Tuberculosis Care Pathways Before and During the COVID-19 Pandemic in Bandung, Indonesia

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For my mum, dad, and sister
For Kulfi and Jalfrezi

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List of Abbreviations

95% CI	Confidence Interval with 5% error rate
ACF	Active case finding
AFB	Acid-fast bacillus
CHC	Community Health Centre
COVET	COVID-19 Effect on TB
CXR	Chest X-ray
EPTB	Extra-pulmonary tuberculosis
IQR	Interquartile range
LTBI	Latent Tuberculosis Infection
MDR/RR-TB	Multidrug resistant/rifampicin resistant tuberculosis
MITBC	McGill International TB Centre
MoH	Ministry of Health
NAAT	Nucleic acid amplification test
NTEP	National TB Elimination Program
NTP	National TB Program
PP	Private Providers
PPA	Patient Pathway Analysis
PTB	Pulmonary tuberculosis
SR	Systematic Review
TB	Tuberculosis
VOC	Variant of Concern

1. Abstract

Background

Before COVID-19 was declared a pandemic, tuberculosis disease (TB) was the world's leading infectious killer, with 10.6 million incident cases and 1.6 TB-related deaths in 2021. The biggest barrier in TB control remains locating the 'missing' people with TB, individuals who remain undiagnosed, or diagnosed but not notified to the National TB Program (NTP). Indonesia accounts for 10% of all missing people with tuberculosis (TB) worldwide. The COVID-19 pandemic widened this gap, and Indonesia saw a massive drop in TB notifications during 2020 and 2021 as compared to previous years. The private provider's share in Indonesia's primary health care sector is above 70% but it contributes to less than 20% of TB case notifications. Studying health seeking behaviours during the pandemic in the private sector will be beneficial in guiding interventions that promote early detection of TB, retention of individuals with TB, and treatment adherence in a sector that is not yet fully engaged with the NTP.

Objective

This cross-sectional study aimed to explore the care pathways of individuals with TB. By investigating delays to initial consultation, diagnosis, treatment, and encounters with healthcare providers until diagnosis, we can learn about the obstacles that individuals with TB face while trying to access care, and what factors potentially influence individuals to drop out of the journey to successful treatment completion.

Methods

Two independent samples of individuals with TB were recruited (pre-COVID-19 in 2017 and during-COVID-19 in 2021) from privately owned clinics and private hospitals in Bandung, Indonesia. We investigated where individuals went to access primary care, diagnostics, treatment management and the time interval between each visit, how many encounters they had with which healthcare providers before obtaining a diagnosis for TB, and the risk factors associated with delays and encounters, adjusting for individual-level factors.

Findings

We recruited 149 individuals in the during-COVID-19 sample and utilised 225 responses from the pre-COVID-19 sample. We calculated descriptive statistics and visualised the two samples' care-seeking journey. A higher proportion of participants sought care with informal providers for their initial consultation after the onset of symptoms during-COVID-19 as compared to pre-COVID-19. Median patient delay increased from 28 days (IQR: 10, 31) to 32 days (IQR: 14, 90) between the two timepoints, median doctor delay increased from 15 days (IQR: 12, 22) to 18 days (IQR: 14, 26), and treatment delay stayed constant at 1 day for the during-COVID-19 sample (IQR: 0, 3) and the pre-COVID-19 sample (IQR: 0, 4). Median number of encounters in the pre-COVID-19 sample was 5 encounters (IQR: 4, 8) and 7 encounters (IQR: 5, 10) in the during-COVID-19 sample. Employed individuals faced lower patient delays as compared to unemployed individuals (adjusted median -20.13, p value: 0.039), and individuals who went to private hospitals for their initial consultation as compared to CHCs underwent a lower number of encounters until they were given a diagnosis (adjusted median -4.29 encounters, p value: 0.001).

