past}} + \beta_{12} X_{\text{previousTB}} + \beta_{13} X_{\text{DRTB}} + \beta_{14} X_{\text{SES\_proxy}} + \beta_{15} X_{\text{closed\_evenings}} + \\ & \beta_{16} X_{\text{EPTB}} + \text{spline}(X_{\text{time\_since\_COVID}}) + \beta_{17} X_{\text{dots\_COVID}} + \\ & \beta_{18} X_{\text{closed\_COVID}} + \text{spline}(X_{\text{adherence}}) + \text{spline}(X_{\text{age}}) \end{aligned}$$

Where: $Y=1$ = treatment complete, level = level of care of clinic (health centre vs. health post), contact_info = phone number and address incomplete / illegible / not provided (vs. complete and legible), smoke_current = currently smokes (vs. never), smoke_past = smoked in the past (vs. never), alcohol_occ = occasional alcohol consumption (vs. never), alcohol_abuse = alcohol abuse / heavy alcohol consumption (vs. never), drugs_current = current drug use (vs. never), drugs_past = past drug use (vs. never), previous TB = prior TB diagnosis (vs. new case), DR-TB = drug-resistant TB (vs. drug-susceptible), SES proxy = proxy for socioeconomic status, based on availability of basic services (light, water, sewage) in the home, and quality of housing materials (any basic services not available or rudimentary housing materials vs. all services available and non-rudimentary housing materials), closed_evenings = health post or health centre closed after 5pm, EPTB = extrapulmonary TB (vs. pulmonary), time_since_covid = weeks since the start of the COVID-19 pandemic (declaration of national emergency due to COVID-19 in Peru, 16 Mar 2020) at time of individual's TB diagnosis, dots_COVID = provision of directly observed therapy (DOTS) altered during COVID-19 (yes vs. no), closed_COVID = health centre or health post closed (for any duration) during COVID-19 (yes vs. no), adherence = number of days with missed doses.

Table S4. Results of sensitivity analysis redefining the COVID-19 covariate as weeks since the start of the COVID-19 pandemic at the time of TB diagnosis.

Predictor (a)	OR	95%CI	
Health post (Ref = health centre) (b)	0.62	0.35	1.09
Contact information incomplete (Ref = contact information complete) (c))	0.72	0.38	1.34
Sex, male (Ref = female)	0.77	0.49	1.21
HIV positive	0.35	0.17	0.71
Diabetes	0.60	0.26	1.42
Smoking (Ref = never smoked)			
Smoked in the past	1.22	0.38	3.88

Smokes currently	0.70	0.12	4.04
Alcohol use (Ref = never drinks alcohol)			
Occasional alcohol consumption	1.05	0.48	2.29
Alcohol abuse	0.67	0.20	2.22
Drug use (Ref = never used drugs)			
Used drugs in the past	0.52	0.10	2.80
Currently uses drugs	0.49	0.10	2.35
Previously diagnosed with TB	0.38	0.21	0.70
DR-TB	0.45	0.28	0.72
Basic sanitation unavailable / rudimentary housing (d)	0.78	0.09	7.03
Clinic closed after 5pm	0.73	0.45	1.17
Extrapulmonary TB	0.69	0.37	1.30
DOTs method altered during COVID-19 (e)	1.74	0.86	3.48
Clinic ever closed during COVID-19 (f) (Ref = never closed)	0.79	0.32	1.96

Ref = reference category

(a) For continuous predictors (weeks since COVID-19 pandemic at time of diagnosis, age, adherence [number of days with missed doses]), see Figure X for spline functions.

(b) The distinction between health posts and health centres indicates the differing level of services available at the two types of clinics, with health centres generally having more staff and equipment, and offering more specialized services compared to health posts (health centres are also usually larger, serving a higher volume of patients).

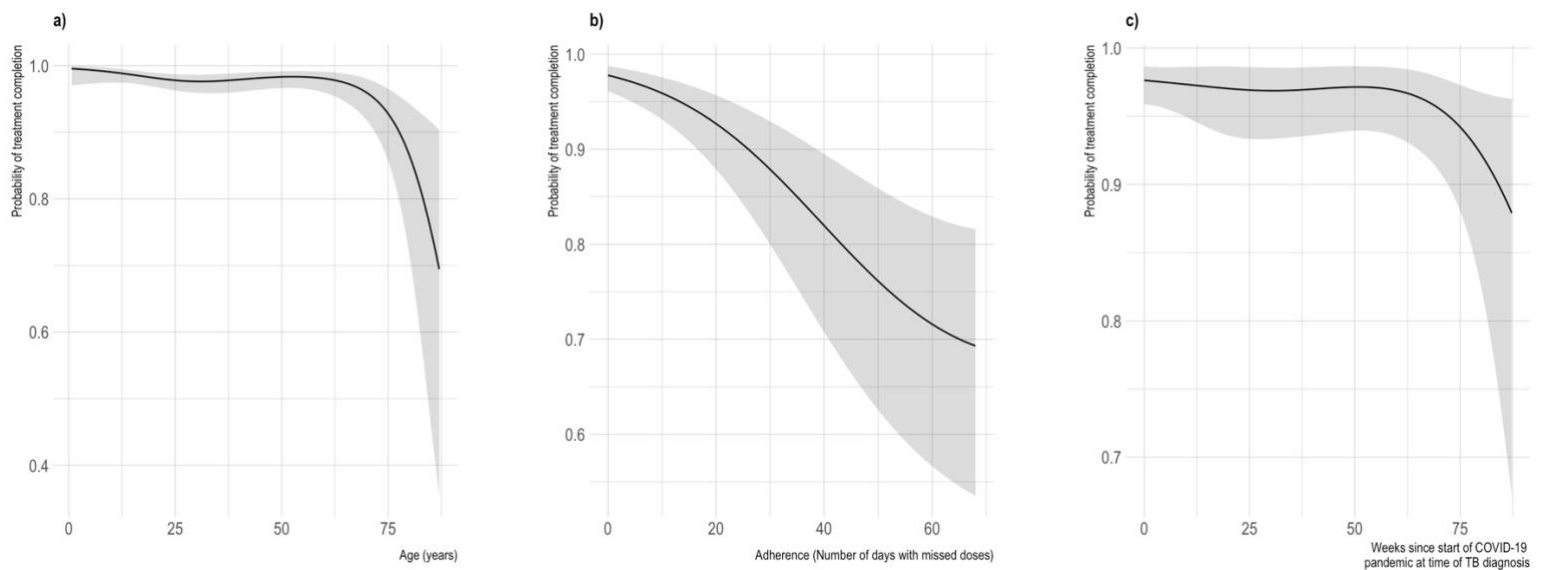
(c) Address or phone number incomplete, ineligible or not provided

(d) Proxy for socioeconomic status. Coded 1 if any basic services (water, light, or sewage system) missing in the home, or home built of rudimentary material. Ref = 0.

(e) All or some people with TB received a supply of medications to take home during COVID-19 (instead of receiving DOTs at clinic). Ref = DOTs continued in clinics, the same as before COVID-19.

(f) Three of the clinics in this sample were closed during COVID-19, one for a period of 2 weeks and the other two for a period of 1 month. All other clinics remained open during COVID-19.

Figure S2. Non-linear relationships of age (a), adherence (number of days with missed doses) (b) and weeks since start of COVID-19 pandemic (c) vs. treatment completion



Penalised spline functions ($df=4$) for age (a), adherence (number of days with missed doses) (b), and weeks since the start of the COVID-19 pandemic at the time of TB diagnosis (c). Shaded area = 95%CI. Plots show predicted values of probability of treatment completion across values of age (a), adherence (b), and weeks since the start of the COVID-19 pandemic at the time of TB diagnosis (c), holding all other covariates constant (at their most common values for categorical variables, at the median value for adherence (in (a) and (c)), at the mean age (in (b) and (c)), and at 0 weeks since COVID-19 (in (a) and (b))). Plots therefore do not represent treatment completion probabilities in the overall population, but rather represent, for example in (a), treatment completion probabilities at different ages for a new case of drug-susceptible, pulmonary TB in a HIV-negative, non-diabetic, non-smoking male with no alcohol or drug consumption, whose home had access to basic services (proxy for socioeconomic status), who presented for TB care at a health centre that was open in the evenings, and who was diagnosed with TB prior to the COVID-19 pandemic. As the distribution of adherence (number of days with missed doses) was highly skewed, plot (b) shows adherence up to the 95th percentile (68 days with missed doses) rather than the maximum (292 days with missed doses), so that the relationship with treatment completion at the most common values of adherence can be seen more clearly.

Equation S3: Logistic regression model for sensitivity analysis using neighbourhood-level income as the indicator of socioeconomic status

$$\begin{aligned} \text{logit}(p(Y = 1|X)) = & \beta_0 + \beta_1 X_{\text{level}} + \beta_2 X_{\text{contact\_info}} + \beta_3 X_{\text{sex}} + \beta_4 X_{\text{HIV}} + \beta_5 X_{\text{diabetes}} + \\ & \beta_6 X_{\text{smoke\_current}} + \beta_7 X_{\text{smoke\_past}} + \beta_8 X_{\text{alcohol\_occ}} + \beta_9 X_{\text{alcohol\_abuse}} + \beta_{10} X_{\text{drugs\_current}} + \\ & \beta_{11} X_{\text{drugs\_past}} + \beta_{12} X_{\text{previousTB}} + \beta_{13} X_{\text{DRTB}} + \beta_{14} X_{\text{income}} + \beta_{15} X_{\text{closed\_evenings}} + \\ & \beta_{16} X_{\text{EPTB}} + \beta_{17} X_{\text{COVID\_full}} + \beta_{18} X_{\text{COVID\_partial}} + \beta_{19} X_{\text{dots\_COVID}} + \\ & \beta_{20} X_{\text{closed\_COVID}} + \text{spline}(X_{\text{adherence}}) + \text{spline}(X_{\text{age}}) \end{aligned}$$

Where: Y=1 = treatment complete, level = level of care of clinic (health centre vs. health post), contact_info = phone number and address incomplete / illegible / not provided (vs. complete and legible), smoke_current = currently smokes (vs. never), smoke_past = smoked in the past (vs. never), alcohol_occ = occasional alcohol consumption (vs. never), alcohol_abuse = alcohol abuse / heavy alcohol consumption (vs. never), drugs_current = current drug use (vs. never), drugs_past = past drug use (vs. never), previous TB = prior TB diagnosis (vs. new case), DR-TB = drug-resistant TB (vs. drug-susceptible), **income = average per capita income of neighbourhood in which TB clinic is located (as people are required present for TB care at the clinic responsible for the area in which they live)**, closed_evenings = health post or health centre closed after 5pm, EPTB = extrapulmonary TB (vs. pulmonary), COVID_full = TB care fully during COVID-19 pandemic, COVID_partial = TB care partially during COVID-19 pandemic, dots_COVID = provision of directly observed therapy (DOTS) altered during COVID-19 (yes vs. no), closed_COVID = health centre or health post closed (for any duration) during COVID-19 (yes vs. no), adherence = number of days with missed doses.

Table S5. Results of sensitivity analysis using neighbourhood-level income as the indicator of socioeconomic status (instead of housing materials and availability of basic services)

Predictors (a)	OR	95%CI	
Health post (Ref = health centre) (b)	0.60	0.34	1.08
Contact information incomplete (Ref = contact information complete) (c))	0.65	0.35	1.21
Sex, male (Ref = female)	0.76	0.48	1.19
HIV positive	0.34	0.17	0.69
Diabetes	0.59	0.25	1.39

Smoking (Ref = never smoked)			
Smoked in the past	1.18	0.36	3.85
Smokes currently	0.75	0.12	4.57
Alcohol use (Ref = never drinks alcohol)			
Occasional alcohol consumption	1.17	0.53	2.56
Alcohol abuse	0.69	0.20	2.37
Drug use (Ref = never used drugs)			
Used drugs in the past	0.54	0.10	2.94
Currently uses drugs	0.50	0.10	2.39
Previously diagnosed with TB			
DR-TB	0.55	0.34	0.90
Neighbourhood-level income (Ref = middle income) (d)			
Lower middle income	0.92	0.45	1.86
Low income	1.50	0.82	2.72
Clinic closed after 5pm			
Extrapulmonary TB	0.66	0.37	1.18
COVID-19 period of TB care (Ref = pre-COVID-19)			
TB care fully during COVID-19	0.57	0.32	1.01
TB care partially during COVID-19	0.56	0.29	1.07
DOTs method altered during COVID-19 (e)			
Clinic ever closed during COVID-19 (f) (Ref = never closed)	1.85	0.87	3.94
	0.72	0.28	1.89

Ref = reference category

(a) For continuous predictors (weeks since COVID-19 pandemic at time of diagnosis, age, adherence [number of days with missed doses]), see Figure X for spline functions.

(b) The distinction between health posts and health centres indicates the differing level of services available at the two types of clinics, with health centres generally having more staff and equipment, and offering more specialized services compared to health posts (health centres are also usually larger, serving a higher volume of patients).

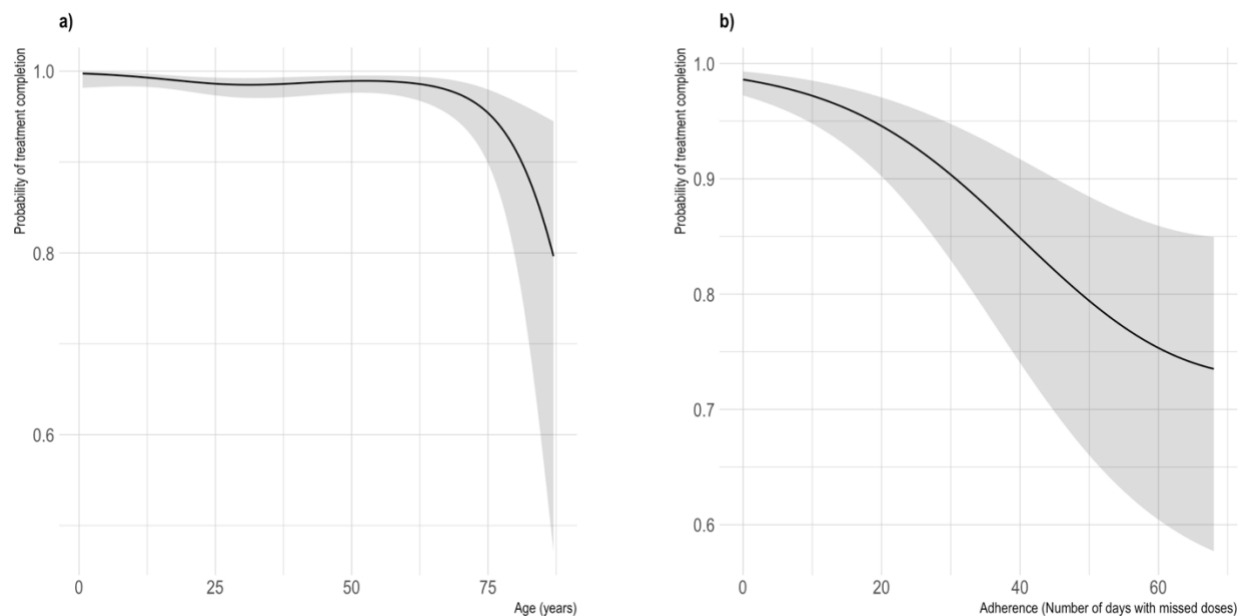
(c) Address or phone number incomplete, ineligible or not provided

(d) Average per capita monthly income of neighbourhood in which TB clinic is located, based on Peru's National Institute of Statistics and Informatics [INEI] 2020 report on neighbourhood-level income.³³ Although at the level of Lima province INEI's income categorization included five categories (in Peruvian Soles: High income: ≥ 2412.45 , upper middle income: 1449.72 - 2412.44, middle income: 1073.01 - 1449.71, lower middle income: 863.72 - 1073.00, and low income: ≤ 863.71), clinics in San Juan de Lurigancho district encompassed only the lower three categories.

(e) All or some people with TB received a supply of medications to take home during COVID-19 (instead of receiving DOTs at clinic). Ref = DOTs continued in clinics, the same as before COVID-19.

(f) Three of the clinics in this sample were closed during COVID-19, one for a period of 2 weeks and the other two for a period of 1 month. All other clinics remained open during COVID-19.

Figure S3. Non-linear relationships of age (a) and adherence (number of days with missed doses) (b) vs. treatment completion



Penalised spline functions ($df=4$) for age (a) and adherence (number of days with missed doses) (b). Shaded area = 95%CI. Plots show predicted values of probability of treatment completion across values of age (a) and adherence (b), holding all other covariates constant (at their most common values for categorical variables, at the median value for adherence (in (a)), and at the mean age (in (b))). Plots therefore do not represent treatment completion probabilities in the overall population, but rather represent, for example in (a), treatment completion probabilities at different ages for a new case of drug-susceptible, pulmonary TB in a HIV-negative, non-diabetic, non-smoking male with no alcohol or drug consumption, who missed one day of TB treatment, who presented for TB care in a low-income neighbourhood, at a health centre that was open in the evenings, and who received TB care prior to the COVID-19 pandemic. As the distribution of adherence (number of days with missed doses) was highly skewed, plot b shows adherence up to the 95th percentile (68 days with missed doses) rather than the maximum (292 days with missed doses), so that the relationship with treatment completion at the most common values of adherence can be seen more clearly.

CHAPTER 5: MANUSCRIPT 3:

Tuberculosis case notifications and outcomes in Peruvian prisons prior to and during the COVID-19 pandemic: A national-level interrupted time series analysis

5.1 Preface

Having examined the impact of the COVID-19 pandemic on the TB care cascade in Lima, Peru in the previous chapter, we now focus in more detail on a specific population at high risk for TB – the incarcerated population of Peru. Given that incarcerated populations in South America face a particularly high burden of TB, and that people in prison may have experienced COVID-19 disruptions differently than the general population, we compare case notifications and treatment outcomes prior to vs. during the COVID-19 pandemic, in the incarcerated and non-incarcerated populations of Peru, using Peruvian National TB Program data.

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Tuberculosis case notifications and outcomes in Peruvian prisons prior to and during the COVID-19 pandemic: A national-level interrupted time series analysis

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5.2 Abstract:

Background: The COVID-19 pandemic has significantly disrupted tuberculosis (TB) programs, making it even more urgent to focus TB elimination efforts on key populations. People experiencing incarceration are at high risk for TB, however, how COVID-19-related disruptions have impacted incarcerated populations with TB is unknown. We therefore assessed TB notifications and outcomes prior to and during the COVID-19 pandemic in incarcerated and non-incarcerated populations in Peru.

Methods: Using Peruvian National TB Program data from Jan 2018 to Dec 2021, an interrupted time series for weekly national drug-susceptible (DS) TB case notifications pre- and during COVID-19 was conducted (with the declaration of the COVID-19 emergency in Peru on 16 Mar 2020 as the cut-off date). The effect of TB care occurring pre- vs. during COVID-19 on TB treatment success in the incarcerated and non-incarcerated populations separately was explored using logistic regression. Missing data on covariates were imputed via multiple imputation by chained equations (MICE).

Results: DS-TB cases notified in prisons from Jan 2018 to Dec 2021 (n=10,134) represented 10% of all cases notified in the country (n=101,507). In the first week of the COVID-19 pandemic declaration, TB case notifications dropped by 61.2% (95%CI: 59.9-62.7%) in the non-incarcerated population and by 17.7% (95%CI: 17.5-17.9%) among the incarcerated population. TB treatment success was significantly lower in people receiving TB care entirely during the COVID-19 pandemic compared to prior to COVID-19 (after adjusting for covariates) in the non-incarcerated population (OR: 0.81, 95%CI: 0.78-0.85). In the incarcerated population, treatment success among those treated during COVID-19 was also lower (than among those treated pre-COVID-19), although not statistically significant (OR: 0.88, 95%CI: 0.76-1.01).

Conclusions: Both incarcerated and non-incarcerated populations experienced a large drop in TB case notifications (although much higher in the non-incarcerated population). TB services in the incarcerated population appear to have been less disrupted than in the non-incarcerated

population during the COVID-19 pandemic, possibly due to access to on-site TB care in prisons not being subject to the barriers to care experienced in the general population during the pandemic (e.g., transport restrictions, lockdowns).

5.3 Background:

The COVID-19 pandemic has set back progress on ending TB globally, with the World Health Organisation (WHO) reporting increases in TB incidence and mortality in recent years.¹⁻³ The COVID-19 pandemic has severely disrupted TB control in Peru,^{4,5} which suffered the 13th largest drop in TB case notifications from 2019 to 2020 of all countries worldwide.³ In light of these disruptions, it is urgent to focus TB elimination efforts on key populations, such as people experiencing incarceration, who are at particularly high risk for TB. We therefore evaluate TB case notifications and treatment outcomes among the incarcerated and non-incarcerated populations in Peru, prior to compared to during the COVID-19 pandemic.

Studies in a variety of countries report an extremely high prevalence and incidence of TB in incarcerated populations.⁶⁻¹² Prisons in South America, however, have been found to have a particularly high burden of TB, with a systematic review estimating a pooled TB prevalence of 1,680 cases / 100,000 persons (95%CI: 830–2,970) in the region.¹² In addition, it is estimated that the WHO region of the Americas had the highest absolute number of TB cases among people in prisons of all regions in 2019, primarily driven by high incidence in Central and South America.¹³ In Peru, results of a 2016 survey of detainees found a prevalence of 2,510 cases / 100,000 persons of self-reported TB diagnosis (detainees reported having been diagnosed by a healthcare provider) during incarceration,¹⁴ with 4.3% of surveyed detainees providing a self-report of TB diagnosis.¹⁵

Findings regarding TB treatment outcomes in prisons in previous studies are variable and context-dependent. Barriers to successful TB treatment may be exacerbated in the prison setting by high rates of tobacco, drug and alcohol use,¹⁶ and some studies report low proportions of treatment success (e.g. 61.5%¹⁷ in Malawi to 72.9%¹⁸ in Nigeria). Other studies however have found higher treatment success among prisoners than among those not incarcerated, including a large study in Brazil (n=17,776 incarcerated, n=160,728 non-incarcerated) that found higher treatment success in the incarcerated population (82.2% vs. 75.1%, p<0.0001) due to more widespread implementation of DOTs in the prison setting.¹⁹

Regarding the impact of the COVID-19 pandemic in places of detention, COVID-19 cases and deaths are much higher in prisons compared to the general population.²⁰⁻²² Prison settings also experienced larger COVID-19-related disruptions as prisons were de-prioritized in the pandemic response (including in COVID-19 vaccine roll-out).^{23,24} In addition, limited health resources in prisons have been diverted towards the pandemic response,^{25,26} resulting in restrictions of detainees' medical appointments outside of prison, long delays in care pathways,²⁵ and, in some cases, the limitation of prison health services to emergency-only levels.²⁴ The pandemic also aggravated already-dire staff shortages in prisons,²⁴ and although some settings enacted decarceration measures to alleviate pressure on prison health systems, these were temporary.^{23,27-29}

As of April 2023, over 91,000 people are incarcerated in Peru³⁰, (incarceration rate: 268/100,000 people³¹). **Supplement Figure S1** shows trends in the incarcerated population size over the study period (2018-2021). On average, prisons in the country are at 220% capacity,³⁰ creating aforementioned risks for increased transmission of TB, COVID-19, and other infectious diseases.³² In response to the COVID-19 pandemic, approximately 7,900 detainees have been released since 2020 under the decriminalization laws enacted to reduce the incarcerated population.³³

TB in the incarcerated population in Peru remains understudied. While the existing literature on the burden of TB in Peruvian prisons is limited by self-report,^{14,15} and the influence of prisons in TB transmission to the general population has been demonstrated,³⁴⁻³⁶ there are currently no studies on TB treatment outcomes in incarcerated and non-incarcerated populations in Peru. In addition, the COVID-19 pandemic has now presented further challenges for TB care in both the general population and in prisons. Although TB control globally has been severely disrupted by COVID-19,¹ specific high-risk settings, such as prisons, have not been evaluated despite widespread reports of disrupted health services in prisons.^{10,11} This study therefore aimed to describe DS-TB case notifications in the overall and incarcerated population in each department

(largest administrative division) of Peru, assess trends in weekly national DS-TB case notifications prior to vs. during COVID-19, and identify predictors of treatment success (treatment completion or cure) in incarcerated and non-incarcerated people in Peru, prior to vs. during the COVID-19 pandemic.

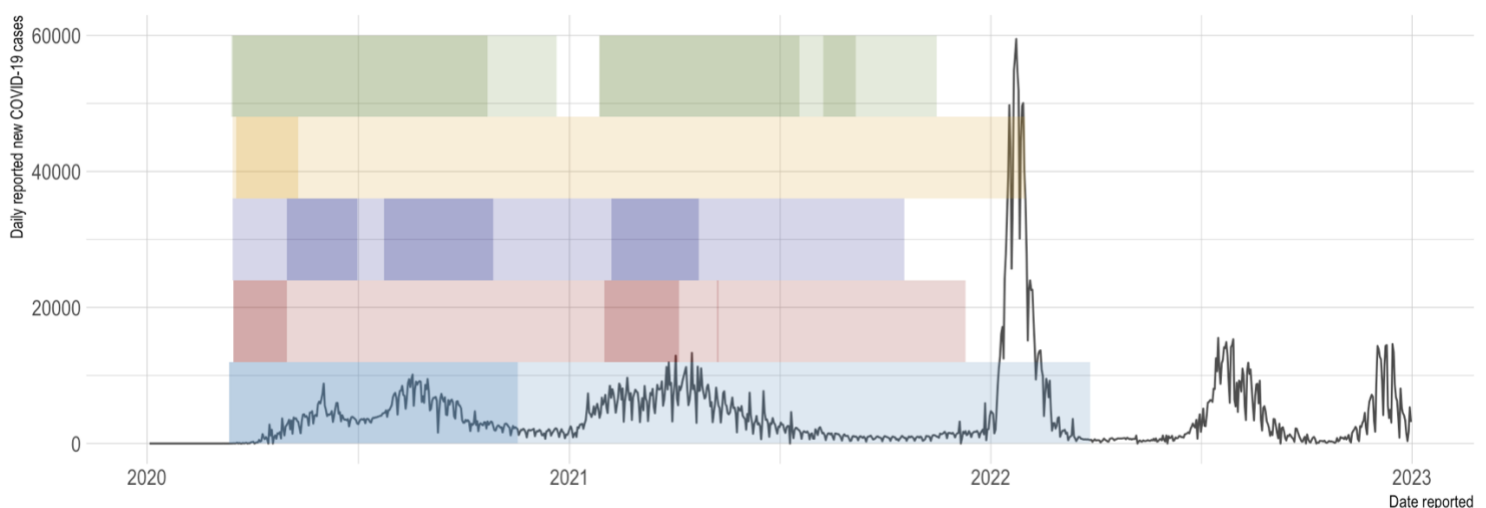
5.4 Methods:

Study setting and population:

We included all adults (aged ≥ 18 years) diagnosed with drug-susceptible TB (pulmonary and extrapulmonary) from 1 Jan 2018 to 31 Dec 2021 (see section below for aim-specific timeframes within this period) and reported in the Peruvian national TB program database, Sistema de Información Gerencial de Tuberculosis (SIGTB).³⁷

For context on disruptions during the COVID-19 pandemic in Peru, COVID-19 case surges as well as the associated restrictions (closures of schools, workplaces, transport, etc.) are shown in **Figure 1** (COVID-19 cases from the WHO COVID-19 database,³⁸ and COVID-19 measures/policies from the Oxford COVID-19 Government Response Tracker³⁹).

Figure 1. Daily new COVID-19 cases reported in Peru,³⁸ and COVID-19-related restrictions (Jan 2020 – Dec 2022)³⁹



COVID-19-related restrictions/policies

Local travel restrictions

- Travel between regions not recommended
- Travel between regions restricted

Stay-at-home orders

- Stay-at-home order with exceptions (e.g. exercise, groceries)
- Stay-at-home order with minimal exceptions (e.g. once a week / one person at a time)

Transport closures

- Significantly reduced routes/volumes/means of transport, or recommended closure
- Closed

Workplace closures

- Closure of some sectors
- Closure of all sectors (except essential services)

School closures

- Closure at some levels/categories (e.g. public/private or grade-level differences)
- Closure at all levels/categories

COVID-19 cases are from the WHO COVID-19 database.³⁸

COVID-19 measures/policies are from the Oxford COVID-19 Government Response Tracker.³⁹

Work closure policies not available for 2021-12-10 to 2022-09-30

Transport closure policies and local travel restrictions not available for 2021-11-15 to 2022-06-30

Data source:

SIGTB³⁷ includes information on all notified TB cases in Peru, including TB diagnoses within the prison system, as well as basic demographic and clinical information (age, sex, HIV status, diabetes status, type of TB (pulmonary/extra-pulmonary), drug-resistance status, treatment outcome).

For the purpose of this study, TB among incarcerated individuals is defined as cases diagnosed during incarceration, with those receiving a TB diagnosis after release from a prior incarceration not being included in this category. This is because incarceration status is only available in SIGTB for those receiving a TB diagnosis during incarceration (prior incarceration status and length of incarceration is not captured).

Timeframes and COVID-19 period definitions:

Definitions of pre- vs. during COVID-19 periods for each aim are described below.

Aim 1: To compare department-level case-notifications pre- and during COVID-19, case notifications in the one-year timeframe prior to COVID-19 were compared to notifications in the first year of the COVID-19 pandemic. Aim 1 includes those diagnosed between 15 March 2019 to 15 March 2020 (pre-COVID-19) and those diagnosed between 16 March 2020 to 16 March 2021 (during COVID-19).

Aim 2: Aim 2 (ITS of weekly case notifications) includes all cases notified between 1 Jan 2018 and 31 Dec 2021. As pandemic restrictions and the declaration of a national state of emergency came into effect in Peru on 16 March 2020,⁴⁰ the week of 16 March 2020 is defined as the first week of COVID-19 in the ITS analysis.

Aim 3: This aim includes those diagnosed between 1 Jan 2018 and 16 Mar 2021. As aim 3 assesses TB treatment outcomes rather than case notifications, treatment time is taken into account in the categorization of COVID-19 periods into three categories: TB care occurring pre-COVID-19, partially during COVID-19, and fully during COVID-19. For example, those on a 6-month standard regimen for DS-TB were defined as having received TB care prior to COVID-19 if they were diagnosed between 1 Jan 2018 and 15 Sep 2019, meaning they would have been expected to complete their 6-month treatment prior to the start of COVID-19 restrictions on 16 Mar 2020. Similarly, those on a 6-month regimen diagnosed between 16 Sep 2019 and 15 Mar 2020 were defined as having received their TB care partially during COVID-19, and those diagnosed 16 Mar 2020 to 16 Mar 2021 were defined as receiving their TB care fully during COVID-19. For detail on COVID-19 period definitions adapted to those receiving longer regimens (9-month and 12-month), see **Table 1**.

Table 1. COVID-19 period definitions for assessing tuberculosis treatment outcomes (Aim 3) prior to and during COVID-19 in Peru

TB treatment regimen	Regimen treatment time	TB care pre-COVID-19	TB care partially during COVID-19	TB care fully during COVID-19
2HREZ/4(HR)3^(a)	6 months	Diagnosed 1 Jan 2018 - 15 Sep 2019 (≥ 6 months prior to start of COVID-19 restrictions)	Diagnosed 16 Sep 2019 - 15 Mar 2020	Diagnosed 16 Mar 2020 - 16 Mar 2021
2HREZ/7HR^(b)	9 months	Diagnosed 1 Jan 2018 - 15 June 2019 (≥ 9 months prior to start of COVID-19 restrictions)	Diagnosed 16 June 2019 - 15 Mar 2020	
2HREZ/10HR^(c)	12 months	Diagnosed 1 Jan 2018 - 15 Mar 2019 (≥ 12 months prior to start of COVID-19 restrictions)	Diagnosed 16 Mar 2019 - 15 Mar 2020	

H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

(a) Daily* HREZ for 2 months, HR for 4 months on 3 days per week (Standard DS-TB regimen)

(b) Daily* HREZ for 2 months, daily* HR for 7 months (DS-TB regimen in people living with HIV)

(c) Daily* HREZ for 2 months, daily* HR for 10 months (Extrapulmonary DS-TB regimen)

* Except Sundays⁴¹

Statistical analysis:

Department-level DS-TB case notifications in the incarcerated & non-incarcerated populations pre- & during COVID-19 (Aim 1):

Departments are the largest administrative division of Peru (followed by provinces and districts), and there are 25 departments in the country in total (24 plus the constitutional province of Callao).⁴² TB case notifications in the incarcerated population were compared with the general population in each department by calculating incidence rate ratios (IRR) (**Supplement Section 1**).¹² Department-level IRRs are also presented for the pre-COVID-19 time period (diagnoses between 15 March 2019 to 15 March 2020) and during the COVID-19 pandemic (diagnoses between 16 March 2020 to 16 March 2021).

Interrupted time series analysis of DS-TB case notifications pre- & during COVID-19 (Aim 2):

An interrupted time series was conducted for weekly DS-TB case notifications in SIGTB from 1 Jan 2018 to 31 Dec 2021 (209 weeks in total). The start of the COVID-19 pandemic was considered the date of the declaration of the national emergency due to COVID-19, 16 Mar 2020 (week 116 of 209). As this was a Monday, weeks in the time series were defined as starting on Mondays.

To model weekly case counts, a negative binomial model was used to account for overdispersion of the data. We present observed case notifications and counterfactual trends expected in the absence of the COVID-19 pandemic.⁴³ Three separate models were fit, for case notifications among 1) the total population of Peru 2) the non-incarcerated population, and 3) the incarcerated population.

Based on the observed temporal trend in case notification in the total population, three time periods were defined: Phase 1, the pre-COVID-19 phase (weeks 1 to 115, i.e., 1 Jan 2018 to 15 Mar 2020), phase 2 - the recovery phase (weeks 116 to 151, i.e., 16 Mar 2020 to 22 Nov 2020), and phase 3 - the post-recovery phase (weeks 152 to 209, i.e., 23 Nov 2020 to 31 Dec 2021). In phase 2, cases increased linearly after the initial drop due to COVID-19, and in phase 3 the temporal trend began to resemble phase 1. Seasonality trends were modelled using harmonic terms. In the simplest case, the same harmonic term was used for the duration of the time series. However, if the seasonality pattern changed across phases, distinct harmonic terms were used for each phase. Dichotomous indicators were used to modify the intercept, slope, and harmonic terms for the respective phases (**Supplement Figures S2-S4**).

All models included the log of the population size as an offset term, to account for fluctuations in the source population. In particular, notable changes in the incarcerated population occurred due to decarceration efforts during the COVID-19 pandemic (**Supplement Figure S1**). Estimates of the total population size were based on annual population projections from the Peruvian

census,⁴⁴ the population size for those incarcerated was based on monthly counts of the incarcerated population from Peru's penitentiary institute database,⁴⁵ and the non-incarcerated population size was based on annual population estimates from the national census, minus the average annual incarcerated population. Model equations are shown in the supplement (**Equations S1-S3**).

Counterfactual values for expected case notifications in the absence of COVID-19 were estimated using the Phase 1 (pre-COVID-19) model parameters. As the incarcerated population decreased in the COVID-19 pandemic period (see **Supplement Figure S1**) as a result of COVID-19-related decarceration policies, the monthly incarcerated population sizes used in the counterfactual scenario were incrementally increased by $n=388$, the average monthly change in the incarcerated population size in the year prior to the COVID-19 pandemic (2019).

DS-TB treatment outcomes in the incarcerated & non-incarcerated populations pre- & during COVID-19 (Aim 3):

The impact of receiving TB care prior to, partially during or fully during the COVID-19 pandemic (according to definitions in **Table 1**) on TB treatment success in the incarcerated and non-incarcerated populations was explored using logistic regression (see supplement, **Equation S4**). Relevant covariates adjusted for included sex, age, HIV status, diabetes status, smoking, extrapulmonary vs. pulmonary TB, new vs. relapse case, TB treatment adherence, and health insurance type. The non-linear relationship between age and likelihood of treatment success was modelled flexibly using penalised splines. Separate models were fit for 1) the total population, 2) the non-incarcerated population, and 3) the incarcerated population.

Lacking other indicators of socioeconomic status in the national database, health insurance type was included as a proxy for socioeconomic status. There are various categories of health insurance in Peru; Seguro Integral de Salud (SIS), Seguro Social de Salud (EsSalud), and private insurance.⁴ SIS is Peru's free public health insurance, serving the lower-income population,

while EsSalud is insurance provided to workers via their employer (note: individuals employed in the police or armed forces have separate health insurance financed by the Ministry of Defence.⁴ This is included in the worker's insurance category for the purpose of our analysis). Lastly, for additional benefits, private insurance can also be obtained by those able to pay higher premiums. Health insurance type is therefore expected to be a relevant (although imperfect) proxy for socioeconomic status.

As only the number of doses at exit (end of follow-up, completion, or death, etc) were available in the national TB program database, adherence is estimated based on the number of doses at exit, vs. total doses expected for the individual's treatment regimen and their time on treatment before exit. Implausibly high values for doses at exit were recoded as missing.

TB treatment success was defined as either cure or treatment completion. Treatment drop-out, treatment failure, the development of drug-resistant TB, or death were classified as unsuccessful treatment outcomes. The development of drug-resistance or other reasons for permanent treatment suspensions or changes were also classified as failures of first-line treatment, as per updated WHO treatment outcome definitions.⁴⁶

Covariates with missing data included diabetes (8.2% missing), HIV (7.3% missing), adherence (2.6% missing), health insurance type (0.2% missing), smoking (0.2% missing), site (pulmonary/extrapulmonary) of TB (0.01% missing), and COVID-19 period (0.004% missing - due to missingness of treatment regimen, pre/during COVID-19 TB treatment was not assigned in these cases, given this was defined based on expected treatment length). Missing data on covariates were imputed by multiple imputation by chained equations (MICE), and the imputed data used in final analyses. Individuals with missing outcome data (2.9%) were excluded from analyses. Sensitivity analyses were conducted to assess robustness of results, including the effect on model estimates of the use of MICE for imputation of missing covariate data compared to complete case analysis, and classifying those with missing outcome data as having unsuccessful outcomes.

Power calculation:

Our sample size was fixed by design, as it included all adult TB notifications in Peru in the study period. However, based on a treatment success rate of 83% for all forms of TB in 2019 (Pre-COVID-19), according to WHO estimates for Peru,⁴⁷ and assuming a 10% decrease in treatment success during COVID-19 to be programmatically important, we would detect this difference at 80% power with a sample size of 270 in each group (pre- and during-COVID-19 cohort). We are therefore adequately powered to detect the expected difference (see pre- and during-COVID-19 group sizes by incarceration status in **Table 3**). Specifically, in the non-incarcerated population (cohort with TB treatment entirely during COVID-19 n=16,369), we could detect up to a 1.2% difference in treatment success with 80% power, whilst in the incarcerated population (cohort with TB treatment entirely during COVID-19 n=1,986), we could detect a 3.5% difference with 80% power.⁴⁸ In addition, logistic models are sufficiently powered when meeting the 5 events per variable (EPV) criterion,⁴⁹ so at the expected event rates of treatment completion (83% pre-COVID-19, 73% during-COVID-19), the model (**Supplement Equation S4**) is powered to accommodate the 14 covariates.

Research ethics:

Ethics approval was obtained by McGill University (McGill IRB: A09-M51-21A) and Universidad Peruana Cayetano Heredia (UPCH IRB SIDISI: 209660). Approval to use SIGTB data was granted by the Peruvian national TB program. The study protocol was also presented to representatives of the Peruvian National Penitentiary Institute. This study is registered in the Peruvian National Institute of Health's study registry (PRISA) (EI00002907).

5.5 Results:

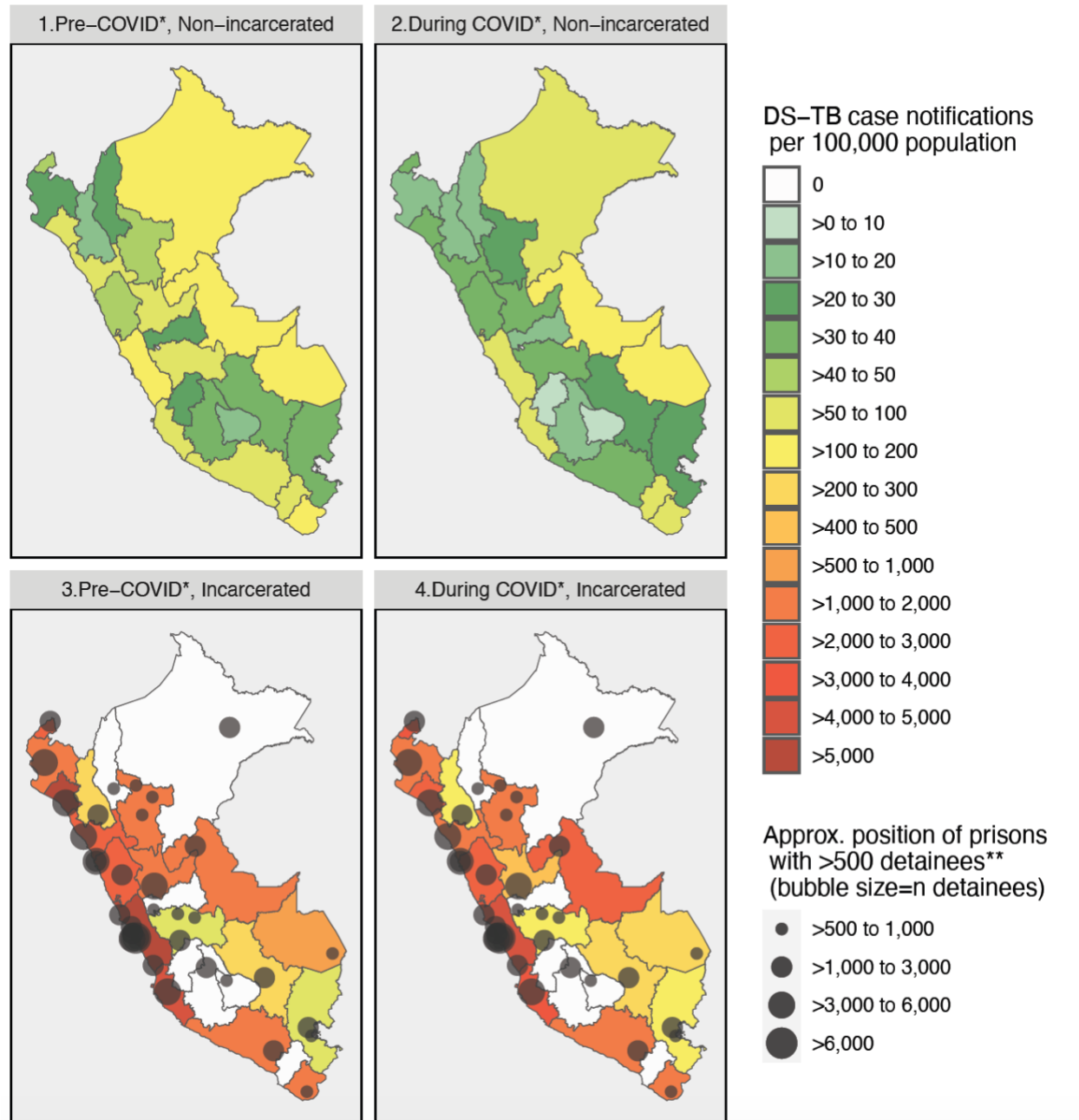
DS-TB case notifications in the incarcerated & non-incarcerated populations pre- & during COVID-19, by region (department)

This aim was based on case notifications in the year prior to COVID-19 (15 Mar 2019 – 15 Mar 2020) and the first year of COVID-19 (16 Mar 2020 – 16 Mar 2021) (see aim-specific timeframes

above). Between 15 Mar 2019 and 16 Mar 2021, 48,352 adult DS-TB cases were notified in Peru, of which 4,776 (9.9%) were incarcerated at the time of their TB diagnosis. Department-level case notifications per 100,000 people are shown in **Figure 2**, by incarceration status and COVID-19 period, and including approximate locations of the country's largest prisons.

To compare case notifications in the prison population to the overall population of each department, incidence rate ratios (IRRs) are presented in **Figure 3**. It should be noted that IRRs here represent notifications in prisons in each department divided by overall notifications in the department, and notifications do not necessarily represent true incidence given under-diagnosis and under-notification of incident TB cases. Exact IRRs by department are listed in Supplement **Table S1**. IRRs between prisons and the total population are high. Overall, IRRs during COVID-19 increased compared to pre-COVID-19 IRRs, due to the larger drop in notifications in the general population compared to in the incarcerated population (covered in more detail in the time series analysis in aim 2).

Figure 2. Drug-susceptible tuberculosis case notifications in the incarcerated vs. non-incarcerated population, per 100,000 people, Pre-and during COVID-19, in Peru, by department (March 2019 to March 2021)



Denominators for incidence in incarcerated and non-incarcerated populations:

- Pre-COVID-19 incarcerated: average incarcerated population of department, Mar 2019 to Feb 2020 (from publicly available INPE data).⁴⁵
- During COVID-19 incarcerated: average incarcerated population of department, Mar 2020 to Feb 2021 (from publicly available INPE data).⁴⁵

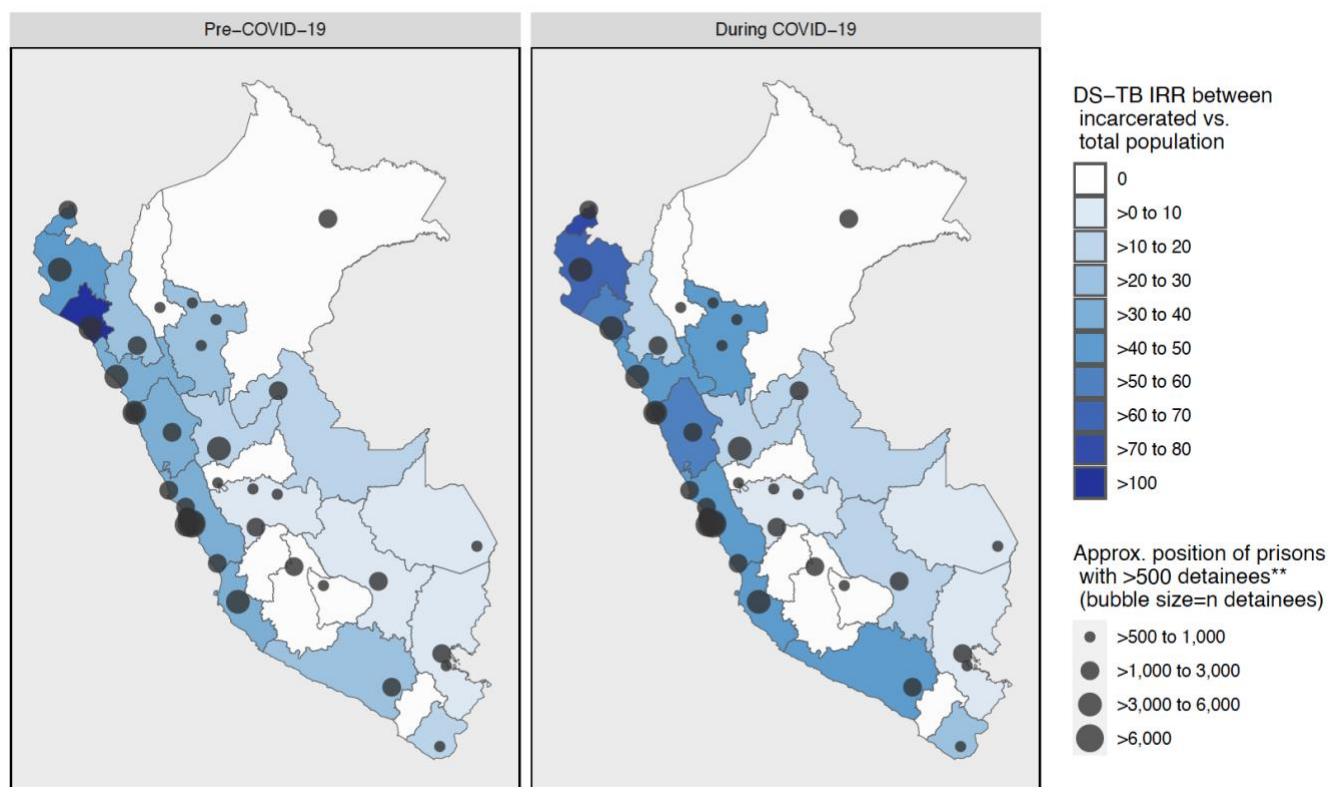
- *Pre-COVID-19 non-incarcerated: census projection for overall 2019 department population,⁴² minus department's pre-COVID prisoner population above.*
- *During COVID-19 non-incarcerated: census projection for overall 2020 department population,⁴² minus department's during-COVID prisoner population above.*

* *Pre-COVID-19 = DS-TB diagnosis between 15 March 2019 and 15 March 2020.*

During COVID-19 = DS-TB diagnosis between 16 March 2020 (start of COVID-19 restrictions in Peru) and 16 March 2021.