Discussion

COVID-19 has disrupted care seeking for TB, as evidenced by higher patient delays, and higher median number of encounters until diagnosis. It is evident that once individuals are identified as having TB, they are connected to treatment quickly, despite some being referred for treatment management to different providers. Care pathways for TB in urban Indonesia remain complex, and the need for private provider engagement is now more urgent and crucial than ever.

Resume

Contexte

L'Indonésie est l'un des trois pays qui ensemble comptent plus de 46% de tous les patients tuberculose (TB) manquants dans le monde, et plus de la quête de soins se passe dans le secteur privé. La pandémie de COVID-19 a aggravé cette différence et l'Indonésie a connu la plus forte baisse des notifications de tuberculose en 2020 et 2021 par rapport aux années précédentes. L'étude des comportements des individus en quête de soins pendant la pandémie sera bénéfique pour orienter les interventions qui favorisent la détection précoce des cas de tuberculose, la rétention des personnes atteintes de tuberculose tout au long de la cascade de soins et l'observance du traitement.

Objectif

Cette étude transversale répétée visait à comparer les retards pré-COVID-19 et pendant la COVID-19 à la consultation initiale, au diagnostic et au traitement, ainsi que le nombre de rencontres avec des fournisseurs de soins jusqu'au diagnostic, et a utilisé la régression quantile pour étudier les facteurs liés aux retards et nombre de rencontres.

Méthodes

Les personnes ont été recrutées dans des cliniques privées et des hôpitaux privés à Bandung, en Indonésie. À l'aide de deux enquêtes transversales, une menée entre 2017 et 2019, et une répétition menée pendant la vague Delta de la pandémie de COVID-19 (2021-2022), nous avons interrogé les personnes nouvellement diagnostiquées avec la tuberculose sur leur parcours en quête de soins avec les fournisseurs de santé. Toutes les visualisations et analyses statistiques ont été réalisées avec R.

Résultats

Nous avons recruté 149 personnes pendant la COVID-19 et utilisé 225 réponses de pré-COVID-19. Une proportion plus élevée de participants ont visité des prestataires informels pour leur consultation initiale après l'apparition des symptômes pendant la COVID-19 par rapport à pré-COVID-19. Pré-COVID-19, 45.8% des personnes diagnostiquées par des praticiens privés ont été référées à des centres de santé communautaires (CSC) pour la gestion du traitement, tandis que 86,9% des personnes diagnostiquées par des praticiens privés pendant la pandémie ont été référées à des CSC pour la gestion du traitement. Le délai médian du patient est passé de 28 jours (EI : 10 , 31) à 32 jours (EI : 14, 90) entre les deux moments, le délai médian du médecin est passé de 15 jours (EI : 12, 22) à 18 jours (EI: 14, 26) et le délai de traitement est resté constant à 1 jour pre-COVID-19 (EI : 0, 4) et durant-COVID-19 (EI : 0, 3). Le nombre médian de rencontres pré-COVID-19 était de 5 (EI: 4, 8) et de 7 (EI: 5, 10) pendant la COVID-19. Les personnes occupées ont vécu des retards de traitement inférieurs à ceux des personnes sans emploi (médiane ajustée -20.13 jours, IC à 95%: -39.14, -1.12, p value : 0.039), et les personnes qui se sont rendues chez des praticiens privés ou des hôpitaux privés pour leur première consultation au lieu des CSC ont eu un nombre inférieur de rencontres jusqu'à ce qu'ils reçoivent un diagnostic (médiane ajustée -4.29 rencontres, IC à 95%: -6.76, -1.81, p value : 0.001).

Discussion

La COVID-19 a perturbé la quête de soins pour la tuberculose, comme en témoignent les retards plus importants chez les patients et le nombre médian plus élevé de rencontres jusqu'au diagnostic. Cependant, il est évident qu'une fois que les individus sont identifiés comme ayant la tuberculose, ils sont rapidement connectés au traitement, bien que certains soient référés pour la gestion du traitement à différents prestataires. Les parcours de soins pour la tuberculose restent complexes et la nécessité d'un engagement des prestataires privés est maintenant plus urgente et cruciale que jamais. L'augmentation de la capacité de diagnostic et le renforcement des liens entre les prestataires de niveaux inférieur et supérieur pourraient être constructifs pour réduire les retards des patients et le changement de prestataire.