** *Showing only prisons with >500 detainees as of March 2019 (n=37 out of a total of 69 prisons in the country at the time)⁴⁵*

Figure 3. Drug-susceptible tuberculosis incidence rate ratio between the incarcerated and total population pre- and during COVID-19* in Peru, by department (March 2019 to March 2021)



IRR=Incidence rate ratio=DS-TB case notifications per 100,000 in prisons / overall DS-TB case notifications per 100,000 in department.

Denominators for incidence in incarcerated and total population:

- *Pre-COVID-19, incarcerated: average incarcerated population of department, Mar 2019 to Feb 2020 (from publicly available INPE data).*⁴⁵
- *During COVID-19, incarcerated: average incarcerated population of department, Mar 2020 to Feb 2021 (from publicly available INPE data).*⁴⁵
- *Pre-COVID-19, total population: census projection for overall 2019 department population*⁴²
- *During COVID-19, total population: census projection for overall 2020 department population*⁴²

* *Pre-COVID-19 = DS-TB diagnosis between 15 March 2019 and 15 March 2020.*

During COVID-19 = DS-TB diagnosis between 16 March 2020 (start of COVID-19 restrictions in Peru) and 16 March 2021.

** *Showing only prisons with >500 detainees as of March 2019 (n=37 out of a total of 69 prisons in the country at the time)*⁴⁵

Interrupted time series analysis of DS-TB case notifications pre- & during COVID-19:

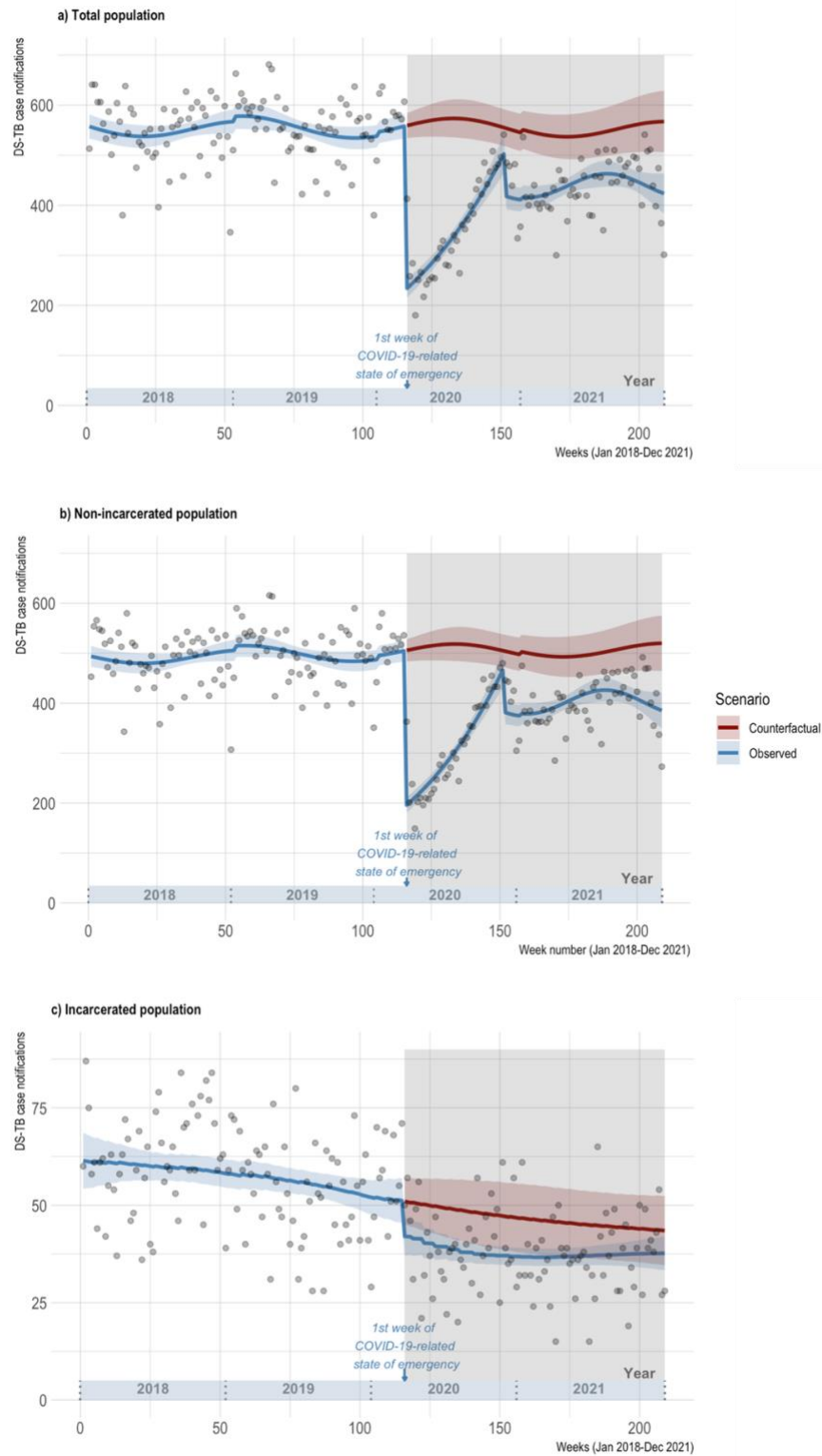
From 1 Jan 2018 to 31 Dec 2021, 101,507 adult DS-TB cases were notified in the national TB program database, of which 10,134 (10.0%) were notified in individuals who were incarcerated at the time of their TB diagnosis. Observed weekly case notifications and the counterfactual trend of notifications expected in the absence of the COVID-19 pandemic in the total, non-incarcerated, and incarcerated populations are shown in **Figure 4**. Case notifications as rates per 100,000 population in the incarcerated and non-incarcerated populations are provided in **Supplement Figure S4**.

Case notifications among the total Peruvian population (**Figure 4a**) dropped sharply in the first week of the enactment of COVID-19-related restrictions in Peru (week 116) compared to the counterfactual expected number of cases in the same week, with 234 predicted cases (95%CI: 215-253) in the observed scenario (start of COVID-19) compared to 559 cases (95%CI: 534-584) in the counterfactual scenario (absence of COVID-19). This represents a 58.1% drop in cases (95%CI: 56.7-59.7) in the observed vs. counterfactual scenarios (**Table 2**).

Upon stratifying non-incarcerated and incarcerated populations, it becomes clear that the overall drop in case notifications was greater among the non-incarcerated population. Among

the non-incarcerated population (**Figure 4b**), 196 cases (95%CI: 180-212) were predicted in week 116 under the observed scenario, vs. 506 cases (95%CI: 484-528) expected in the absence of COVID-19, suggesting a 61.2% (95%CI: 59.9-62.7%) drop in notifications in the first week of the pandemic. Among the incarcerated population (**Figure 4c**), however, 42 cases (95%CI: 37-47) were expected in week 116 under the observed scenario, vs. 51 cases (95%CI: 45-57) in the absence of COVID-19, representing only a 17.7% (95%CI: 17.5-17.9%) drop. The linear components of the trends in the pre-COVID-19 and during COVID-19 phases are described in **Supplement Table S2**.

Figure 4. Interrupted time series of weekly DS-TB case notifications in Peru pre- and during COVID-19, 2018-2021



Red & blue shaded areas = 95%CI

Points = actual weekly case counts

Gray shaded area = COVID-19 pandemic period (following COVID-19-related national state of emergency declaration in Peru on 16 March 2020)³⁷

Table 2. Observed and counterfactual weekly DS-TB case notifications (a) in the first week of the COVID-19 emergency declaration in Peru

Scenario	Total population			Non-incarcerated population			Incarcerated population		
	Cases	95%CI		Cases	95%CI		Cases	95%CI	
Observed	234	215	253	196	180	212	42	37	47
Counterfactual	559	534	584	506	484	528	51	45	57
Observed vs. Counterfactual	% Drop	95%CI		% Drop	95%CI		% Drop	95%CI	
	58.1	56.7	59.7	61.2	59.9	62.7	17.7	17.5	17.9

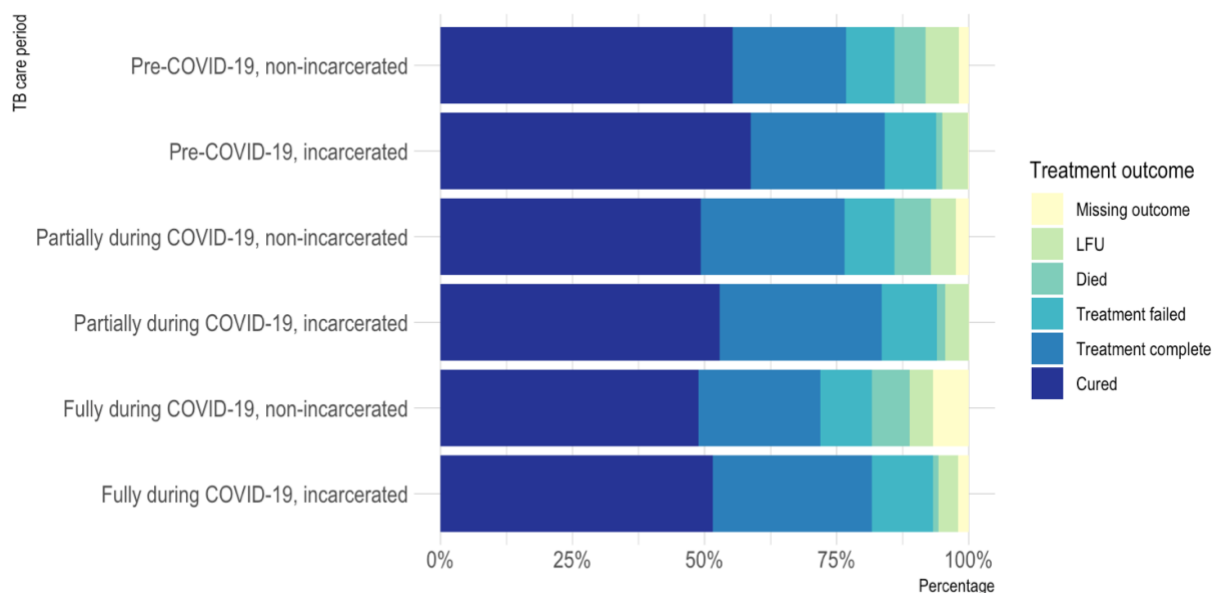
(a) Based on predicted values from each model

DS-TB treatment outcomes in the incarcerated & non-incarcerated populations pre- & during COVID-19:

Treatment outcomes were assessed among 80,535 adults with DS-TB notified between 1 Jan 2018 to 16 Mar 2021. Of 83,039 cases notified in this period, n=140 (0.2%) were excluded due to treatment suspension after an erroneous diagnosis of TB, and n=2,364 (2.9%) were excluded due to missing treatment outcome. The incarcerated population had a lower proportion of missing outcome data than the non-incarcerated population (0.6% vs. 3.1%, respectively) (**Supplement Table S3** and **Figure 5**). This could be either due to easier on-site follow-up of patients in prisons, or due to the fact that incarcerated patients are more likely to be assigned an outcome of lost to follow-up (rather than missing) upon release from prison. Interestingly, the proportion of those with good adherence ($\geq 80\%$ of expected doses taken) was also lower in those with a missing outcome compared to those with an outcome available in the non-incarcerated population (**Supplement Table S3**). This could potentially bias results given that those with low adherence are expected to also have a lower likelihood of treatment success, however, as sensitivity analyses showed that exclusion of those with missing outcome vs. their recategorization as having had an unsuccessful outcome did not significantly alter estimates, this is not expected to have biased the findings (see sensitivity analysis section).

Table 3 summarizes the characteristics of those included (n=80,535), 8,554 (10.6%) of whom were incarcerated at the time of their TB diagnosis. 47,133 individuals received their TB care pre-COVID-19, n=15,044 partially during COVID-19, and n=18,355 fully during COVID-19 (n=3 missing COVID-19 grouping as missing data on treatment regimen for these 3 cases precluded COVID-19 period assignment). Those receiving their TB diagnosis during incarceration were younger than the non-incarcerated population (mean (SD): 32.2 (10.4) vs. 41.2 (18.5)), and a higher proportion were male (99.5% vs. 61.4%), were smokers, and had TB previously, but a lower proportion had diabetes (**Table 3**). The incarcerated population was also more adherent to TB treatment, likely due to stricter treatment monitoring in prisons.

Figure 5. *DS-TB Treatment outcomes in Peru, Jan 2018-Mar 2021, by COVID-19 period and incarceration status*



*TB care period: Receiving TB care pre-COVID-19, partially during, or fully during COVID-19, based on expected length of treatment time (6m, 9m or 12m regimen). See **Table 1** for COVID-19 period explanations. LFU: lost to follow-up.*

Table 3. Characteristics ^(a) of DS-TB patients in Peru by COVID-19 period and incarceration status, 1 Jan 2018-16 Mar 2021.

	Non-incarcerated			Incarcerated		
	Pre-COVID-19	Partially during COVID-19	Fully during COVID-19	Pre-COVID-19	Partially during COVID-19	Fully during COVID-19
Total	N = 41,986	N = 13,623	N = 16,369	N = 5,147	N = 1,421	N = 1,986
Age (years) ^(b)	41.1 (18.8)	41.9 (18.7)	40.9 (17.7)	32.0 (10.3)	32.3 (10.5)	32.5 (10.5)
Sex (male)	25,787 (61.4%)	8,457 (62.1%)	9,978 (61.0%)	5,122 (99.5%)	1,409 (99.2%)	1,977 (99.5%)
Extrapulmonary TB	8,624 (20.5%)	3,230 (23.7%)	2,935 (17.9%)	410 (8.0%)	183 (12.9%)	227 (11.4%)
Type of case						
New	37,416 (89.1%)	12,217 (89.7%)	14,591 (89.1%)	3,725 (72.4%)	951 (66.9%)	1,337 (67.3%)
Previous treatment stopped or failed	1,395 (3.3%)	425 (3.1%)	465 (2.8%)	74 (1.4%)	18 (1.3%)	26 (1.3%)
Relapse	3,175 (7.6%)	981 (7.2%)	1,313 (8.0%)	1,348 (26.2%)	452 (31.8%)	623 (31.4%)
HIV positive	2,117 (5.4%)	1,029 (8.2%)	825 (5.6%)	139 (2.8%)	71 (5.1%)	59 (3.0%)
Diabetes	3,908 (9.9%)	1,317 (10.1%)	1,842 (12.3%)	100 (3.4%)	49 (3.5%)	63 (3.3%)
Smoking	1,896 (4.5%)	569 (4.2%)	645 (4.0%)	2,532 (49.2%)	733 (51.6%)	781 (39.4%)
Type of health insurance						
Private	182 (0.4%)	51 (0.4%)	60 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Employer's ^(c)	9,727 (23.2%)	3,188 (23.5%)	3,614 (22.1%)	8 (0.2%)	2 (0.1%)	5 (0.3%)
Public ^(d)	25,195 (60.1%)	8,762 (64.6%)	11,810 (72.4%)	5,090 (98.9%)	1,403 (98.9%)	1,975 (99.6%)
None	6,796 (16.2%)	1,564 (11.5%)	836 (5.1%)	47 (0.9%)	14 (1.0%)	2 (0.1%)
TB treatment outcome						
Cured	23,651 (56.3%)	6,871 (50.4%)	8,577 (52.4%)	3,026 (58.8%)	752 (52.9%)	1,044 (52.6%)
Died	2,513 (6.0%)	961 (7.1%)	1,265 (7.7%)	62 (1.2%)	22 (1.5%)	21 (1.1%)
Dropped out	2,681 (6.4%)	664 (4.9%)	768 (4.7%)	248 (4.8%)	62 (4.4%)	74 (3.7%)
Treatment complete	9,213 (21.9%)	3,804 (27.9%)	4,046 (24.7%)	1,309 (25.4%)	435 (30.6%)	610 (30.7%)
Treatment failed	3,928 (9.4%)	1,323 (9.7%)	1,713 (10.5%)	502 (9.8%)	150 (10.6%)	237 (11.9%)
Good adherence (>80 of expected doses taken)	36,574 (90.0%)	12,405 (93.2%)	15,083 (94.2%)	4,952 (97.8%)	1,375 (98.4%)	1,950 (98.9%)

(a) Missing data on covariates (among all, non-incarcerated, incarcerated, respectively): diabetes status (8.2%, 6.0%, 27.0%), HIV status (7.3%, 7.8%, 2.8%), adherence (2.6%, 2.8%, 1.4%), health insurance type (0.2%, 0.3%, 0.09%), smoking status (0.2%, 0.2%, 0.07%), extrapulmonary/pulmonary TB (0.01%, 0.02%, 0.0%), and COVID-19 period (0.004%, 0.004%, 0.0%).

(b) Age: Mean (SD). All other covariates: n (%).

(c) Seguro Social de Salud (EsSalud) or police/armed forces

(d) Seguro Integral de Salud (SIS)

As models were fit separately for 1) non-incarcerated, 2) incarcerated, and 3) all (incarcerated and non-incarcerated) cases notified, missing data patterns were explored for all three datasets. The missing data pattern was arbitrary (non-monotone) in all three models. Missingness at random (MAR) is the likely missingness mechanism; missingness completely at random (MCAR) was ruled out (Little's test $p < 0.001$). (See **Table 3** caption for breakdown of covariate missingness by incarceration status). Multiple imputation by chained equations (MICE) was used to impute missing values for covariates. Imputation diagnostics are described in **Supplement Section 3**.

Results of the main analysis (using the imputed data) are shown in **Table 4**. TB treatment success was significantly lower in those receiving TB care entirely during the COVID-19 pandemic compared to prior to COVID-19 in the overall population (OR=0.81, 95%CI: 0.78-0.85) and the non-incarcerated population (OR=0.81 95%CI: 0.77-0.85) when adjusting for other covariates. It was also lower in the incarcerated population (although not statistically significant) (OR=0.88, 95%CI: 0.76-1.01). The effect was less pronounced for those receiving TB care *partially* during COVID-19 (suggesting less disruption in this time period), being significant in the overall and non-incarcerated populations (OR=0.93, 95%CI: 0.89-0.98), and again not significant in the incarcerated population (OR=0.91, 95%CI: 0.77-1.08). This suggests COVID-19-related disruptions adversely affected TB care in Peru overall, especially in those receiving all of their TB care during the pandemic, but that disruptions experienced in the community may have had a lower impact on incarcerated populations.

Factors that significantly reduced the likelihood of treatment success in the overall population (adjusting for other covariates) included male sex, smoking, living with HIV, and relapse or previous treatment for TB. Having only public or no health insurance (compared to private health insurance), considered a proxy for socioeconomic status in our study, was also

associated with lower treatment success. In the incarcerated population however, sex, smoking and health insurance type were not significant predictors of treatment outcome. This is possibly due to factors facilitating TB management in prisons in Peru, including on-site treatment monitoring and follow-up, detainee peer-supporter programs, and special food support provided to detainees with TB, which may contribute to standardizing / equalizing access to TB care among the incarcerated population (relative to the higher variation in access to care among the non-incarcerated), consequently attenuating the effect of other factors (socioeconomic status, etc) in the incarcerated population. Lastly, the protective effect of adherence is also well-established in other studies, although the strong effect observed here may be an underestimation of the true effect, given that expected doses were based on initial regimen assigned, and therefore inadequately reflect adherence in patients whose treatment was extended (who are also more likely to have had poorer outcomes).

Table 4. Effect of COVID-19, incarceration, and other covariates^(a) on DS-TB treatment success (adjusted odds ratios for treatment success from logistic regression, using imputed^(b) values for missing covariates)

	All			Non-incarcerated			Incarcerated		
	OR	95%CI		OR	95%CI		OR	95%CI	
COVID-19 period: (Ref=TB care pre-COVID-19)									
TB care fully during COVID-19	0.82	0.78	0.85	0.81	0.78	0.85	0.88	0.76	1.01
TB care partially during COVID-19	0.93	0.89	0.98	0.94	0.89	0.98	0.91	0.77	1.08
Sex, male (Ref=female)	0.81	0.77	0.84	0.79	0.76	0.82	0.93	0.40	2.16
HIV positive	0.43	0.40	0.46	0.43	0.40	0.47	0.69	0.50	0.94
Diabetes	0.98	0.92	1.04	0.99	0.93	1.06	0.74	0.52	1.04
Extrapulmonary TB	1.40	1.33	1.47	1.38	1.31	1.45	2.13	1.64	2.76
Type of case: (Ref=new case)									
Previous TB treatment stopped or failed	0.38	0.35	0.41	0.40	0.36	0.44	0.54	0.35	0.84
Relapse	0.78	0.74	0.83	0.72	0.68	0.77	0.79	0.69	0.90
Smoking	0.86	0.81	0.91	0.61	0.56	0.66	1.03	0.91	1.16
Insurance type: (Ref=private insurance)							Insurance type: (Ref=employer's insurance) (c)		
Employer's insurance (d)	0.76	0.54	1.08	0.75	0.53	1.06			
Public insurance (e)	0.67	0.48	0.95	0.64	0.45	0.90	0.83	0.19	3.71

None	0.68	0.48	0.97	0.69	0.49	0.97	1.49	0.26	8.38
Good adherence ($\geq 80\%$ of expected doses taken)	7.90	7.46	8.38	7.52	7.09	7.98	18.71	12.88	27.18

(a) For (non-linear) effect of age covariate, see **Figure 6**.

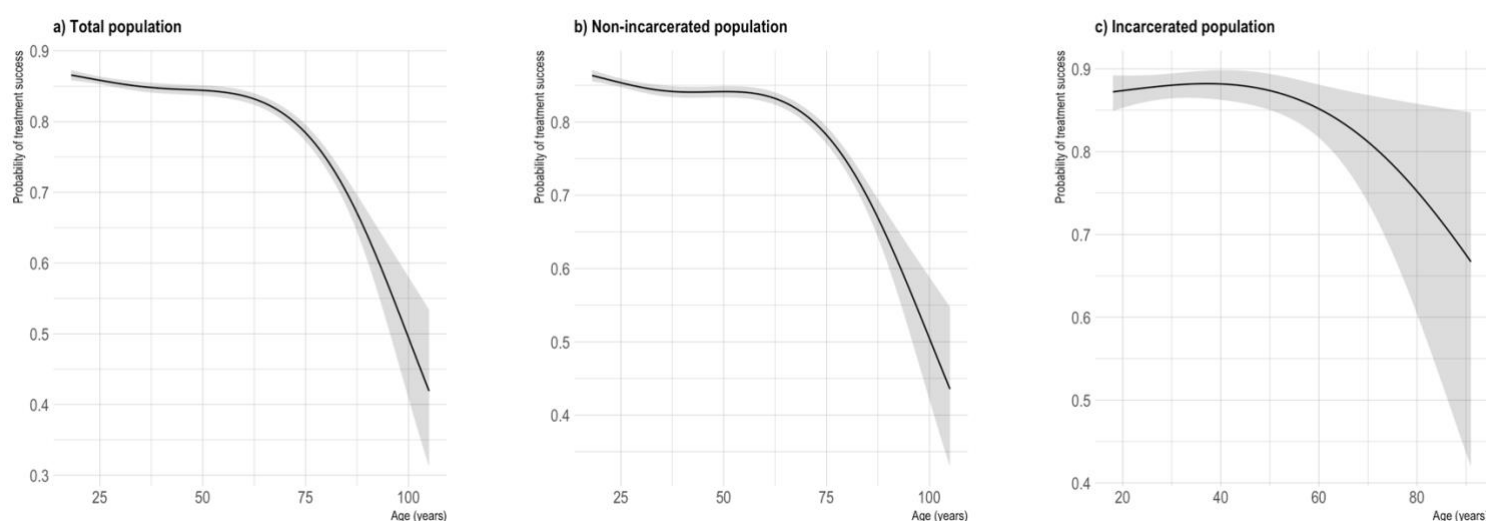
(b) Via multiple imputation by chained equations (MICE)

(c) None with private insurance in incarcerated population

(d) Seguro Social de Salud (EsSalud) or police/armed forces

(e) Seguro Integral de Salud (SIS)

Figure 6. Non-linear relationship of age vs. treatment success



Penalised spline functions for age ((a) $df=4$, (b) $df=4$ and (c) $df=2$). Plots show predicted values of probability of treatment success across values of age, holding all other covariates constant (COVID-19 period = Pre-COVID-19, sex = male, HIV = negative, diabetes = no, smoking = no, adherence category $\geq 80\%$ of doses taken, insurance type = public, case type = new, site of TB = pulmonary) i.e., these predictions do not represent treatment success probabilities for the overall population but for a new case of pulmonary TB in a HIV-negative, non-diabetic, non-smoking, $\geq 80\%$ adherent male with public health insurance, receiving TB care pre-COVID-19. Shaded area = 95%CI.

Sensitivity analysis:

In the first sensitivity analysis, estimates using MICE to impute missing *covariate* data (the main analysis) were compared to estimates resulting from complete case analysis only (removal of observations with missing covariate data). Estimates are similar across both analyses, as shown

in **Supplement Figure S6**. The second sensitivity analysis compared approaches to handling missing *outcome* data, comparing estimates from complete case analysis (deletion of those with missing outcome, the main analysis) to re-classifying those with missing outcome as having had an unsuccessful outcome – again, estimates across these approaches are similar (**Supplement Figure S7**).

5.6 Discussion:

This country-wide analysis of TB case notifications and treatment outcomes in the non-incarcerated and incarcerated populations of Peru prior to and during the COVID-19 pandemic highlights that the burden of TB is extremely high in prisons compared to the overall population, which is in line with previous studies in other South American countries¹² but had prior to this not yet been described in Peru.

Further, although it is known that TB case notifications dropped dramatically in Peru during COVID-19,³ our analysis shows that this drop was much more pronounced in the non-incarcerated population than in the incarcerated population, suggesting reduced disruption of TB services in the prison setting. This is likely due to on-site TB screening at entry into prisons as well as uninterrupted identification of symptomatic patients by health promoters and TB nurses in prisons in Peru, which continued to facilitate case detection in the incarcerated population even during COVID-19.

In addition, we show that, in the non-incarcerated population, TB treatment success was significantly lower in those who received their TB care entirely or partially during the COVID-19 pandemic, compared to pre-COVID-19, but that this was not the case in the incarcerated population. A possible explanation for this is that, particularly during COVID-19-associated lockdowns, barriers to seeking care may have been accentuated in non-incarcerated populations who faced clinic closures or reduced clinic hours,⁵⁵ or who had to commute to clinics in the context of transport restrictions, while incarcerated populations retained on-site access to care (as the on-site TB clinic sections of prisons remained accessible during the usual

hours throughout the pandemic). Further, the adverse effect of TB care disruptions during COVID-19 on treatment outcomes may have been attenuated in prisons due to enhanced TB screening (e.g., at entry into prison and regularly thereafter) or treatment monitoring in this population. This is plausible especially in light of specific interventions implemented to improve TB management in prisons in Peru, financed by The Global Fund,^{56,57} including early TB screening initiatives (at prison entry and annually).⁵⁷

Unfortunately, lacking data on symptom onset, we could not explore diagnostic delays (i.e. time from symptom onset to diagnosis). A suitable indicator of disease severity was also unavailable in SIGTB and could therefore not be used as a proxy for diagnostic delay. We therefore could not explore whether earlier diagnosis acted as a mediator of the effect of COVID-19 period on TB treatment success. Earlier diagnosis in prisons compared to in the non-incarcerated population however is possible, given that detainees receive a physical health evaluation at entry, and that detainee health promoters and peer-supporters assist in identifying TB symptoms early among cellmates.

Other limitations of our study include challenges inherent in the use of secondary data collected for routine programmatic purposes. This includes the fact that cases are often under-notified in national TB program databases,^{58,59} including SIGTB,⁶⁰ with notified TB cases in Peru representing 81.4% of the estimated national burden prior to COVID-19 (in 2019)⁶¹ and 60.9% of the estimated burden in 2020.⁶¹ This suggests that estimates of the effect of receiving TB treatment during vs. prior to COVID-19 on treatment success could be biased towards the null, if patients with poorer treatment outcomes were less likely to be notified during the pandemic.

Another limitation is the lack of a dynamic indicator of incarceration status in national TB program data. As incarceration is only captured in the SIGTB database for those who received a TB diagnosis while incarcerated, the present analysis could not consider prior incarceration, incarceration after case notification, or length of incarceration. Although the majority of incarcerated individuals in Peru serve sentences longer than 5 years,⁶² individual-level data on

length of stay would have allowed a more precise – and dynamic - definition of incarceration status in the analysis. In addition, other data limitations necessitated reliance on imperfect indicators. For example, the lack of data on individuals' socioeconomic status meant that health insurance type was used as an imperfect proxy. Similarly, our estimates of the effect of adherence on treatment outcomes are limited due to having information only on the number of doses at exit, but not the proportion of doses missed throughout an individual's treatment. As a result, the adherence proportion was estimated based on individuals' total doses expected for their treatment regimen and their time on treatment before exit, possibly leading to imperfect classification of true adherence.

Strengths of our study include its size and representativeness of all case notifications in the country. In addition, we sought to underline the urgent yet under-studied public health concern of TB in prisons, highlighting the impact of this disease in a neglected population. Prisons must not be overlooked in the overall TB response, firstly because the right to health extends to individuals experiencing incarceration, as it does to everyone. Incarcerated populations should therefore not be subjected to conditions that put their health at much higher risk than the general population. Secondly, our analysis suggests a lower extent of COVID-related TB care disruptions in prisons, and other South American analyses show higher TB treatment success in prisons compared to the general population.¹⁹ This indicates that prisons are unique settings in which TB prevention and treatment is both urgent yet feasible, making clear that prisons should be key priorities for TB elimination efforts.

5.7 Contributors:

Study conceptualisation: CUG, LM, MP, LF. Data curation and analysis/visualisation: LF, SH.

Study supervision: CUG, MP, LM, SH. Writing of original draft: LF. Review and editing: CUG, MP, LM, SH, AB, GCC, JRV, RCT, MCA. Access and verification of all data reported in the study: LF. All authors agreed with the decision to submit for publication.

5.8 Conflicts of interest:

MP serves as an advisor to several non-profit organizations including Bill & Melinda Gates Foundation, WHO, Stop TB Partnership and FIND. He has no financial or industry conflicts. CUG has received research support from the International Development Research Centre (Canada) and the Canadian Institutes of Health Research, the National Institutes of Health, FIND, and Abbott for projects unrelated to this work. CUG has also received honoraria from Molbio and Abbott for presentations unrelated to this work. The other authors declared no conflicts of interest.

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5.12 Supplement

Supplement Section 1 (Aim 1):

Incidence Rate Ratio (IRR) calculations and data sources:

$$\text{IRR} = \frac{\text{DS-TB case notifications per 100,000 in incarcerated population of department}}{\text{DS-TB case notifications per 100,000 in total population of department}}$$

Denominators for incidence in incarcerated population:

- Pre-COVID-19: average incarcerated population of department, Mar 2019 to Feb 2020 (from publicly available INPE data).¹
- During COVID-19: average incarcerated population of department, Mar 2020 to Feb 2021 (from publicly available INPE data).¹

Denominators for incidence in total population:

- Pre-COVID-19: census projection for overall 2019 department population²
- During COVID-19: census projection for overall 2020 department population²

Table S1. IRRs for DS-TB in the prison vs. total population in Peru, by department

Department	Incidence rate ratio (IRR) (a)	
	Pre-COVID-19 (b)	During COVID-19 (b)
Amazonas	0.00	0.00
Ancash	39.96	56.02
Apurimac	0.00	0.00
Arequipa	24.76	40.51
Ayacucho	0.00	0.00
Cajamarca	20.17	10.52
Callao	0.00	0.00
Cusco	7.13	10.33
Huancavelica	0.00	0.00
Huanuco	19.17	11.19
Ica	33.76	42.29
Junin	1.99	5.55
La Libertad	31.12	44.27
Lambayeque	100.33	58.48
Lima	35.44	42.10
Loreto	0.00	0.00
Madre de Dios	6.90	1.92
Moquegua	0.00	0.00
Pasco	0.00	0.00
Piura	40.26	61.26
Puno	2.58	6.11
San Martin	28.10	41.96
Tacna	16.04	22.63
Tumbes	48.28	71.19
Ucayali	10.52	19.36

a) IRR=incidence in prisons / overall incidence in department

b) Pre-COVID-19 = DS-TB diagnosis between 15 March 2019 and 15 March 2020. During COVID-19 = DS-TB diagnosis between 16 March 2020 (start of COVID-19 restrictions in Peru) and 16 March 2021.

Supplement Section 2 (Aim 2):

Equation S1: Negative binomial regression for weekly DS-TB case notifications in the total population:

$$\log(TB\_cases\_total) = \beta_0 + \beta_1 X_{phase2} + \beta_2 X_{phase3} + \beta_3 X_{time} + \beta_4 X_{phase1:sin\_phase1} + \beta_5 X_{phase2:time} + \beta_6 X_{phase3:time} + \beta_7 X_{phase3:sin\_phase3} + \log(population\_total)$$

Where:

- TB_cases_total = weekly DS-TB case notifications in the total population of Peru
- Phase 1 = pre-COVID-19: weeks 1-115 (COVID-19 national state of emergency declared in week 116). Coded 1 in weeks 1-115, 0 otherwise.
- Phase 2 = recovery period (linear increase following initial drop in cases), weeks 116-151. Coded 1 in weeks 116-151, 0 otherwise.
- Phase 3 = post-recovery period (resumption of harmonic trend similar to pre-COVID-19), weeks 152 onwards. Coded 1 in weeks 152-209, 0 otherwise.
- Time = Weeks (1 to 209)
- Sin_phase1 = harmonic trend for phase 1, $\sin(3\pi Time/115)$. (See **Figure S1**).
- Sin_phase3 = harmonic trend for phase 3, $\sin(2\pi Time/58)$. (See **Figure S1**).
- Population_total = the total population size, based on annual (2018, 2019, 2020 and 2021) population projections from the Peruvian census³

Equation S2: Negative binomial regression for weekly DS-TB case notifications in the non-incarcerated population:

$$\log(TB\_cases\_noninc) = \beta_0 + \beta_1 X_{phase2} + \beta_2 X_{phase3} + \beta_3 X_{time} + \beta_4 X_{phase1:sin\_phase1} + \beta_5 X_{phase2:time} + \beta_6 X_{phase3:time} + \beta_7 X_{phase3:sin\_phase3} + \log(population\_noninc)$$

Where:

- TB_cases_noninc = weekly DS-TB case notifications in the non-incarcerated population of Peru
- $Phase\ 1$ = pre-COVID-19: weeks 1-115 (COVID-19 national state of emergency declared in week 116). Coded 1 in weeks 1-115, 0 otherwise.
- $Phase\ 2$ = recovery period (linear increase following initial drop in cases), weeks 116-151. Coded 1 in weeks 116-151, 0 otherwise.
- $Phase\ 3$ = post-recovery period (resumption of harmonic trend similar to pre-COVID-19), weeks 152 onwards. Coded 1 in weeks 152-209, 0 otherwise.
- $Time$ = Weeks (1 to 209)
- Sin_phase1 = harmonic trend for phase 1, $\sin(3\pi Time/115)$. (See **Figure S2**).
- Sin_phase3 = harmonic trend for phase 3, $\sin(2\pi Time/58)$. (See **Figure S2**).
- $Population\_noninc$ = the non-incarcerated population size. The non-incarcerated population size is based on annual (2018, 2019, 2020 and 2021) population projections from the Peruvian census,³ minus the average annual incarcerated population, from Peru's penitentiary institute database¹

Equation S3: Negative binomial regression for weekly DS-TB case notifications in the incarcerated population:

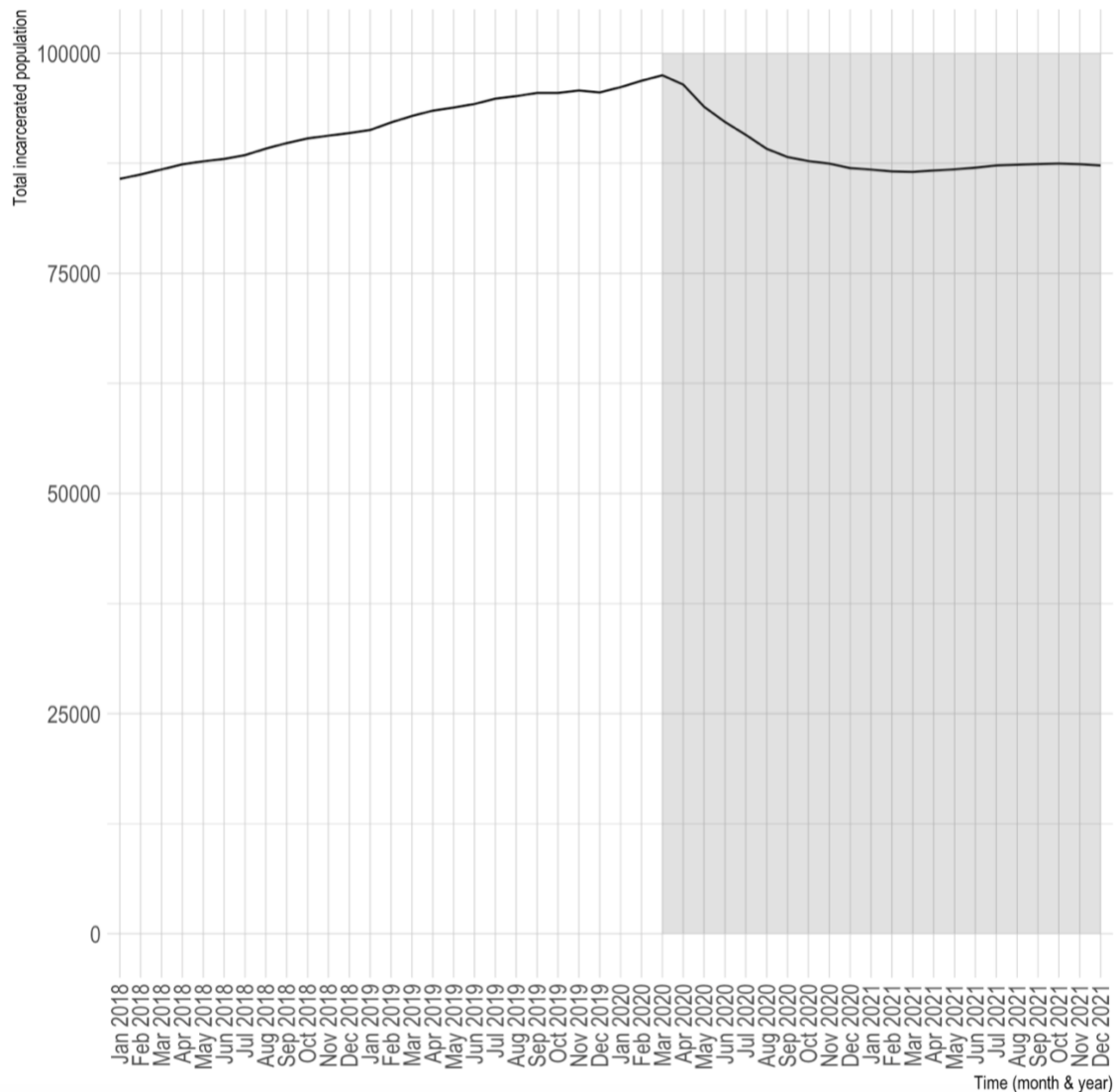
$$\log(TB\_cases\_incarc) = \beta_0 + \beta_1 X_{COVID-19} + \beta_2 X_{Time} + \beta_3 X_{COVID:Time} + \beta_4 X_{t.sin} + \log(population\_incarc)$$

Where:

- TB_cases_incarc = weekly DS-TB case notifications in the incarcerated population of Peru
- $COVID-19$ = indicator variable for COVID-19 period, coded 0 pre-COVID (weeks 1 to 115) and coded 1 during COVID (weeks 116 to 209).
- $Time$ = weeks (1 to 209)
- $t.sin$ = harmonic trend, $\sin(2\pi Time/209)$. (See **Figure S3**).

- *Population_incarc* = the incarcerated population size, based on monthly counts of the incarcerated population from Peru's penitentiary institute database¹

Figure S1. Total number of people experiencing incarceration in Peru, by month, 2018-2021



Population estimates from Peruvian National Penitentiary Institute (INPE)¹

Shaded area: COVID-19 pandemic period

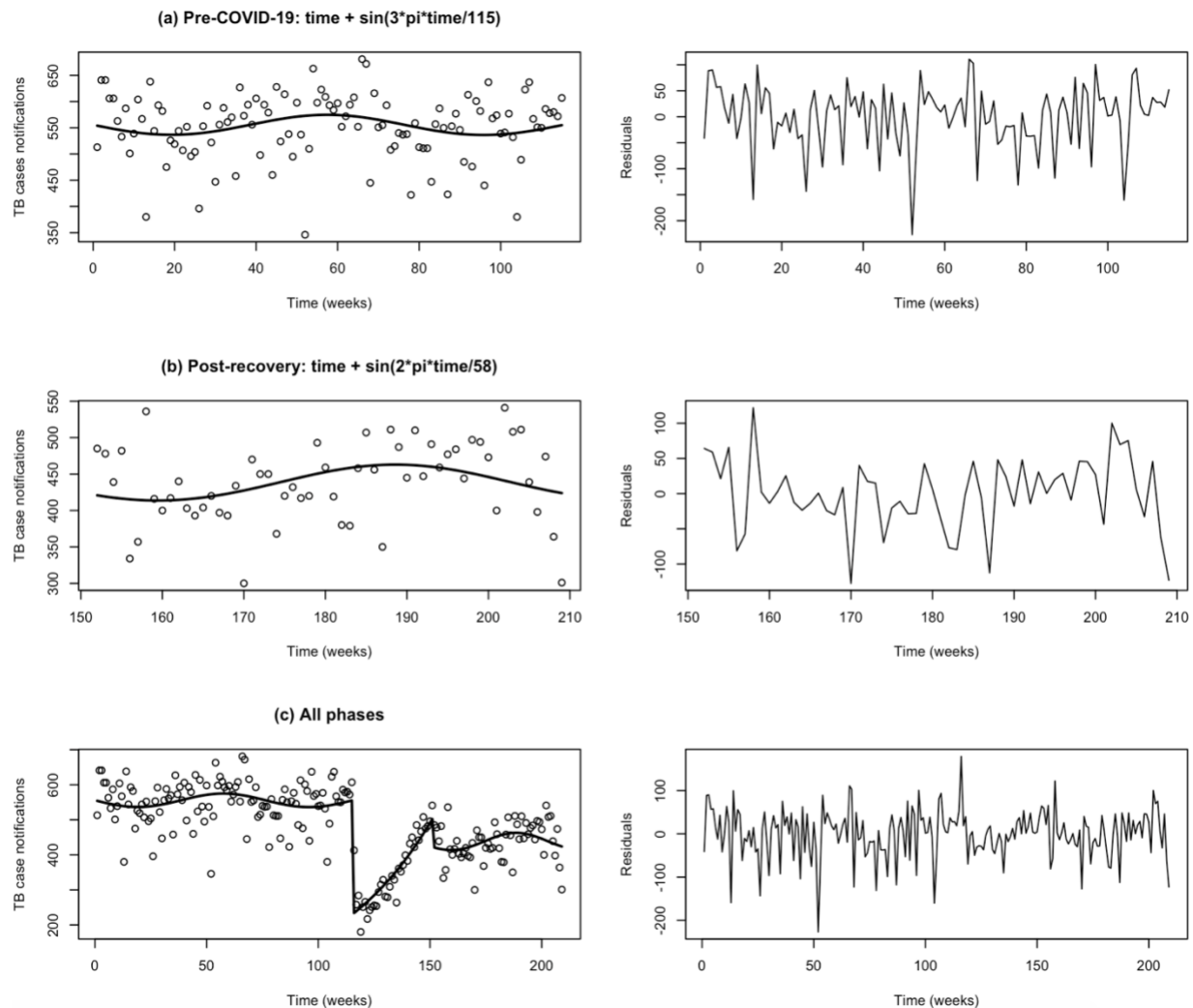
Observed values vs. fitted trend and detrended residuals for TB case notifications over time:

Figures S2-S4 show the harmonic terms used to model time in the non-linear phases, and the corresponding detrended residuals. Harmonic terms were defined as appropriate to the trend,

e.g. $\sin\left(\frac{w \times \pi \times time}{total\ time}\right)$ where w is the number of waves in the phase, $time$ is the week number (e.g. from 1 to 209) and $total\ time$ is the total number of weeks in the phase.

In addition to the detrended residuals, Durbin-Watson (DW) test results of 1.91 ($p=0.267$), 1.89 ($p=0.216$), and 2.03 ($p=0.574$) in the total population, non-incarcerated population, and incarcerated population models, respectively, indicate no significant autocorrelation (DW values close to 2 and $p>0.05$ suggest absence of significant autocorrelation).

Figure S2: Observed values vs. fitted trend (left) and detrended residuals (right) for the total population model (non-incarcerated and incarcerated)

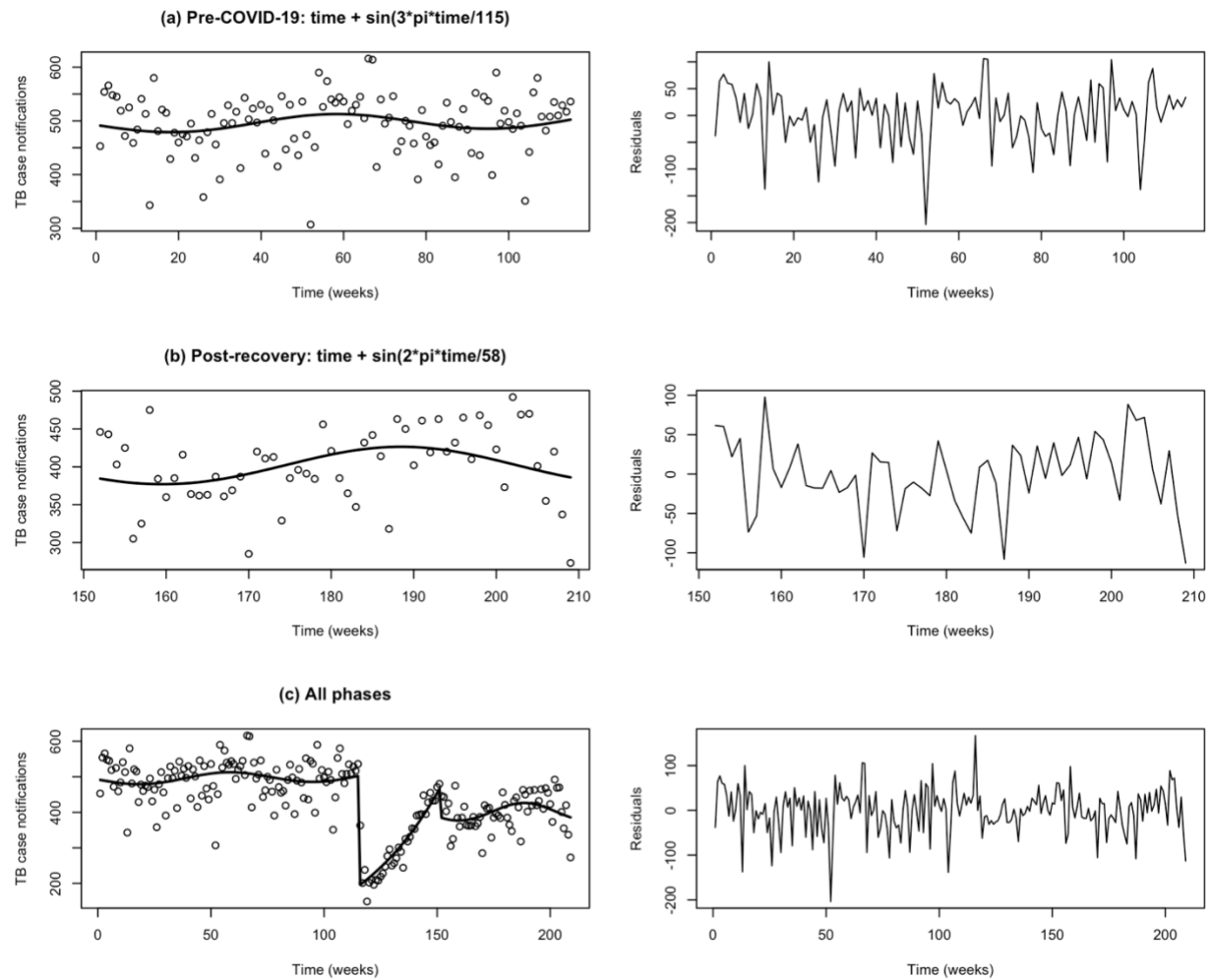


Phase 1: Pre-COVID-19 (Week 1 to 115)

Phase 2: During COVID-19, recovery phase (Week 116 to 151)

Phase 3: During COVID-19, post-recovery phase (Week 151 to 209)

Figure S3: Observed values vs. fitted trend (left) and detrended residuals (right) for the non-incarcerated population model



Phase 1: Pre-COVID-19 (Week 1 to 115)

Phase 2: During COVID-19, recovery phase (Week 116 to 151)

Phase 3: During COVID-19, post-recovery phase (Week 151 to 209)

Figure S4: Observed values vs. fitted trend (left) and detrended residuals (right) for the incarcerated population model

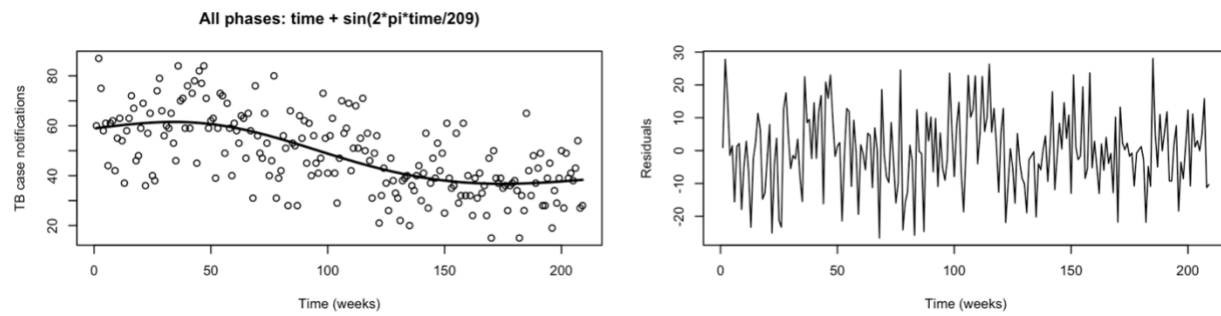


Figure S5. DS-TB case notification rates (per 100,000 population) in Peru pre- and during COVID-19, 2018-2021.