2. Introduction

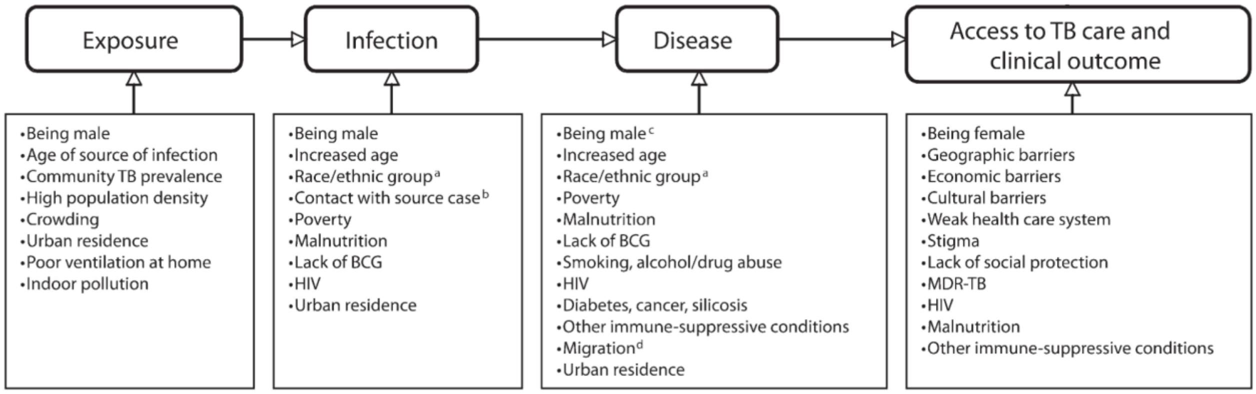
The COVID-19 pandemic has undone years' worth of progress in the fight against tuberculosis (TB)[1,2]. Modelling analyses show that an additional 43 million people could develop TB over the next eight years, resulting in an additional 6.6 million TB deaths[3]. Indonesia is a high TB burden country that has been significantly affected by the COVID-19 pandemic, based on the findings that case notifications decreased by 14% and treatment coverage decreased by 47%, it is evident that the COVID-19 pandemic has had disastrous implications in TB control. Our study utilised two cross-sectional surveys conducted before and after the onset of the pandemic. We quantified the delays that individuals with TB faced while trying to access care for their illness, their journey through the care cascade, the encounters individuals had with healthcare providers before they for a TB diagnosis, and examine the factors associated with patient delay and the number of encounters. We found that the care-seeking of individuals with TB did become more complex during the COVID-19 pandemic as compared to before the pandemic. The care-seeking delays were longer, and on average, more visits to informal healthcare providers before diagnosis were taking place. However, post-diagnostic delays remained relatively unchanged between the two time-points. Our study is the first to report on TB care pathways in Indonesia since the onset of the pandemic, with pre-pandemic comparison in the same setting. The results enrich our understanding of the impact of the COVID-19 pandemic on the functioning of private healthcare markets. Recommendations from our study include publicizing the success of the health care system in quickly connecting individuals with TB to treatment to promote care-seeking in the formal health sector, ramping up active case finding projects so that individuals who would be delaying their care-seeking are found, and conducting more pharmacy engagement strategies to involve the informal health sector in referring individuals with presumptive TB from pharmacies to national TB program associated facilities.