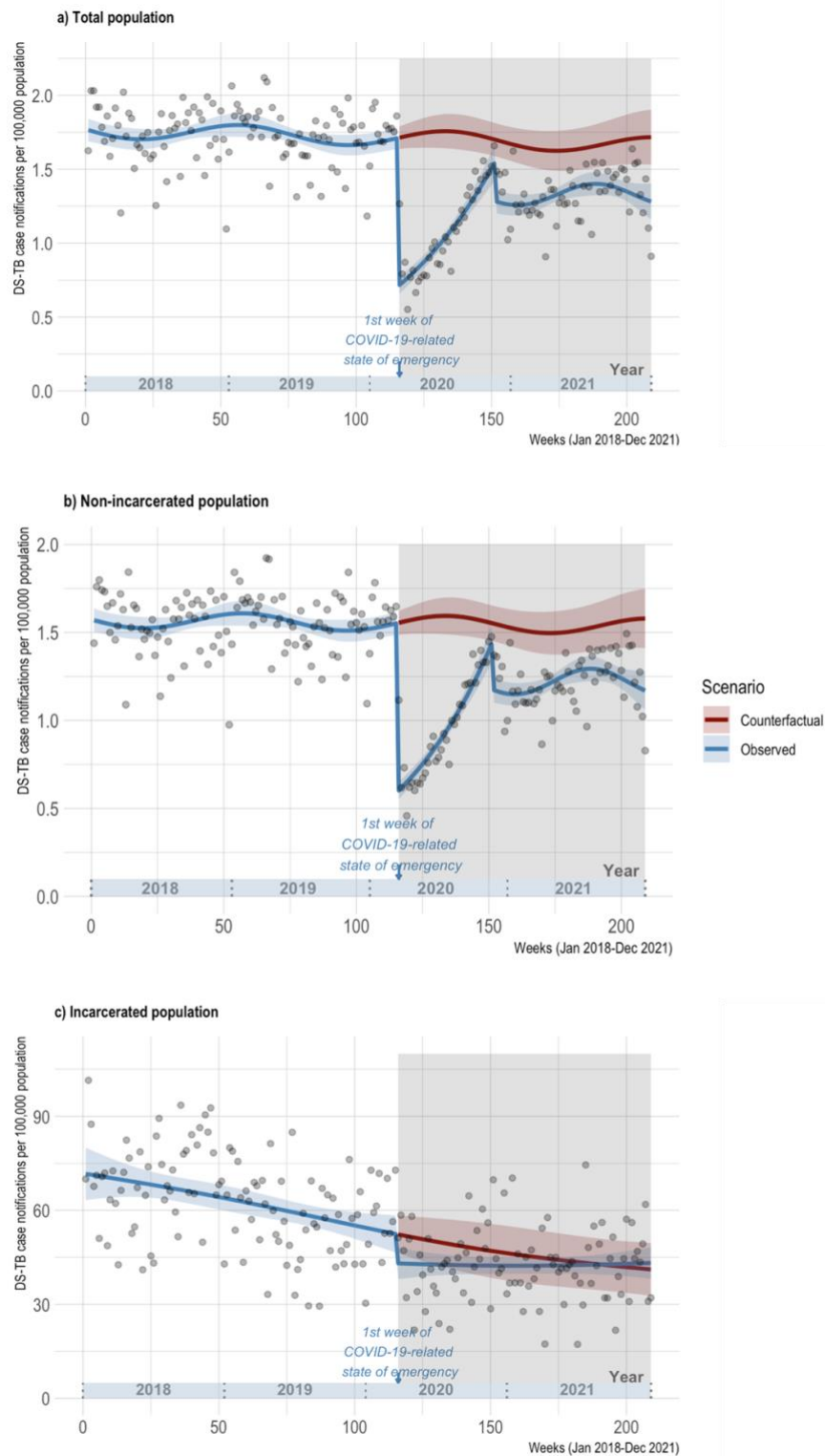


Table S2. Linear component of trends in DS-TB case notifications in Peru pre- and during the COVID-19 pandemic

	Phase 1			Phase 2			Phase 3		
Total population (a)									
	Incidence rate ratio (b)	95%CI		Incidence rate ratio (b)	95%CI		Incidence rate ratio (b)	95%CI	
Per week	1.00	1.00	1.00	1.02	1.02	1.03	1.00	1.00	1.00
Per month	1.00	1.00	1.00	1.09	1.07	1.11	1.00	0.99	1.01
Non-incarcerated population (a)									
	Incidence rate ratio (b)	95%CI		Incidence rate ratio (b)	95%CI		Incidence rate ratio (b)	95%CI	
Per week	1.00	1.00	1.00	1.03	1.02	1.03	1.00	1.00	1.00
Per month	1.00	1.00	1.00	1.10	1.09	1.12	1.00	0.99	1.01
Incarcerated population (c)									
	Pre-COVID-19			During COVID-19					
	Incidence rate ratio (d)	95%CI		Incidence rate ratio (d)			95%CI		
Per week	1.00	1.00	1.00	1.00			1.00	1.00	
Per month	0.99	0.98	0.99	1.00			0.99	1.01	

(a) Phases in the non-incarcerated and total population models:

Phase 1 = pre-COVID-19: weeks 1-115 (COVID-19 national state of emergency declared in week 116). Coded 1 in weeks 1-115, 0 otherwise. Phase 2 = recovery period (linear increase following initial drop in cases), weeks 116-151. Coded 1 in weeks 116-151, 0 otherwise. Phase 3 = post-recovery period (resumption of harmonic trend similar to pre-COVID-19), weeks 152 onwards. Coded 1 in weeks 152-209, 0 otherwise.

(b) Slope for linear component of trend in each phase, i.e., increase in cases per week in each phase (where 'time' = weeks [1-209]): Phase 1: $e^{\beta_{time}}$. Phase 2: $e^{(\beta_{time} + \beta_{phase\ 2:time})}$. Phase 3: $e^{(\beta_{time} + \beta_{phase\ 3:time})}$.

See **Supplement Equations S1 and S2** for full models, and **Supplement Figures S1 and S2** for harmonic terms.

(c) Phases in the incarcerated population model: During COVID-19: Indicator for COVID-19, equal to 0 prior to COVID-19 and equal to 1 in first week of COVID-19 restrictions and thereafter (as of week 116, declaration of COVID-19-related national state of emergency).

(d) Slope for linear component of trend pre-COVID-19 and during COVID-19, i.e., increase in cases per week in each phase (where 'time' = weeks [1-209]): Pre-COVID-19: $e^{\beta_{time}}$. During COVID-19: $e^{(\beta_{time} + \beta_{covid:time})}$.

See **Supplement Equation S3** for full model, and **Supplement Figure S3** for harmonic term.

In the total and non-incarcerated population, cases increased by 2% (95%CI: 2-3%) each week in Phase 2 (IRR: 1.02, 95%CI: 1.02-1.03), the recovery period in which cases increased gradually after the large initial drop in the first week of COVID-19. In Phase 3 (post-recovery), the trend in cases returned to having no significant change in cases per week (IRR: 1.00, 95%CI: 1.00-1.00),

similar to the pre-COVID-19 trend. In the incarcerated population, there was a 1% decrease in case notifications per month in the pre-COVID-19 period (95%CI: 1-2%), and no change in cases per month in the during-COVID-19 period.

Supplement Section 3 (Aim 3):

Table S3. Summary of characteristics of DS-TB patients in Peru with available vs. missing treatment outcome data:

	Total population		Non-incarcerated population		Incarcerated population	
	Outcome available	Outcome missing	Outcome available	Outcome missing	Outcome available	Outcome missing
Total	N = 80,535	N = 2,364	N = 71,981	N = 2,311	N = 8,554	N = 53
Age (years)	40.3 (18.1)	42.8 (18.2)	41.2 (18.5)	42.9 (18.3)	32.2 (10.4)	35.9 (13.7)
Sex, male	52,732 (65.5%)	1,462 (61.8%)	44,224 (61.4%)	1,409 (61.0%)	8,508 (99.5%)	53 (100.0%)
Extrapulmonary TB	15,609 (19.4%)	712 (30.1%)	14,789 (20.5%)	701 (30.3%)	820 (9.6%)	11 (20.8%)
Type of case						
New	70,238 (87.2%)	2,136 (90.4%)	64,225 (89.2%)	2,090 (90.4%)	6,013 (70.3%)	46 (86.8%)
Previous treatment stopped or failed	2,405 (3.0%)	54 (2.3%)	2,287 (3.2%)	54 (2.3%)	118 (1.4%)	0 (0.0%)
Relapse	7,892 (9.8%)	174 (7.4%)	5,469 (7.6%)	167 (7.2%)	2,423 (28.3%)	7 (13.2%)
HIV positive	4,240 (5.7%)	132 (6.6%)	3,971 (6.0%)	131 (6.8%)	269 (3.2%)	1 (2.0%)
Diabetes	7,279 (9.8%)	234 (11.1%)	7,067 (10.4%)	230 (11.1%)	212 (3.4%)	4 (9.1%)
Smoking	7,156 (8.9%)	94 (4.0%)	3,110 (4.3%)	81 (3.5%)	4,046 (47.3%)	13 (24.5%)
Type of health insurance						
Private	293 (0.4%)	8 (0.3%)	293 (0.4%)	8 (0.3%)	0 (0.0%)	0 (0.0%)
Employer's (a)	16,545 (20.6%)	1,071 (45.5%)	16,530 (23.0%)	1,071 (46.5%)	15 (0.2%)	0 (0.0%)
Public (b)	54,237 (67.5%)	1,179 (50.1%)	45,769 (63.8%)	1,126 (48.9%)	8,468 (99.1%)	53 (100.0%)
None	9,259 (11.5%)	97 (4.1%)	9,196 (12.8%)	97 (4.2%)	63 (0.7%)	0 (0.0%)
COVID-19 period						
Pre-COVID-19 TB care	47,133 (58.5%)	802 (33.9%)	41,986 (58.3%)	791 (34.2%)	5,147 (60.2%)	11 (20.8%)
TB care fully during COVID-19	18,355 (22.8%)	1,230 (52.0%)	16,369 (22.7%)	1,189 (51.4%)	1,986 (23.2%)	41 (77.4%)
TB care partially	15,044 (18.7%)	332 (14.0%)	13,623 (18.9%)	331 (14.3%)	1,421 (16.6%)	1 (1.9%)

during COVID-19						
Good adherence (>=80% of expected doses taken)	72,342 (92.3%)	120 (78.9%)	64,065 (91.6%)	116 (78.4%)	8,277 (98.1%)	4 (100.0%)

(a) Seguro Social de Salud (EsSalud) or police/armed forces (b) Seguro Integral de Salud (SIS)

Missing data on covariates (in total population): Extrapulmonary/pulmonary TB: n=12, HIV: n=6,269, diabetes: n=6,866, smoking: n=138, health insurance type: n=210, COVID-19 period: n=3, adherence: n=4,343.

Equation S4

Logistic regression for DS-TB treatment outcomes:

(Separate models for the total, incarcerated, and non-incarcerated populations)

$$\text{logit}(p(Y = 1|X)) = \beta_0 + \beta_1 X_{\text{COVID-19\_full}} + \beta_2 X_{\text{COVID-19\_partial}} + \text{spline}(X_{\text{age}}) + \beta_3 X_{\text{sex}} + \beta_4 X_{\text{HIV}} + \beta_5 X_{\text{diabetes}} + \beta_6 X_{\text{EPTB}} + \beta_7 X_{\text{type\_relapse}} + \beta_8 X_{\text{type\_previous}} + \beta_9 X_{\text{smoking}} + \beta_{10} X_{\text{insurance\_employer}} + \beta_{11} X_{\text{insurance\_public}} + \beta_{12} X_{\text{insurance\_none}} + \beta_{13} X_{\text{adherence}}$$

Where:

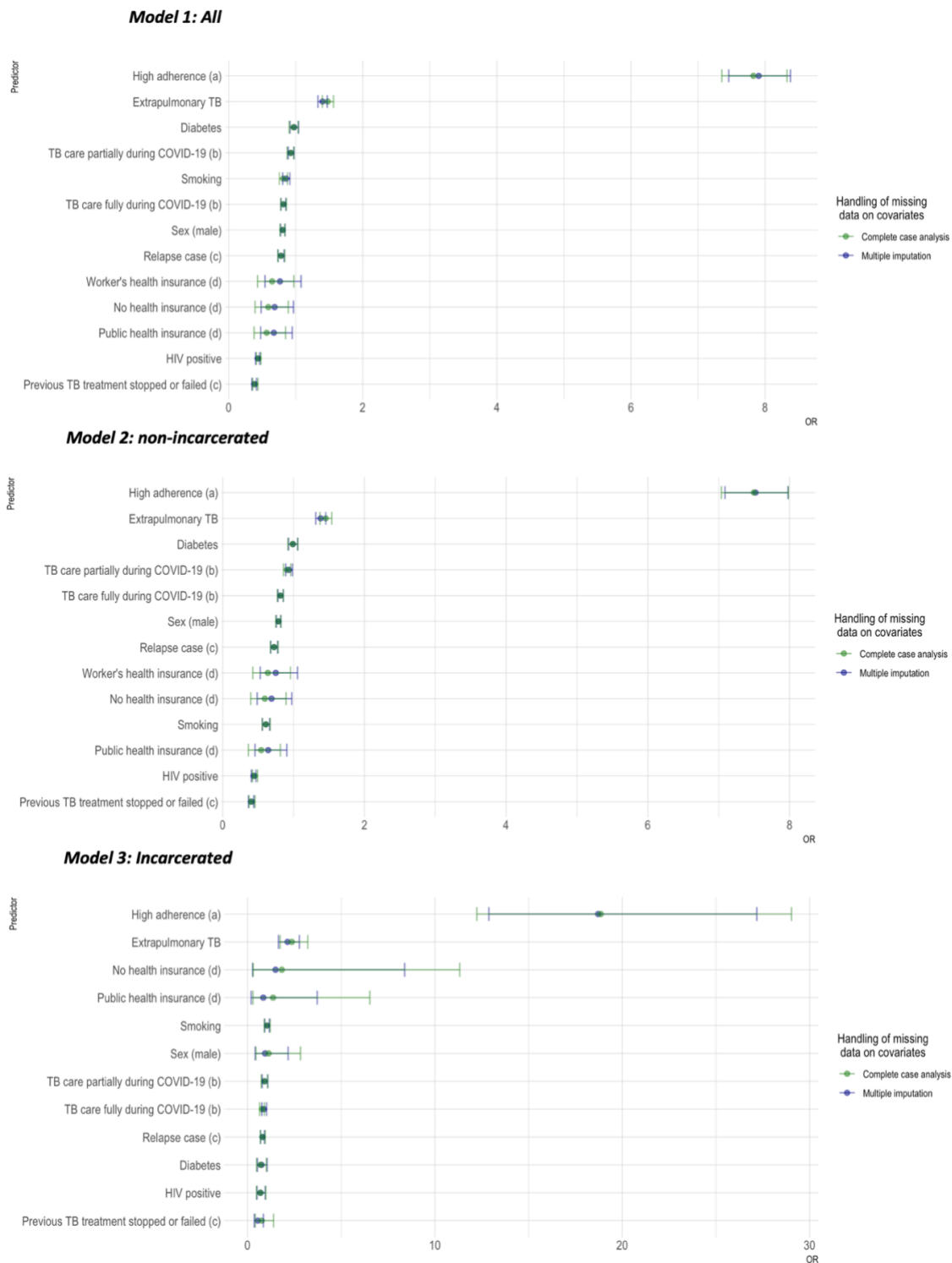
- $Y=1$: DS-TB treatment success (cure or treatment complete)
- COVID-19_full : TB care fully during the COVID-19 pandemic (vs. pre-COVID-19)
- COVID-19_partial : TB care partially during the COVID-19 pandemic (vs. pre-COVID-19)
- EPTB : extrapulmonary TB (vs. pulmonary TB)
- Type_relapse : Type of case: relapse (vs. new case)
- Type_previous : Type of case: previous TB treatment stopped or failed (vs. new case)
- $\text{Insurance\_employer}$: Employer's health insurance (vs. private insurance)
- Insurance_public : Public health insurance (vs. private insurance)
- Insurance_none : No health insurance (vs. private insurance)
- Adherence : >= 80% of expected doses taken (vs. <80%)

Imputation diagnostics:

Multiple imputation by chained equations (MICE) was used to impute missing values for covariates. Counts across strata of the imputed categorical variables (HIV status, extrapulmonary vs pulmonary TB, diabetes, adherence, covid period, type of health insurance, and smoking) were similar between the original and imputed datasets (chi-squared p values ranging from 0.095 to >0.999 for the aforementioned variables), suggesting imputations were successful (the distribution of the imputed data does not differ significantly from the original). For the continuous covariate (age), the Kolmogorov-Smirnov (K-S) test indicated that the imputed datasets originated from the same distribution as the original (all K-S test p values >0.999 for comparisons of original vs. imputed age data for the first five imputed datasets of all three models (all, incarcerated, and non-incarcerated)).

Sensitivity analyses:

Figure S6. Comparison of adjusted odds ratios for treatment success using complete case analysis vs. multiple imputation by chained equations for missing covariate data



Error bars=95%CI for OR

(a) $\geq 80\%$ of doses taken

(b) Reference category: Pre-COVID-19

(c) Reference category: New TB case

(d) Reference category: Models 1 and 2: Private health insurance. Model 3: Worker's health insurance.

Figure S7. Comparison of adjusted odds ratios for treatment success under different approaches of handling missing treatment outcome data



Error bars=95%CI for OR

(a) $\geq 80\%$ of doses taken

(b) Reference category: Pre-COVID-19

(c) Reference category: New TB case

(d) Reference category: Models 1 and 2: Private health insurance. Model 3: Worker's health insurance.

5.13 Supplement references:

1. Instituto Nacional Penitenciario (INPE). Poblacion penal por situacion juridica y genero segun departamiento. 2023. <https://www.inpe.gob.pe/estad%C3%ADstica1.html>
2. Instituto Nacional de Estadística e Informática. Peru: Estimaciones y proyecciones de población por departamento, provincia y distrito. 2018-2020. 2020. https://www.inei.gob.pe/media/MenuRecursivo/publicaciones_digitales/Est/Lib1715/libro.pdf
3. Instituto Nacional de Estadística e Informática. Población estimada y proyectada por sexo y tasa de crecimiento, según años calendarios. 2023. <https://m.inei.gob.pe/estadisticas/indice-tematico/population-estimates-and-projections/>

CHAPTER 6: MANUSCRIPT 4:

Case fatality among people with TB enrolled in a private health sector TB treatment support program in Bihar, India during the first year of the COVID-19 pandemic

6.1 Preface

As case fatality estimates among TB patients enrolled in a private sector TB treatment adherence support program prior to the COVID-19 pandemic are available in previous work, we examined case fatality among a cohort of 4,000 patients enrolled in the same program in the first year of COVID-19, to compare pre- and during-COVID-19 case fatality. Given that loss to follow-up in TB patient cohorts can introduce bias in estimates of TB outcomes, we provide selection-bias-corrected estimates through inverse probability of selection weighting.

This manuscript has been submitted to *PLOS Global Public Health*.

Case fatality among people with TB enrolled in a private health sector TB treatment support program in Bihar, India during the first year of the COVID-19 pandemic

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6.2 Abstract

Background: Experiencing 28% of the global tuberculosis (TB) burden, India's TB epidemic is the largest in the world. Due to COVID-19-related disruptions to TB programs, India has also seen the largest drop in TB case notifications of any country globally. In the context of these disruptions, progress towards global and national TB elimination goals, including specific targets for reductions in TB mortality, has been set back. It is therefore urgent to examine case fatality among people treated for TB in India during the pandemic and compare these estimates to pre-pandemic estimates.

Methods: A random sample of 4,000 adults enrolled in World Health Partners (WHP), a private sector TB treatment support program in Bihar, India in the first year of COVID-19 (Mar 2020-Mar 2021) were contacted via phone to collect information on TB case fatality and other relevant covariates. Inverse probability of selection (IPS) weighting was used to obtain selection-bias-corrected in-treatment and post-treatment case fatality estimates. Predictors of case fatality were identified by estimating adjusted hazard ratios (HRs) using the Cox proportional hazards model, to account for differing follow-up times of participants. A primary analysis was conducted, analogous to a pre-pandemic study among a cohort enrolled in the same program. A secondary analysis included additional covariates not available in the pre-pandemic study but expected to be important predictors of case fatality.

Results: WHP enrolled 19,826 adult TB patients in the first year of COVID-19 (Mar 2020 to Mar 2021). Of our random sample of 4,000 patients, n=2,962 (74.1%) answered the follow-up call. Unweighted and IPS-weighted in-treatment case fatality in the primary analysis were 6.12% (95%CI: 5.31-6.97%) and 6.07% (95%CI: 5.22-6.93%), respectively. Post-treatment case fatality estimates were 0.97% (95%CI: 0.61- 1.33%) (unweighted) and 1.27% (95%CI: 0.79-1.79) (IPS-weighted). These estimates were lower than pre-pandemic estimates (p=0.036 and <0.001 for in-treatment and post-treatment case fatality respectively). Only age was a significant predictor of case fatality in the treatment phase IPS-weighted Cox proportional hazards model, with older

individuals more likely to die (HR: 1.03, 95%CI: 1.02-1.05). No significant associations were found in the post-treatment phase model.

Conclusions: Although not higher than pre-pandemic estimates, the observed case fatality in this private sector cohort of people treated for TB during COVID-19 in Bihar, India is above the level needed to reach the 2025 and 2030 End TB Strategy targets for reductions in TB deaths, underlining the extent of pandemic-related setbacks to TB elimination. In addition, as this is a cohort enrolled in a PPSA program offering support services beyond standard care, it is likely that case fatality in the general population of people with TB in India is even higher than that observed here.

6.3 Background

India experienced 28% of the global TB burden in 2021,¹ making the country's TB epidemic the largest in the world. Specifically, India had an estimated tuberculosis (TB) incidence of 210 (178-244) cases per 100,000 people in 2021.² Alarming, the disruptive impact of the COVID-19 pandemic on TB programs globally^{1,3-6} have been especially felt in India,⁷ which suffered an 38% reduction in TB case notifications at the beginning of the pandemic;⁸ a larger shortfall than any other country.⁴

The Indian government declared COVID-19 a 'notified disaster' on 14 Mar 2020,⁹ and an initial lockdown was enacted across the country on 25 Mar 2020.¹⁰ Having reported almost 45 million COVID-19 cases and over 500,000 associated deaths (although heavily undercounted)¹¹ as of July 2023,¹² over-burdened health systems and increased barriers to access to care during the pandemic have hindered TB care and prevention, including fewer children receiving the BCG vaccine,⁷ longer diagnostic delays,¹³ and fewer patients being started on and successfully completing TB treatment.⁷ In addition, pandemic-related disruptions have aggravated existing social determinants of TB in India, including poverty¹⁴ and malnutrition.¹⁰

Even prior to COVID-19, the landscape of TB care in India was complex, with patients navigating fragmented and privatized health systems, resulting in diagnostic delays and loss to follow-up.¹⁵ In particular, India's large private health sector plays a significant role in TB care (with 60-85% of TB patients first presenting for care at private sector facilities),¹⁶ giving rise to unique challenges during COVID-19, including increased out-of-pocket costs being borne by patients,¹⁷ and closures of private clinics during lockdown.¹⁶

The quality of TB care provided in the private sector has been extensively evaluated via standardized patient studies, finding highly variable quality of care.¹⁸ To bridge the gap between private and public health care for TB, Private Provider Support Agencies (PPSAs) have emerged as a key strategy of India's National TB Elimination Program, with the aim of improving the quality of TB care,¹⁹ for example through provision of free diagnosis and

treatment, and adherence monitoring. Unfortunately, such PPSA or intermediary agencies have also reported disruptive impacts of the COVID-19 pandemic on their operations, hindering private provider engagement efforts in TB.¹⁷

In this context, COVID-19-related disruptions to TB programs globally, and especially in India, have jeopardized the already fragile progress on TB elimination. In particular, the World Health Organization (WHO) reported that, due to the COVID-19 pandemic, global TB deaths increased in 2020 for the first time since 2005,⁴ setting back progress towards WHO End TB goals, which aim to reduce TB-related mortality by 90% by 2030 (compared to 2015 levels).²⁰ The government of India has set an even earlier deadline of 2025 for TB elimination in its National Strategic Plan.²¹ Given the scale of disruptions to TB services in India, an increase in case fatality among people with TB during the pandemic is likely, making it urgent to assess case fatality in patients diagnosed with TB during COVID-19.

A national-level study examining reported TB mortality in India during the COVID-19 pandemic demonstrates a 15.4% decrease in reported TB deaths in 2020 compared to 2019.²² However, given the large decline in TB case detection during COVID-19, it is likely that this decrease in deaths reflects solely a decrease in reporting of cases and outcomes, rather than a true decrease in TB-related deaths. A modelling study predicting additional TB deaths due to missed cases (under-notification) during the pandemic estimated a 19.5% (14.5-24.7%) increase in TB deaths in 2020.¹⁰

As these studies are limited either by reliance on reported deaths,²² which are likely under-notified, or predictions,¹⁰ estimates of case fatality derived from follow-up of TB patient cohorts are needed. A major challenge with such studies is the fact that patients who are unable to be reached for follow-up are more likely to have had poor TB treatment outcomes than patients who are available for follow-up, resulting in biased estimates. A follow-up study of people with TB enrolled in a PPSA program in Patna, Bihar, India, adjusting for potential selection bias, was carried out by our team prior to the pandemic, and estimated TB case fatality at 7.27% during

treatment, and 3.32% 2 years post-treatment.²³ To examine TB case fatality during COVID-19, we carried out a similar follow-up study in patients diagnosed with TB in the first year of the COVID-19 pandemic (Mar 2020 – Mar 2021) and enrolled in the same PPSA program. We aimed to estimate in-treatment and post-treatment case fatality and identify predictors of in-treatment and post-treatment case fatality in this cohort, as well as compare our during-COVID-19 case fatality estimates to pre-COVID-19 estimates.

6.4 Methods

Research ethics:

This study was a follow-up survey to ongoing routine, programmatic service delivery by World Health Partners (WHP), a PPSA program in Bihar, India. Ethics approval for the follow-up analysis was therefore obtained from the Bihar state TB program office, and from McGill University (A02-M12-22A).

Engagement of communities affected by TB:

To ensure this work is relevant to and respectful of the experiences of communities affected by TB, a summary of the research protocol was shared with a panel of five TB survivors and advocates for discussion and incorporation of their feedback into the work.

Study setting: The WHP PPSA program

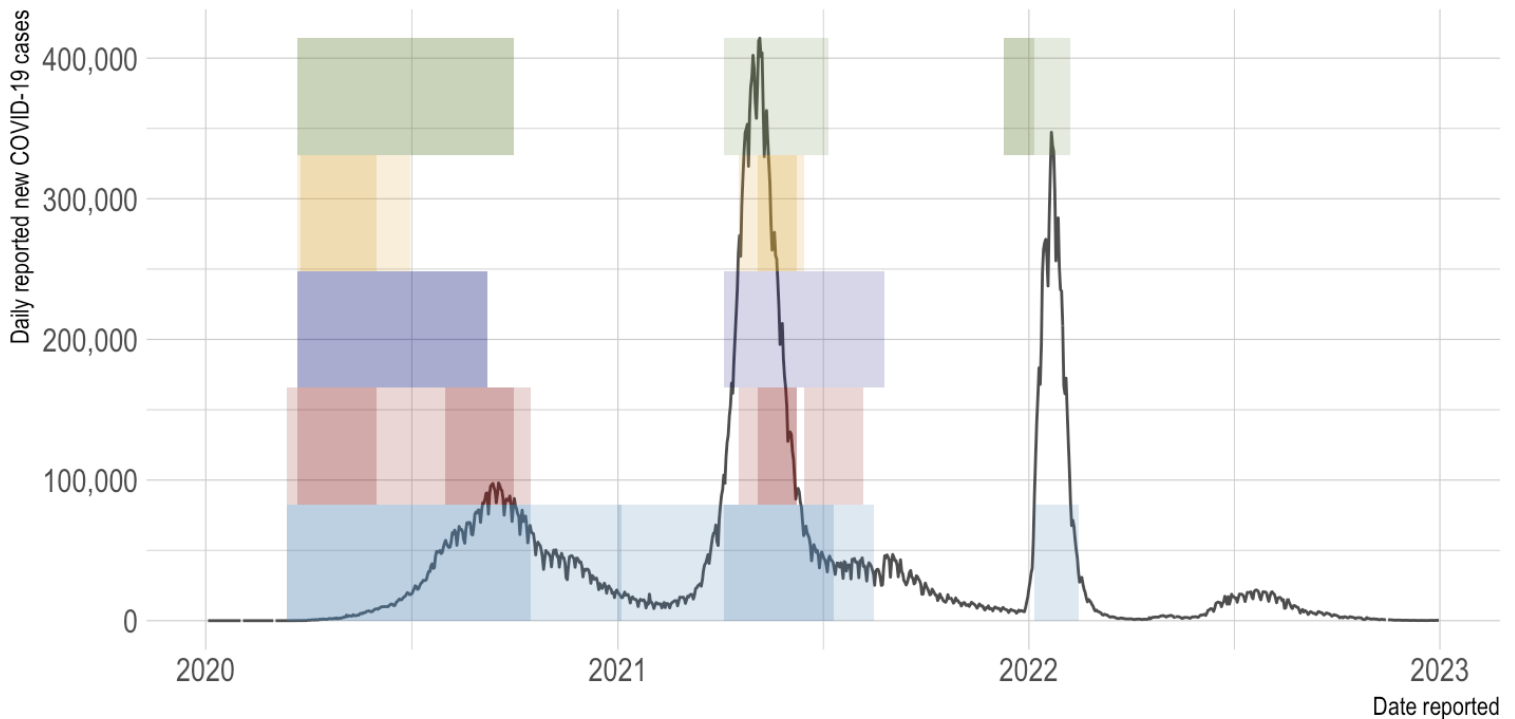
The PPSA program, based in Patna, Bihar was established in 2013. Being donor-funded at the outset and operating only in Patna district, the program became government funded and was expanded to operate in 7 other districts (Gaya, Bhojpur, Nalanda, Bhagalpur, Munger, Katihar and Saharsa) in Bihar state as of June 2020.

TB diagnosis and treatment are provided free of charge to patients enrolled in the program, and free testing for co-morbidities (HIV and diabetes) is also available. At the diagnosis stage, the PPSA program's field officers coordinate sample collection and transport to testing sites,

therefore improving linkage between public and private testing facilities and care providers. People diagnosed with drug-resistant TB are referred to the public sector. The program actively maps new care providers to engage, with over 1,400 providers now engaged in the program across the 8 districts in which it operates. Once patients are on TB treatment, treatment adherence support is provided through treatment coordinators who conduct home visits, as well as through call centre staff who conduct biweekly calls to determine treatment adherence and update patient outcomes. The program also provides monthly stipends to patients for food support.

Like other TB programs, the PPSA program experienced COVID-19-related disruptions to its operations, including difficulties doing household visits and reductions in case notifications due to clinic closures. For context regarding COVID-19 restrictions in the study setting, daily new COVID-19 cases reported in India,²⁴ along with specific COVID-19 related restrictions (e.g. workplace closures, internal movement restrictions, etc.) enacted in Bihar state²⁵ are shown in **Figure 1**. In the first year of the pandemic (March 2020 to March 2021) the WHP PPSA program enrolled 24,275 TB patients, of which 19,826 were adults (≥ 18 years old). The current study sample (see section below) was drawn from these adults.

Figure 1. Daily new COVID-19 cases reported in India²⁴ and COVID-19-related restrictions²⁵ in Bihar State (Jan 2020 to Dec 2022)



COVID-19-related restrictions/policies

Local travel restrictions

- Travel between regions not recommended
- Travel between regions restricted

Stay-at-home orders

- Stay-at-home order with exceptions (e.g. exercise, groceries)
- Stay-at-home order with minimal exceptions (e.g. once a week / one person at a time)

Transport closures

- Significantly reduced routes/volumes/means of transport, or recommended closure
- Closed

Workplace closures

- Closure of some sectors
- Closure of all sectors (except essential services)

School closures

- Closure at some levels/categories (e.g. public/private or grade-level differences)
- Closure at all levels/categories

COVID-19 cases are from the WHO COVID-19 database.²⁴

COVID-19 measures/policies are from the Oxford COVID-19 Government Response Tracker.²⁵

Study sample:

A random sample of 4,000 participants was drawn on 15 March 2022 from all adult patients (19,826) in the WHP PPSA program who were diagnosed with TB in the first year of COVID-19 (March 2020 - March 2021).

Data collection:*Information available in the PPSA program database:*

The program records age, sex, site of TB disease (extra-pulmonary/pulmonary), type of case (new or previous TB), district of residence and district of enrolment, diagnosis and enrolment dates, treatment start and end dates, HIV status, diabetes status, treatment adherence (the proportion of doses taken, based on the program's treatment monitoring calls), and treatment outcome.

Primary data collection via phone surveys:

Patients in the study sample or their next of kin were contacted via phone to determine the patient's vital status as well as collect information on covariates not available in the program's routine database. Phone surveys were conducted between March 2022 and Nov 2022. Consent was obtained at the outset of each call, and consenting participants were asked whether they had a COVID-19 test (and if so, its result), they had a diagnosis of COVID-19 by a healthcare provider, they received a COVID-19 vaccine (and if so, how many doses), they smoke currently or have smoked in the past, they had recurrent TB, their self-reported treatment duration (as some patients continue treatment beyond that provided by the program), and, if next of kin answered the call, whether the patient is alive or has died. The dates of these events (where applicable) were also recorded. In addition, due to the lack of indicators of socioeconomic status in the routine PPSA data, participants were also asked about their highest level of education completed. In alignment with the previous PPSA follow-up study,²³ patient addresses were also classified as being in "slum" or "non-slum" areas as an indicator of socioeconomic status. All participants or their next of kin were called regardless of WHP-reported treatment outcome, in order to collect data on the variables not available at baseline. Up to three phone

calls were attempted for each participant. Home visits to reach patients (after 3 failed calls) were not conducted, given the ongoing pandemic and the fact that they were low yield in the previous study.²³ EpiCollect5 (Oxford Big Data Institute) was used for call data entry.

Definitions of follow-up phases and case fatality are provided in **Box 1**.

Box 1. Follow-up phases and case fatality definitions:

Treatment duration	In line with the prior study, WHP-reported treatment duration was used unless a participant reported continuing treatment beyond the WHP-recorded treatment duration, in which case the self-reported duration was used.
Treatment phase	Time (in months) between treatment start date (WHP-recorded) and treatment completion (WHP-recorded, unless patient reported additional treatment, see above).
In-treatment case fatality	A death (from any cause) ^a occurring during the treatment phase. This aligns with WHO definitions of TB mortality as a death for any reason during or before starting TB treatment. ²⁶
In-treatment case fatality ratio	The number of deaths during treatment divided by the number of patients starting the treatment phase.
Post-treatment phase	Time (in months) between the end of the treatment phase (see above) and the call date.
Post-treatment case fatality	A death (from any cause) ^a occurring in the post-treatment phase.
Post-treatment case fatality ratio	The number of post-treatment deaths divided by the number of patients starting the post-treatment phase.
End of follow-up	Call date (for those alive at the time of the call) or death date.

^a All-cause mortality includes COVID-19 deaths.

Sample size:

Although we expected a non-response rate of approximately 47% based on the pre-COVID-19 PPSA follow-up study,²³ applying IPSW allows recovery of the initial sample size of 4,000. Assuming an in-treatment CFR of 7% based on the prior study,²³ this would allow estimation of the in-treatment CFR within a margin of error (MOE) of 0.79%. Among the 3,720 individuals reaching the post-treatment phase, assuming 10% loss to follow-up during treatment (based on WHP program experiences), 3,348 would remain for assessment of post-treatment case-fatality. Assuming a post-treatment CFR of 3%,²³ the post-treatment CFR would be estimated

with a MOE of 0.58%. We consider these estimates sufficiently precise to be meaningful for TB programs. In addition, our sample size provided adequate power to detect differences in during-COVID-19 CFRs compared to those in the pre-COVID-19 study,²³ with detection of a 2% increase in in-treatment CFR during COVID-19 at 80% power requiring a sample size of n=2,886 (or n=1,506 for the post-treatment CFR).

Data analysis:

We conducted a primary and a secondary analysis. The primary analysis included only variables that were available in the pre-COVID-19 follow-up study,²³ to facilitate comparability. The secondary analysis included additional variables that were available in the current study but not in the pre-COVID-19 study and that were expected to be important predictors of case fatality (see *secondary analysis* sub-section).

Inverse probability of selection weighting:

It is possible that patients who could not respond to the survey are more likely to have experienced unfavourable treatment outcomes, including death. Therefore, analyses based only on the subsample responding to the survey are likely to produce biased estimates. Inverse probability of selection (IPS) weights²⁷ were therefore applied to the observed cohort. This involves specification of a selection model predicting individuals' probability of response to the phone survey, based on baseline characteristics. These weights are then used to re-weight the sample in subsequent analyses, giving higher weights to individuals less likely to respond to the survey, and thereby correcting for the aforementioned selection bias.

In the primary analysis, covariates included in the selection model were those that were available at baseline, expected to be associated with response to the phone survey as well as the outcome (death), and analogous to those in the selection model of the pre-COVID-19 study.²³ The selection model is shown in **Supplement Equation S1**. Specifically, covariates included were age, sex, site of disease (pulmonary/extrapulmonary), previous/new TB, slum/non-slum residence, WHP-reported treatment duration (in months), treatment adherence

(proportion of doses taken), time since treatment start (months since start of treatment and Nov 2022), and whether the patients' residence was outside of their district of enrolment in the PPSA program.

Variables in the selection model with missing data included sex (n=4, 0.1%), new/previous TB (n=18, 0.4%), slum/non-slum residence (n=1, 0.03%), WHP-reported treatment duration (n=8, 0.2%), treatment adherence (n=74, 1.8%), months since treatment start (n=8, 0.2%). Given the very low proportion of missing data, a single chained imputation was used to impute missing baseline values.²⁸ Continuous covariates non-linearly related to survey response (WHP-reported treatment duration and time since treatment start) were modelled flexibly using penalised splines.

Observed and unobserved cohorts:

Participants who responded to the survey (and provided valid dates) or were reported by WHP to have died were included in the observed cohort. **Figure 2** describes survey response and inclusion in the observed and unobserved cohorts. The observed cohort (IPS weighted and unweighted) is used in subsequent analyses.

Case fatality estimates:

In-treatment and post-treatment CFRs were estimated according to definitions in **Box 1**. Both IPS weighted and unweighted CFR estimates (and 95% CIs) were bootstrapped 1,000 times. IPS-weighted Kaplan-Meier curves for in-treatment and post-treatment survival are also shown. CFRs estimated in this study (during COVID-19) were compared to CFRs estimated in the pre-COVID-19 follow-up study via the Chi-squared test.

Identification of predictors of case fatality:

Cox proportional hazards models were used to identify predictors of case fatality. Separate models were fit for in-treatment and post-treatment case fatality, using the number of months in the treatment phase or post-treatment phase, respectively, as the time indicator. Results of

both IPS weighted and unweighted models are presented, with 95% CIs bootstrapped 1,000 times. Non-linear relationships between continuous predictors and survival were modelled using penalised splines. Where applicable, interaction terms with time (months of treatment or post-treatment, as applicable) were included for terms that violated the proportional hazards assumption (assessed via Schoenfeld residuals). The treatment and post-treatment phase models are shown in **Supplement Equations S2 and S3**. Covariates in the primary analysis models included those analogous to those in the pre-COVID-19 study (slum/non-slum, new/previous TB, pulmonary/extrapulmonary TB, age, sex, treatment adherence, and whether the patient resided outside of the district in which they were enrolled into the PPSA program).

Secondary analysis:

In addition to the variables used in the primary analysis, the selection model in the secondary analysis (**Supplement Equation S4**) included HIV and diabetes status, as these were available at baseline at the time of the study (captured in routine WHP data, with 10.1 and 11.7% missingness for HIV and diabetes, respectively) and expected to be important predictors of response, but were not available at the time of the pre-COVID-19 study.²³ In addition, to take into account that the expansion and change in financing of the PPSA program may have resulted in operational changes influencing patient outcomes and likelihood of survey response, an indicator for whether the patient was enrolled before or after the program's expansion (June 2020) was also included in the selection model. Missing baseline data were again imputed via a single chained imputation and the imputed data used in the selection model. IPS-weighted and unweighted in-treatment and post-treatment CFRs were estimated using the new weights generated by the expanded selection model.

The secondary analysis treatment phase Cox proportional hazards model included HIV and diabetes status, and two additional variables collected in the phone survey – smoking status (0.8% missing) and the number of COVID-19 vaccine doses received (0.7% missing), imputed via a single chained imputation. Educational attainment (also collected in the phone survey, to allow more granular indication of socioeconomic status than the slum/non-slum variable) was

not included in the final model, as hazards within strata of education were not proportional over time, and introduction of an interaction term with time created convergence issues. The indicator variable for enrolment after the expansion of the PPSA program was also excluded due to convergence issues. COVID-19 co-infection status, although collected in the phone survey, could not be included, as most patients did not report COVID-19 test results (n=1,843, 62.3%), and of those that did report a result (n=1,113), only 14 (1.3%) reported a positive test. Due to challenges in accessing COVID-19 testing,²⁹ as well as stigma around COVID-19 in India, especially during the first year of the pandemic,³⁰ it is possible patients were hesitant to disclose getting tested for COVID-19 or receiving a positive test result.

A secondary analysis for the post-treatment phase Cox proportional hazards model including the additional variables above was not conducted, as the low number of events in the post-treatment phase would not accommodate additional predictors.

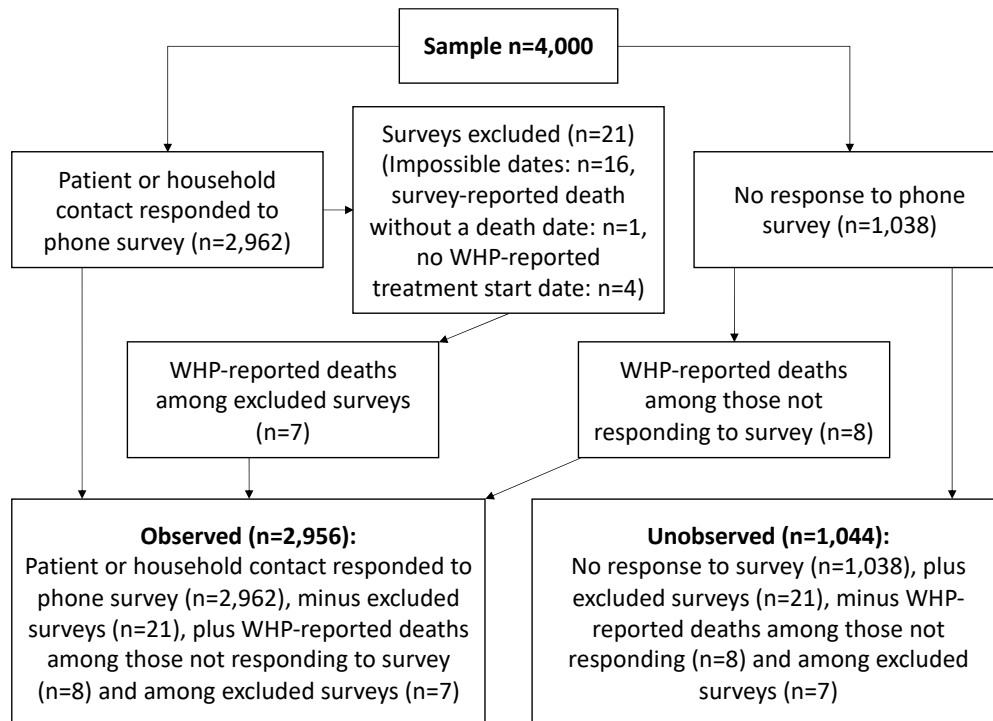
Sensitivity analysis:

Given the difficulties of accessing COVID-19 testing in India, especially early in the pandemic, high missingness was expected for patient-reported COVID-19 test results. A sensitivity analysis using patient-reported diagnosis of COVID-19 by a healthcare provider as an indicator of COVID-19 co-infection (instead of a positive test) was therefore planned, but could not be carried out given that, among the 2,938 people in the observed cohort who responded to the question on healthcare provider diagnoses of COVID-19 (99.4%), none reported having had COVID-19 diagnosed by a healthcare provider.

6.5 Results

Of the 4,000 individuals called, 2,962 (74.1%) answered the phone survey. Valid surveys (n=2,941) as well as WHP-reported deaths among excluded surveys (n=7) (see **Figure 2** for exclusion reasons), and WHP-reported deaths among those who did not respond to the survey (n=8) formed the observed cohort (total observed cohort n=2,956). **Figure 2** describes survey response and inclusion in the final observed cohort.

Figure 2. Flowchart of survey responses and inclusion in observed cohort



Baseline characteristics are shown in **Table 1** for the full cohort (n=4,000), as well as stratified by observed and unobserved cohort. The full cohort had an average age of 39.0 years (SD: 16.5) and was 61.0% male. Those in the observed cohort were younger, more likely to be female, and more likely to have extrapulmonary TB. Adherence (percentage of doses taken, as determined by WHP treatment monitoring calls) was higher in the observed cohort (81.4%, SD: 35.5) than the unobserved cohort (75.2%, SD: 40.5).