3. Literature Review

3.1 Pulmonary Tuberculosis Disease

Despite tuberculosis (TB) disease being preventable and treatable, it is the 13th leading global cause of death, globally, and the second leading infectious killer, after COVID-19[4]. *Mycobacterium tuberculosis* can potentially affect all organs, leading to either pulmonary TB (lung disease) or extrapulmonary TB (skin, lymph nodes, etc.). This bacterial infection spreads when an individual with the disease produces aerosols containing *Mycobacterium tuberculosis* by sneezing, coughing, talking, or spitting, and another person inhales these droplets[5]. Once the droplets are in the lung, the individual may begin developing TB infection which can then progress to active pulmonary tuberculosis disease (PTB) over subsequent months or years. Otherwise, the bacterium can spread from the lungs, via lymphatic fluids or the bloodstream and seed other organs, resulting in extrapulmonary TB. There is a distinction in the people who have active tuberculosis disease, and those who are simply infected (latent tuberculosis infection, LTBI). LTBI is evidenced by a positive tuberculin or interferon-gamma release assay, but a lack of clinical symptoms, radiological abnormalities, and microbiological evidence. Active TB disease is unlikely and will not occur in over 90% of those infected[5–9].

There are several risk factors that may contribute to LTBI progressing to active PTB over time: being doubly infected with HIV, undernutrition, having diabetes, or other immunosuppressing smoking regularly, and being in an environment with high likelihood of continuous exposure to TB[8,10,11]. Several social determinants (such as malnutrition, poverty, stigma) also contribute to making TB a prominent and persistent public health issue.[12,13] (**Figure 3.1.1**). Hargreaves *et al* noted that being male is a high-risk factor for TB exposure, infection, and pathogenesis of disease, but access to TB care is more limited for women than for men. Women may also face worse clinical outcomes. TB is more rampant in urban areas than rural areas and individuals are more likely to be exposed in crowded areas with high population densities and the rapid urbanization of cities is a large contributor of the problem[12].



Note. BCG = bacillus Calmette-Guerin; MDR = multidrug resistant; TB = tuberculosis.

[a] TB infection and disease rates are often reported to be higher among Black Africans and Hispanics than among Whites.

[b] Increased TB risk associated with contact with a case of TB depends on the infectivity of the source case, the degree of exposure to the case by the susceptible person, and the degree of susceptibility of a person to infection.

[c] It is unclear whether this observation can be explained by differences in case finding or whether it is due to different susceptibility to TB among sexes. TB disease tends to be more common among males.

[d] Migrants' increased risk of TB in many settings may result from higher exposure to TB in country of origin or experience of worse socioeconomic living conditions compared with residents.

Figure 3.1.1 - Risk factors for different stages of TB pathogenesis and epidemiology, figure and caption taken directly from Hargreaves et al (2011)[12]

Early diagnosis of PTB and timely initiation of treatment can be extremely beneficial in not only a successful recovery of the individual, but also curb TB transmission in the household and community. Delays in diagnosis for people with TB in the community can lead to worse health outcomes, increased risk of mortality, and can prevent an epidemic from being controlled[14].

3.2 Epidemiology of Tuberculosis

It has been estimated that around a quarter of the world is infected with *Mycobacterium tuberculosis*, the bacterium responsible for the contagious and infectious disease, tuberculosis (TB)[6,15], but a vast majority of these people may have cleared the infection while still being positive on immune-based tests[16]. This infectious agent has origins that date as far back as 70,000 years[17], and used to be the world's leading cause of death - until the SARS-CoV2 virus that causes COVID-19 took its place[4]. TB epidemics have occurred throughout history, affecting European and North American nations in the 18th century, and then travelling as far as Japan and Puerto Rico in the 20th century[5]. As living standards improved in the 1900s, and the global North began to have better access to adequate housing, nutrition, and income, TB deaths began to fall[5,18]. Presently, TB manifests is endemic in sub-Saharan Africa and multiple Asian countries[1] and over 70% of the global burden, as defined by incidence, is shared by only eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.