Table 1. Baseline characteristics of people with TB enrolled in a PPSA program in Bihar within the first year of the COVID-19 pandemic

Characteristic	Full cohort (n=4,000)	Observed cohort (n=2,956)	Unobserved cohort (n=1,044)
Age (years)	39.0 (16.5)	36.3 (15.1)	46.8 (17.8)
Sex (male)	2,438 (61.0%)	1,746 (59.1%)	692 (66.3%)
New TB (vs. previous TB)	3,903 (98.0%)	2,893 (98.3%)	1,010 (97.2%)
Pulmonary TB (vs. extrapulmonary)	3,202 (80.0%)	2,325 (78.7%)	877 (84.0%)
Adherence (% of doses taken)	79.8 (36.9)	81.4 (35.5)	75.2 (40.5)
Non-slum residence (a)	3,867 (96.7%)	2,860 (96.8%)	1,007 (96.5%)
Residential district outside of PPSA enrolment district (b)	852 (21.3%)	647 (21.9%)	205 (19.6%)

(a) Slum/Non-slum indicator used as a proxy for socioeconomic status

(b) Whether the patient resided in a district outside of the district in which they were enrolled in the PPSA program (which, as of June 2020, operated in 8 districts of Bihar: Patna, Gaya, Bhojpur, Nalanda, Bhagalpur, Munger, Katihar, and Saharsa)

Variables with missing data: Sex n=4 (0.1%), Previous/new TB case n=18 (0.4%), Adherence n=74 (1.8%), Slum/Non-slum residence n=1 (0.03%).

Primary analysis:

In the primary analysis, the IPS weights applied to the observed cohort (generated via the selection model, see **Equation S1**) ranged from 1.03 to 5.85, but large weights were uncommon (median: 1.23, 10th and 90th percentiles 1.12 and 1.73, respectively), indicating few highly influential observations. The distribution of IPS weights is shown in **Supplement Figure S1**. Covariate balance between the full cohort and the weighted observed cohort is shown in **Table 2**. As shown, the IPS weights allowed good balance between the full and observed cohorts, suggesting that the weighted observed sample is representative of the full cohort.

Table 2. Covariate balance between full cohort and IPS weighted observed cohort (Mean [Variance])

Characteristic	Full cohort	Weighted observed cohort
Age (years)	39.00 (273.27)	39.22 (275.01)
Sex (proportion male) ^a	0.61 (0.24)	0.61 (0.24)
Proportion with new TB (vs previous) ^a	0.98 (0.02)	0.98 (0.02)
Proportion with pulmonary TB (vs. extrapulmonary)	0.80 (0.16)	0.80 (0.16)
Adherence (proportion of doses taken) ^a	0.80 (0.14)	0.79 (0.14)
Proportion with non-slum residence (vs. slum residence) ^a	0.97 (0.03)	0.97 (0.03)
WHP-reported months of treatment ^a	6.37 (3.22)	6.35 (3.29)
Proportion with residential district outside of PPSA enrolment district	0.21 (0.17)	0.21 (0.17)

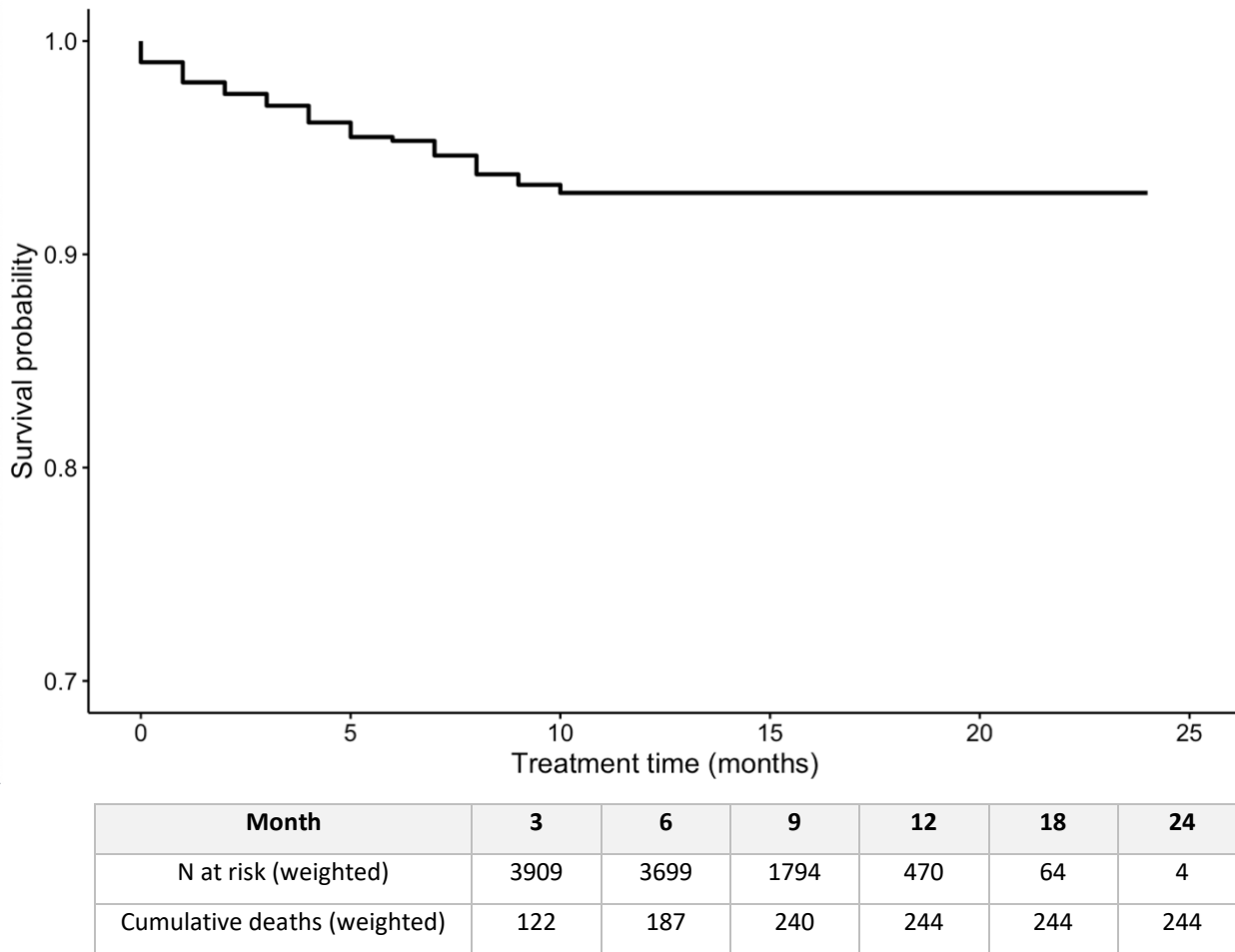
IPS = inverse probability of selection

^a Imputed

The observed cohort had a mean total follow-up time of 19.3 months (max. 27.0 months), with a mean treatment phase duration of 8.0 months (max. 24.0 months), and a mean post-treatment phase duration of 12.0 months (max. 22.5). The weighted mean treatment and post-treatment phase durations were 8.1 and 12.0 months, respectively.

The IPS-weighted Kaplan-Meier curve for treatment phase survival is shown in **Figure 3**. Most deaths occurred within the first 9 months of the treatment phase. IPS-weighted and unweighted treatment phase cumulative hazards at 3, 6, 9, 12, 18, and 24 months are shown in **Supplement Table S1**. Overall unweighted treatment phase case fatality was 6.12% (95%CI: 5.31-6.97%) (IPS weighted CFR: 6.07%, 95%CI: 5.22-6.93%). The unweighted treatment phase CFR from the current study (during COVID-19) is higher than the unweighted CFR estimated in the pre-COVID-19 follow-up study of patients enrolled in the same PPSA program (4.15%, 95%CI: 3.56%-4.83%), however, the IPS weighted during COVID-19 estimate is lower than that of the pre-COVID-19 study (CFR=7.27%, 95%CI: 5.97-8.49%) (Chi-squared test of proportions for weighted CFRs p=0.036). Nonetheless, the CFR estimates in the current study remain above the target CFR (5%) required to reach the End TB Strategy goals.³¹

Figure 3. IPS weighted Kaplan-Meier curve and risk table for treatment phase case fatality among people with TB in Bihar, India, in the first year of the COVID-19 pandemic



The analysis model, identifying predictors of treatment phase fatality are shown in **Table 3**. The non-linear relationship between treatment adherence proportion and survival is shown in **Figure 4**. Only age was significantly associated with in-treatment case-fatality in both the unweighted and weighted models (unweighted model HR: 1.04, 95%CI: 1.03-1.05, weighted model HR: 1.03, 95%CI: 1.02-1.05). Patients residing outside of their PPSA enrolment district had statistically significantly higher case fatality in the unweighted model (HR: 1.50, 95%CI: 1.05-2.13), but not in the weighted model (HR: 1.43, 95%CI: 0.97-2.13). This is similar to findings in the pre-COVID-19 study, where age was the only significant predictor (in both the unweighted and weighted models). The relationship between treatment adherence and

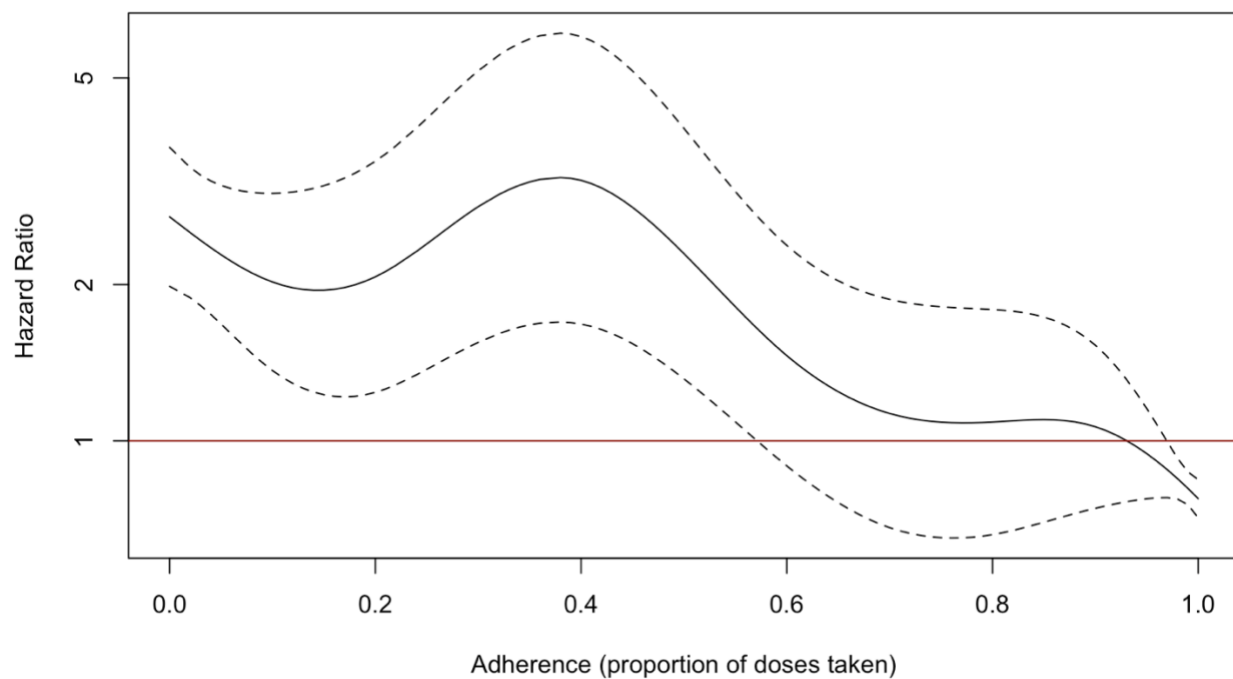
survival was non-linear (**Figure 4**) and was modelled flexibly. 60% or lower adherence significantly increased the hazard of in-treatment death.

Table 3. Predictors of treatment phase case fatality among people with TB in Bihar, India, in the first year of the COVID-19 pandemic

	Unweighted			IPS weighted		
	HR	95%CI		HR	95%CI	
Slum residence (Ref: Non-slum residence)	1.01	0.25	1.98	1.09	0.26	2.22
Previous TB (Ref: New TB)	1.49	0.51	3.04	1.57	0.45	3.44
Pulmonary TB (Ref: Extrapulmonary TB)	1.25	0.87	1.90	1.29	0.88	2.02
Age (years)	1.04	1.03	1.05	1.03	1.02	1.05
Sex, Male (Ref: Female)	0.99	0.73	1.39	0.96	0.69	1.36
District of residence outside PPSA enrolment district	1.50	1.05	2.13	1.43	0.97	2.13

IPS=inverse probability of selection.

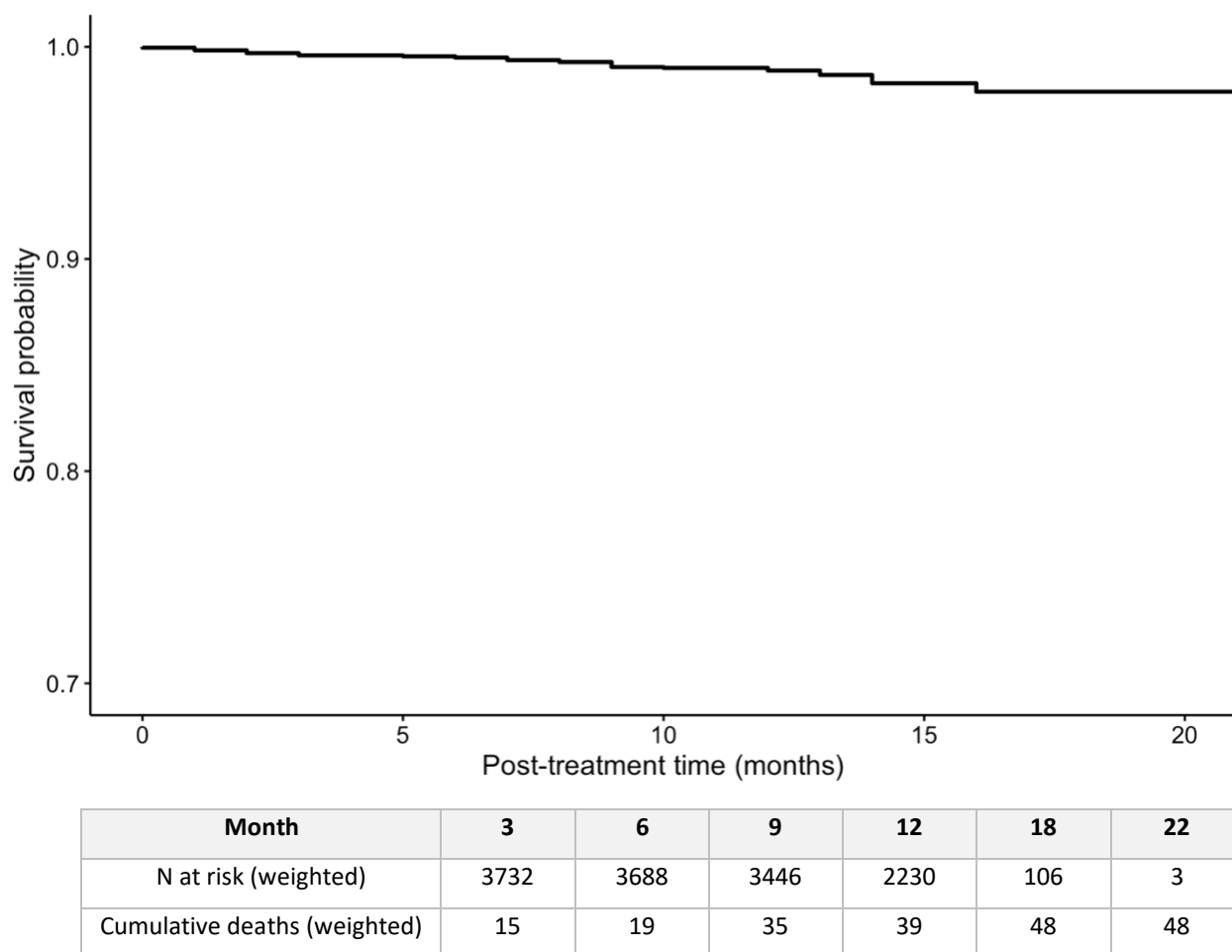
Figure 4. Non-linear relationship between TB treatment adherence proportion and hazard of in-treatment death



IPS-weighted hazard ratios for treatment phase case fatality vs. treatment adherence (imputed), holding other covariates constant. Modelled using penalised splines (df=4). Dashed line = 95%CI of hazard ratios. Red line = null hypothesis hazard ratio (1.0). IPS=inverse probability of selection.

The IPS-weighted Kaplan-Meier curve for post-treatment phase survival is shown in **Figure 5**. IPS-weighted and unweighted post-treatment cumulative hazards at 3, 6, 9, 12, 18, and 22 months are shown in **Supplement Table S2**. Post-treatment case fatality was 0.97% (95%CI: 0.61- 1.33%) (unweighted) and 1.27% (95%CI: 0.79-1.79) (weighted). Post-treatment case fatality in the current study was lower than pre-COVID-19 post-treatment case fatality estimates (3.32% at 24 months, 95%CI: 2.36-4.42%) (Chi squared $p < 0.001$).

Figure 5. IPS weighted Kaplan-Meier curve and risk table for post-treatment case fatality among people with TB in Bihar, India, in the first year of the COVID-19 pandemic



Hazard ratios for post-treatment phase fatality are shown in **Table 4**. No significant associations with post-treatment case fatality were found, possibly due to the low number of events (deaths) in the post-treatment phase.

Table 4. Predictors of post-treatment case fatality among people with TB in Bihar, India, in the first year of the COVID-19 pandemic

	unweighted			weighted		
	HR	95%CI		HR	95%CI	
Slum residence (Ref: Non-slum residence)	1.15	0.00	4.53	0.93	0.00	3.74
Previous TB (Ref: New TB)	2.57	0.00	9.56	1.71	0.00	6.15
Pulmonary TB (Ref: Extrapulmonary TB)	1.01	0.45	3.83	0.87	0.38	3.42
Sex, Male (Ref: Female)	1.38	0.62	3.25	1.47	0.64	3.43
Adherence (proportion of doses taken) (a)	0.71	0.29	3.08	0.68	0.26	3.31
District of residence outside PPSA enrolment district	0.84	0.17	2.15	1.06	0.20	2.77
Age : time (b)	1.00	0.99	1.00	1.00	0.99	1.00

(a) Splines not used as non-linear term for adherence was non-significant

(b) Interaction term between age (years) and post-treatment time (months).

Secondary analysis:

In the secondary analysis, the IPS weights applied to the observed cohort using the expanded selection model (**Supplement Equation S4**) ranged from 1.02 to 6.07, but large weights were uncommon (median: 1.23, 10th and 90th percentiles 1.12 and 1.74, respectively). Weights again produced good balance between the full cohort and the re-weighted observed cohort (**Supplement Table S3**). The weighted mean treatment and post-treatment phase durations remained similar to the primary analysis (8.1 and 12.0 months, respectively). The weighted in-treatment CFR was 6.09 (95%CI: 5.25-6.96), similar to the weighted in-treatment CFR in the primary analysis. The weighted post-treatment CFR was 1.27% (95%CI: 0.80-1.81), again similar to the primary analysis.

Results of the expanded Cox proportional hazards model identifying predictors of in-treatment case fatality are shown in **Supplement Table S4**. In the weighted model, individuals who were

significantly more likely to die during treatment included older individuals (HR: 1.03, 95%CI: 1.03-1.05), people with pulmonary TB (HR: 1.50, 95%CI: 1.01-2.50), and people residing outside of their PPSA enrollment district (HR: 1.70, 95%CI: 1.17-2.58). Receiving a COVID-19 vaccine was protective against all-cause mortality (for one dose as well as two or more doses). Counterintuitively, patients who reported current or past smoking were also significantly less likely to die during treatment (0.34, 95%CI: 0.16-0.60). These predictors were also significant in the unweighted model, except disease site (pulmonary vs. extrapulmonary TB). The relationship between treatment adherence and survival was non-linear (**Supplement Figure S2**), with adherence below approximately 30% significantly associated with a higher hazard of in-treatment case fatality.

Primary and secondary analysis in-treatment and post-treatment CFRs are compared in **Table 5**. Although estimates in primary and secondary analyses are similar, differences are most likely attributable to the inclusion of additional variables in the selection model in the secondary analysis, resulting in differences in IPS weights. Given the similarity between primary and secondary analysis estimates and that a bias analysis on a cohort of patients enrolled in the same PPSA program³² showed that inclusion of additional confounders in the selection model had minimal effect on estimates, we consider our primary analysis results to be reliable (see discussion section).

Table 5. Comparison of IPS weighted case fatality ratio estimates from the primary and secondary analyses

	Primary analysis	Secondary analysis
In-treatment CFR	6.07% (95%CI: 5.22-6.93%)	6.09 (95%CI: 5.25-6.96)
Post-treatment CFR	1.27% (95%CI: 0.79-1.79)	1.27% (95%CI: 0.80-1.81)

IPS = inverse probability of selection

6.6 Discussion

Our findings indicate a selection-bias-corrected in-treatment CFR of 6.07% (95%CI: 5.22-6.93%) among people diagnosed with TB in the private health sector during the COVID-19 pandemic

and enrolled in a PPSA program in Bihar, India. Although this is higher than the unweighted pre-COVID-19 CFR estimated in a prior study in the same program, it is lower than the pre-COVID-19 study's bias-corrected CFR. A possible explanation for this is that due to COVID-19-related barriers to care-seeking for TB, more severely ill patients were less likely to reach care (e.g. be diagnosed and enrolled in the PPSA program). Regardless, our during-COVID-19 CFR is above the CFR target of 5% articulated in the WHO's South-East Asia region-specific strategic plan for reaching the End TB goals.³¹ This underlines that we are not on track to global TB elimination goals, which are especially urgent in a country that shoulders more than one quarter of the total burden of TB cases worldwide.¹ In addition, given that our sample was drawn from patients enrolled in a PPSA program which offers a variety of services beyond the standard of care (adherence support, food support, provider engagement), it is likely that case fatality in the general population in India is even higher than estimated in this study. In particular, it is possible that the disruptive impacts of the COVID-19 pandemic felt in public TB programs (barriers to accessing care) were attenuated in this population, who were more closely followed throughout treatment (regular adherence support calls by PPSA staff). Due to receiving food support, this population may also have been shielded to some extent from the economic impacts of COVID-19 on households, which would otherwise have exacerbated poor TB outcomes (due to malnutrition, etc.).¹⁰

However, our findings are also subject to important limitations. A major limitation is survey non-response, given that individuals who could not respond to the survey may be more likely to have experienced unfavourable TB treatment outcomes, which would bias estimates that are based only on the observed sample. For this reason, IPS weights were applied to re-weight the sample based on their probability of response (conditional on baseline covariates), thereby assigning higher weights to individuals less likely to respond and adjusting for selection bias. Despite this effort to reduce bias, residual confounding in the selection model remains a limitation. In particular, given that information on socioeconomic status (such as income) is not collected at baseline in routine WHP data, this could not be included in the selection model, and the slum / non-slum residence indicator was therefore used as an imperfect proxy of

socioeconomic status. The similarity between weighted and unweighted in-treatment CFRs however indicates low selection bias in our study, possibly due to the relatively high survey response rate of 74.1% (the pre-COVID-19 PPSA follow-up study had a response rate of 53.2%). It is also possible that patient follow-up within the PPSA program has improved since the previous study, resulting in fewer in-treatment deaths going unreported by the program.

In addition to the lack of a more granular proxy for socioeconomic status in baseline program data, other important baseline covariates have limited granularity, such as the pulmonary vs. extrapulmonary TB indicator. Although pulmonary TB was found to be significantly associated with mortality in the weighted secondary analysis model, given the heterogeneous presentations of TB, more specific categories for TB disease localization would be more informative.

It should also be noted that the CFRs presented here represent all-cause mortality, meaning that it is possible that a considerable percentage of deaths in the current study (as opposed to the pre-COVID-19 study) were due to COVID-19, especially given the higher risk of mortality among patients co-infected with COVID-19 and TB.³³

A further limitation is that, by nature of the survey-based design, we relied on patient self-report for many important variables. This limited the reliability of some data collected. For example, we could not assess the effect of COVID-19 co-infection on case fatality (in the secondary analysis) due to low reporting of positive COVID-19 test results. The barriers to accessing COVID-19 testing²⁹ as well as stigma associated with COVID-19 in India make it likely that many patients who had COVID-19 were not tested³⁴ or were uncomfortable reporting their test results.³⁰ Although we planned to address the problem of low COVID-19 testing rates through a sensitivity analysis, using patient-reported diagnosis of COVID-19 by a healthcare provider, no patients reported such a diagnosis. The limited reliability of self-reported data is also evident in the fact that we could not assess TB recurrence given that only 8 patients reported valid recurrence dates (within the post-treatment phase). In addition, the

counterintuitive protectiveness of smoking against case fatality observed in the secondary analysis is most likely due to the fact that smoking status was unavailable at baseline, and that self-reported smoking during follow-up calls was unreliable, possibly leading to residual confounding. Given the stigma associated with smoking among people with TB, it is possible that patients who successfully quit were more likely to report past smoking. However, a bias analysis³² simulating smoking, HIV and malnutrition prevalence among the pre-COVID-19 PPSA cohort found that their inclusion in the selection model did not substantially change estimates, suggesting that our primary analysis remains robust even without inclusion of these variables.

Lastly, other than COVID-19, the PPSA program also underwent significant changes during the study period, changing from donor to government funding, and expanding operations to 7 additional districts. This reduces comparability between the pre-COVID-19 estimates in the prior follow-up study (at which time the program operated only in one district and was donor-funded) and our during-COVID-19 estimates. In addition, it is possible that differences in treatment outcomes during COVID-19 are not only the result of the pandemic but also the result of the programmatic and operational changes, introducing secular trends that are not attributable to COVID-19 disruptions alone.

Nevertheless, our results show fairly high TB case fatality, which is concerning, especially given India's accelerated timeline of reaching the End TB goals 5 years before the global target. Regaining lost progress on TB elimination as programs recover from COVID-19 will require improving TB case-detection and reducing loss to follow-up along the TB care cascade, including through treatment adherence support,³⁵ as is being done in the PPSA program. PPSAs and their work engaging TB care providers to bridge gaps in fragmented health systems are therefore key to supporting TB elimination.

6.7 Contributors

Study conceptualisation: MP, LF. Data curation: AR. Data analysis/visualisation: LF, SH. Study supervision: MP, NJ. Writing of original draft: LF. Review and editing: LF, SH, MP, NJ, AR. Access

and verification of all data reported in the study: LF. All authors agreed with the decision to submit for publication.

6.8 Conflicts of Interest

MP serves as an advisor to several non-profit organizations, including Bill & Melinda Gates Foundation, WHO, Stop TB Partnership and FIND. He has no financial or industry conflicts.

6.9 Funding

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6.12 Supplement

Section 1: Primary analysis

Equation S1. Selection model for prediction of probability of response based on baseline covariates, used to generate inverse probability of selection weights

$$\text{logit}(p(R = 1 | X)) = \beta_0 + \beta_1 X_{age} + \beta_2 X_{sex} + \beta_3 X_{SiteofDisease} + \beta_4 X_{PreviousOrNew} + \beta_5 X_{Residence} + \beta_6 X_{OutsideEnrolDist} + \text{spline}(tx\_duration) + \beta_7 X_{adherence} + \text{spline}(since\_tx)$$

Where: $R = 1$ = Responded to phone survey, $SiteofDisease$ = Extrapulmonary/pulmonary TB, $Previous/new$ = previous or new TB case, $Residence$ = Slum/non-slum residence, $OutsideEnrolDist$ = Residential district outside PPSA enrolment district, $tx\_duration$ = WHP-reported months of treatment duration, $adherence$ = proportion of doses taken, $since\_tx$ = months since start of treatment and Nov 2022 (last month of phone survey)

Figure S1. Distribution of inverse probability of selection (IPS) weights

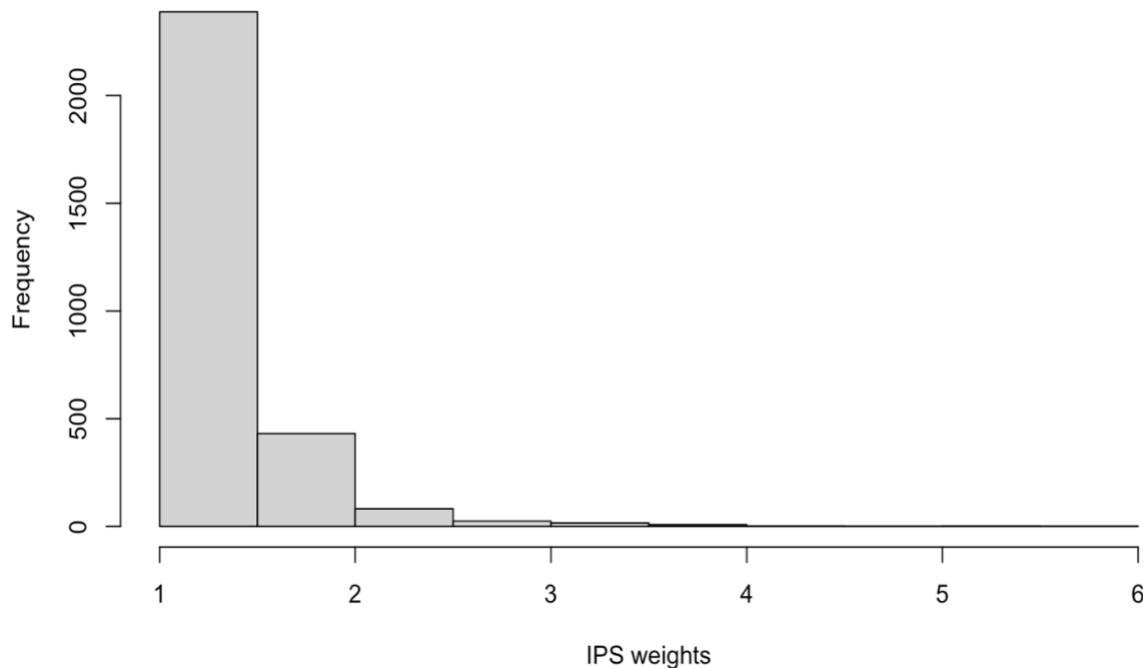


Table S1. IPS weighted and unweighted cumulative hazard of death by treatment phase months

Months of treatment	Unweighted					IPS Weighted				
	N at risk	Cumulative deaths	Cumulative hazard	95%CI		N at risk	Cumulative deaths	Cumulative hazard	95%CI	
3	2867	102	3.50	2.79	4.11	3909	122	3.07	2.45	3.62
6	2722	144	4.98	4.10	5.66	3699	187	4.77	3.91	5.45
9	1258	179	7.01	5.80	7.79	1794	240	6.95	5.71	7.76
12	303	181	7.39	6.04	8.25	470	244	7.36	5.96	8.27
18	41	181	7.39	6.04	8.25	64	244	7.36	5.96	8.27
24	2	181	7.39	6.04	8.25	4	244	7.36	5.96	8.27

IPS = inverse probability of selection

Table S2. IPS weighted and unweighted cumulative hazard of death by post-treatment phase months

Months post treatment	Unweighted					IPS Weighted				
	N at risk	Cumulative deaths	Cumulative hazard	95%CI		N at risk	Cumulative deaths	Cumulative hazard	95%CI	
3	2753	8	0.29	0.09	0.49	3732	15	0.41	0.12	0.69
6	2722	10	0.36	0.14	0.59	3688	19	0.51	0.19	0.83
9	2560	19	0.71	0.39	1.02	3446	35	0.96	0.52	1.39
12	1642	22	0.87	0.50	1.23	2230	39	1.13	0.64	1.60
18	63	27	1.97	0.59	3.30	106	48	2.14	1.02	3.21
22	2	27	1.97	0.59	3.30	3	48	2.14	1.02	3.21

IPS = inverse probability of selection

Equation S2. Cox proportional hazards model for in-treatment case fatality

$$\ln(h(t | X)) = \ln(h_0(t)) + \beta_1 X_{sex} + \beta_2 X_{age} + \beta_3 X_{SiteOfDisease} + \beta_4 X_{previousOrnew} + \beta_5 X_{residence} + \beta_6 X_{OutsideEnrolDist} + \text{spline}(\text{adherence})$$

Where: $h(t)$ is the hazard over time, SiteofDisease = Extrapulmonary/pulmonary TB, Previous/new = previous or new TB case, Residence = Slum/non-slum residence, OutsideEnrolDist = Residential district outside PPSA enrolment district, adherence = proportion of doses taken.

Equation S3. Cox proportional hazards model for post-treatment case fatality

$$\ln(h(t | X)) = \ln(h_0(t)) + \beta_1 X_{sex} + \beta_2 X_{age:time} + \beta_3 X_{SiteOfDisease} + \beta_4 X_{previousOrnew} + \beta_5 X_{residence} + \beta_6 X_{OutsideEnrolDist} + \beta_7 X_{adherence}$$

Where: $h(t)$ is the hazard over time, age: time = interaction term between age (years) and time (post-treatment phase months), SiteofDisease = Extrapulmonary/pulmonary TB, Previous/new = previous or new TB case, Residence = Slum/non-slum residence, OutsideEnrolDist = Residential district outside PPSA enrolment district, adherence = proportion of doses taken.

Section 2: Secondary analysis

Equation S4 – Selection model (secondary analysis)

$$\text{logit}(p(R = 1 | X)) = \beta_0 + \beta_1 X_{age} + \beta_2 X_{sex} + \beta_3 X_{SiteofDisease} + \beta_4 X_{PreviousOrNew} + \beta_5 X_{Residence} + \beta_6 X_{OutsideEnrolDist} + \text{spline}(tx\_duration) + \beta_7 X_{adherence} + \text{spline}(since\_tx) + \beta_8 X_{HIV} + \beta_9 X_{Diabetes} + \beta_{10} X_{After\_expansion} +$$

Where: $R = 1$ = Responded to phone survey, SiteofDisease = Extrapulmonary/pulmonary TB, Previous/new = previous or new TB case, Residence = Slum/non-slum residence, OutsideEnrolDist = Residential district outside PPSA enrolment district, tx_duration = WHP-reported months of treatment duration, adherence = proportion of doses taken, since_tx = months since start of treatment and Nov 2022 (last month of phone survey), After_expansion = enrolled after PPSA program expansion (June 2020).

Table S3. Covariate balance between full cohort and IPS weighted observed cohort (Mean [Variance]), using expanded selection model (Equation S4)

Characteristic	Full cohort	Weighted observed cohort
Age (years)	39.00 (273.27)	39.22 (275.98)
Sex (proportion male) ^a	0.61 (0.24)	0.61 (0.24)
Proportion New TB (vs previous) ^a	0.98 (0.02)	0.98 (0.02)
Proportion with pulmonary TB (vs. extrapulmonary)	0.80 (0.16)	0.80 (0.16)
Adherence (proportion of doses taken) ^a	0.79 (0.14)	0.79 (0.14)
Proportion with non-slum residence (vs. slum residence) ^a	0.97 (0.03)	0.97 (0.03)
WHP-reported months of treatment ^a	6.36 (3.23)	6.35 (3.29)
Proportion with residential district outside of PPSA enrolment district	0.21 (0.17)	0.21 (0.17)
Proportion HIV positive ^a	0.01 (0.01)	0.01 (0.01)
Proportion with diabetes ^a	0.07 (0.07)	0.08 (0.07)
Proportion enrolled after program expansion	0.94 (0.06)	0.94 (0.06)

IPS = inverse probability of selection

^a Imputed

Equation S5 – Treatment phase Cox proportional hazards model (secondary analysis)

$$\ln(h(t | X)) = \ln(h_0(t)) + \beta_1 X_{sex} + \beta_2 X_{age} + \beta_3 X_{SiteOfDisease} + \beta_4 X_{previousOrnew} + \beta_5 X_{residence} + \beta_6 X_{OutsideEnrolDist} + \text{spline}(\text{adherence}) + \beta_7 X_{HIV} + \beta_8 X_{Diabetes} + \beta_9 X_{Smoking} + \beta_{10} X_{COVIDvax1} + \beta_{11} X_{COVIDvax2}$$

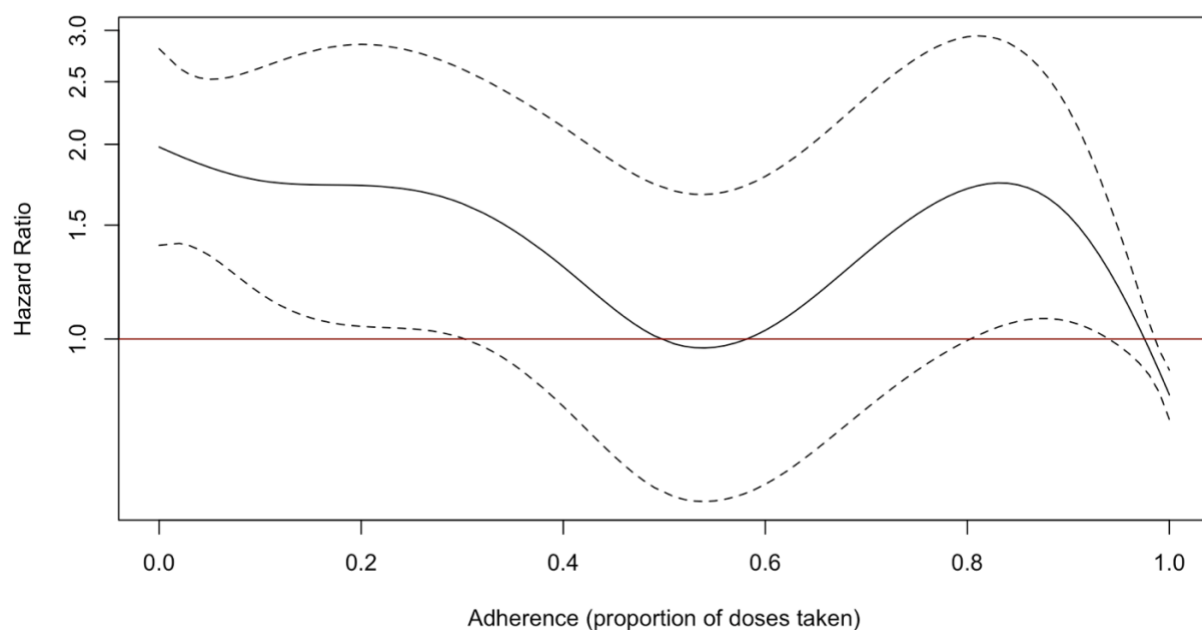
Where: $h(t)$ is the hazard over time, SiteofDisease = Extrapulmonary/pulmonary TB, Previous/new = previous or new TB case, Residence = Slum/non-slum residence, OutsideEnrolDist = Residential district outside PPSA enrolment district, adherence = proportion of doses taken, smoking = current/past smoking (vs. never), COVIDvax1 = one dose of COVID-19 vaccine received, COVIDvax2 = 2 or more doses of COVID-19 vaccine received.

Table S4. Predictors of in-treatment case fatality among people with TB in Bihar, India, in the first year of the COVID-19 pandemic (secondary analysis)

	Unweighted			IPS weighted		
	HR	95%CI		HR	95%CI	
Slum residence (Ref: Non-slum residence)	0.74	0.22	1.50	0.79	0.21	1.52
Previous TB (Ref: New TB)	1.05	0.43	2.58	1.05	0.42	2.57
Pulmonary TB (Ref: Extrapulmonary TB)	1.40	0.96	2.31	1.50	1.01	2.50
Age (years)	1.04	1.03	1.05	1.03	1.03	1.05
Sex, Male (Ref: Female)	1.36	0.95	2.01	1.43	0.94	2.20
District of residence outside PPSA enrolment district	1.54	1.08	2.31	1.70	1.17	2.58
HIV positive	1.76	0.61	13.40	1.63	0.58	15.55
Diabetic	0.70	0.34	1.33	0.63	0.29	1.28
Smoking (current or past, Ref: never)	0.37	0.21	0.60	0.34	0.16	0.60
Number of doses of COVID-19 vaccine received (Ref: none)						
1 dose	0.05	0.02	0.10	0.05	0.02	0.10
2 doses or more	0.01	0.01	0.02	0.01	0.01	0.02

IPS=inverse probability of selection.

Figure S2. Non-linear relationship between TB treatment adherence proportion and hazard of in-treatment death (secondary analysis)



CHAPTER 7: SUMMARY AND CONCLUSIONS

7.1 Summary of results

In this thesis, different indicators of disruptions to TB programs and TB care during the COVID-19 pandemic are measured, including changes in TB case notifications, TB treatment outcomes, and case fatality. In addition to measuring specific indicators, disruptions across the whole pathway of care are also evaluated through the construction of TB care cascades.

In the first manuscript, we reviewed the value of the TB care cascade model and highlighted that current data gaps such as the lack of data digitization, the lack of reliable TB burden estimates, under-notification of TB cases in fragmented and privatized health systems, and the lack of post-treatment follow-up of people with TB hinder the construction of accurate TB care cascades. We called on global bodies and funders to support NTPs in addressing these gaps in order to allow evidence-informed programmatic decision-making based on robust care cascade estimates.

Keeping in mind the limitations and measurement challenges described in the first manuscript, in the second manuscript, we constructed the first active TB care cascade for Lima province, Peru, finding that prior to COVID-19, the largest gap in the care cascade was the treatment completion gap (the difference between those initiating and completing treatment), whilst during COVID-19, the largest gap is now the pre-diagnostic gap (the difference between the number of people estimated to have TB and the number accessing testing).

In the third manuscript, we focused on a key population, people experiencing incarceration, and found that although TB burden in this population is high, people in prison experienced a smaller extent of COVID-19-related disruptions to TB services (although disruption was still present). This included a lower reduction in TB case notifications following the declaration of the COVID-19 emergency (17.7% reduction [95%CI: 17.5-17.9%] in the incarcerated vs. 61.2% reduction [95%CI: 59.9-62.7%] in the non-incarcerated population).

In the final manuscript, we estimated selection-bias-corrected in-treatment and post-treatment CFRs of 6.07% (95%CI: 5.22-6.93%) and 1.27% (95%CI: 0.79-1.79), respectively, among a cohort of people diagnosed with TB in the first year of the COVID-19 pandemic in the private sector in India, finding that both were lower than pre-COVID-19 in-treatment and post-treatment CFRs.³

7.2 Significance of the work

Manuscript 1 aggregates the experiences of researchers across six countries regarding challenges to the accurate estimation of TB care cascades, which, if addressed, would represent not only important improvements in data quality, but also facilitate evidence-based TB program decision-making to improve patient outcomes. Our finding in **Manuscript 2** regarding the shift from treatment completion being the largest gap in the pre-COVID-19 care cascade to accessing testing being the largest gap in the during-COVID-19 cascade underlines that the bottlenecks in care delivery for TB in Peru have fundamentally changed during COVID-19. This provides useful information for the NTP to target scarce resources towards the most-affected gap in the cascade (for example, through active case-finding campaigns to address the backlog of undetected cases). **Manuscript 3** is the first national-level study in Peru on the impact of COVID-19 on TB care in incarcerated populations. Having highlighted that the burden of TB in this population is extremely high, but that TB care was less disrupted in prisons than in the general population identifies an opportunity to focus TB elimination efforts on prison settings in the country, which would in turn support TB elimination in the general population. Lastly, in **Manuscript 4**, the CFRs estimated among the cohort of people with TB in a private sector program in India are higher than necessary to achieve End TB Strategy targets,⁸ highlighting the progress needed to achieve TB elimination.

7.3 Strengths and limitations

The strengths of this work include its scope, evaluating COVID-19-related disruptions to TB care in two different settings (Peru and India) in two continents, as well as among specific subgroups of interest (incarcerated populations). In addition, this work uses various approaches and methods to assess different indicators of COVID-19-related disruptions to TB programs (case

notifications, treatment outcomes, care cascade gaps), which is appropriate considering the multi-faceted impacts the pandemic has had on TB. Lastly, our work is strengthened by its use of large cohorts for the studies that involved primary data collection (n=4,000 in India and n=1,513 in Peru) and otherwise by access to a large national-level database (SIGTB)² for the studies that used secondary data.

Our study estimating the DS- and DR-TB care cascades in Lima province, Peru (**Manuscript 2**), is limited by the various measurement challenges for care cascades discussed in **Manuscript 1** and summarized in **Section 7.1** above. Broadly, the lack of national prevalence surveys for Peru limit the accurate estimation of the first step in the cascade, in turn limiting the accuracy of gaps between this first step and subsequent steps. Accurate estimation of further steps in the cascade is also limited by the use of routine NTP data with incomplete coverage (under-notification). Utilizing the same NTP data source, our study investigating the impact of the COVID-19 pandemic on TB notifications and outcomes in the non-incarcerated and incarcerated populations in Peru (**Manuscript 3**) was subject to similar limitations with respect to under-notification in routine programmatic data. Further limitations specific to this study included the lack of a dynamic indicator of incarceration status or information on length of incarceration, as only incarceration at time of diagnosis was available. Finally, the main limitations in **Manuscript 4** (estimating case fatality among people diagnosed with TB in the first year of the COVID-19 pandemic in India) included the fact that this was a private sector cohort who is likely to have received services beyond the general standard of care, meaning that they may have experienced better treatment outcomes than the general population in India. In addition, it is possible that during pandemic restrictions, sicker patients were less able to seek care, and therefore less likely to be diagnosed and enrolled in the PPSA program, which may contribute the lower CFRs observed in our study (compared to pre-COVID-19).

7.4 Directions for future work

This work has highlighted several avenues for future work. Firstly, our commentary on TB care cascades (**Manuscript 1**) and our cascade analysis in Peru (**Manuscript 2**) underline the need for

national TB prevalence surveys, to generate accurate estimates of TB burden in the country. In addition, estimates of diagnostic performance of TB tests in regions outside of Lima are needed, to allow estimation of care cascades in other regions of the country. As health systems and diagnostic capacity is highly concentrated in the capital region, care cascades in other regions may show important differences in care delivery gaps, but their accurate construction requires region-specific parameters.

The study on TB notifications and outcomes in the non-incarcerated and incarcerated populations of Peru (**Manuscript 3**) has raised multiple questions for further investigation. Firstly, given that the present analysis focused on drug-susceptible TB and that Peru is one of 30 high burden countries for drug-resistant TB,⁹⁵ the impact of COVID-19 on drug-resistant TB notifications and outcomes in the non-incarcerated and incarcerated populations should also be explored. Further analyses that link individual-level penitentiary databases with NTP data to obtain additional relevant variables, such as indicators of length of incarceration would also be valuable, as our study was limited to incarceration at time of diagnosis as the sole indicator of incarceration status (which, realistically, is dynamic).

In addition, although we have shown that the burden of TB is extremely high in Peru's prisons compared to in the general population, it is unknown whether most people are already infected with TB at entry into prison and subsequently develop active TB disease, or whether TB infection is acquired in prison. As screening for TB infection is not routinely conducted at entry into prisons in Peru, a study determining baseline prevalence of TB infection at entry into prison as well as prospectively determining incidence of active TB among a sample of people experiencing incarceration would be highly valuable to inform TB prevention efforts in this high-risk population. We plan to explore these questions and others related to the burden of TB in prisons in Peru in my postdoctoral work.

Lastly, our study in India (**Manuscript 4**) highlighted that estimates of case fatality in public sector TB programs are needed, since our private sector estimates represent a population who

received care beyond what may be available to the general population (such as TB treatment adherence support). In addition, as our estimates represent all-cause mortality, further studies could estimate TB-specific fatality, for example via verbal autopsies.

7.5 Conclusion

It is clear that the COVID-19 pandemic represents a devastating setback for TB elimination globally, but to mitigate the impact of COVID-19-related disruptions on TB programs and patient outcomes, this impact must be measured. This thesis therefore evaluated various indicators of TB care disruptions in two high TB burden countries during the COVID-19 pandemic. Our analysis in India highlights that current case fatality among people with TB falls short of the reductions in TB deaths required to achieve global and domestic TB elimination goals. Our analyses in Peru have identified important changes in the largest gaps across the TB care cascade during the pandemic, as well as differential effects in a key population (people experiencing incarceration), providing useful information for program planning as the NTP gradually recovers from COVID-19 and can renew efforts to end TB.

BACK MATTER

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Doctoral training publications list:

Publications in Peer-Reviewed Journals:

1. **Faust L**, Naidoo P, Caceres-Cardenas G, Ugarte-Gil C, Muyoyeta M, Kerkhoff AD, Nagarajan K, Satyanarayana S, Rakotosamimanana N, Grandjean Lapierre S, Adedeji Adejumo O, Kuye J, Oga-Omenka C, Pai M, Subbaraman R. Improving measurement of tuberculosis care cascades to enhance people-centered care. *Lancet Infect Dis*. 2023 Aug 28:S1473-3099(23)00375-4.
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