There were an estimated 1.6 million TB related deaths among individuals (including people living with HIV) in 2021, an increase from 1.4 million TB deaths in 2019[2]. The worldwide average incidence rate of TB in 2021 was 134 cases per 100 000 population, with an absolute incidence of 10.6 million people worldwide in 2021. TB occurred mostly in the WHO regions of South and East Asia (43%), Africa (23%) and the Western Pacific (18%) in 2021[2] (**Figure 3.2.1)**. In 2021, an estimated 10.6 million people (95% CI: 9.9–11 million) fell ill with TB, increase of 4.5% from 10.1 million (95% CI: 9.5–10.7 million) in 2020[2].

Estimated TB incidence in 2021, for countries with at least 100 000 incident cases

The countries that rank first to eighth in terms of numbers of cases, and that accounted for about two thirds of global cases in 2021, are labelled.

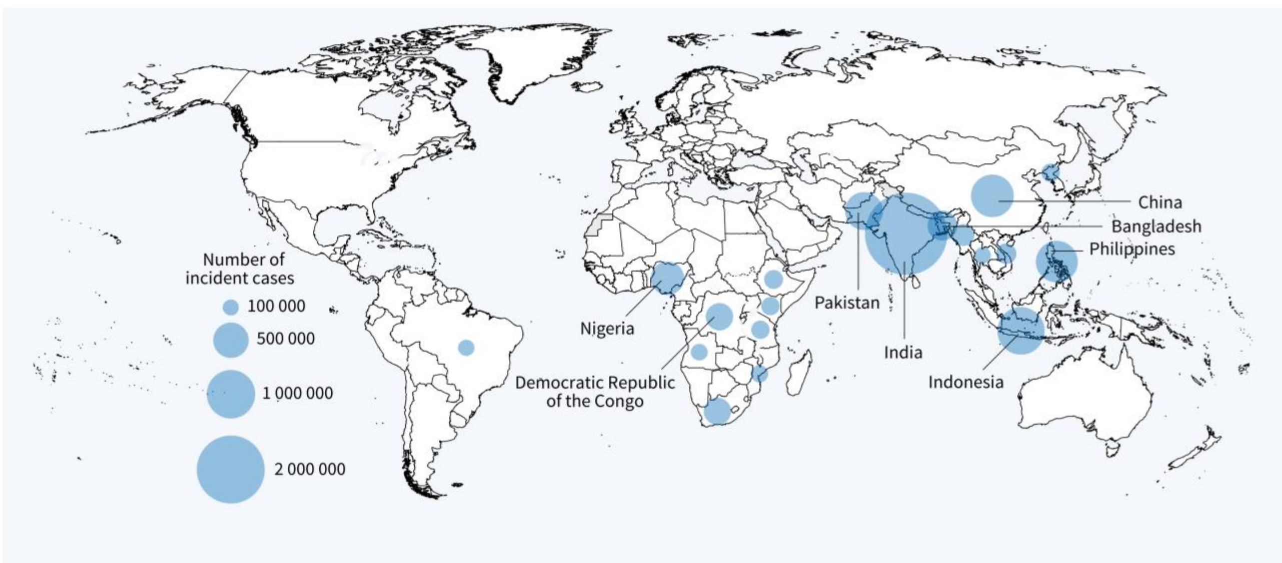


Figure 3.2.1 – Estimated TB incidence in 2021, for countries with at least 100 000 incident cases. Figure and caption taken from Global Tuberculosis Report 2022[2]

Even before the pandemic, the incidence rates for TB around the world were not declining at a promising rate[1,19]. The United Nations Sustainable Development Goals include ending the TB epidemic by 2030 under Goal 3. Three targets have been set as the End TB goals for 2030 (**Figure 3.2.1**): a 90% reduction in the number of TB deaths, an 80% reduction in the TB incidence rate (new cases per 100 000 population per year) compared with levels in 2015, and no family affected by TB to face any catastrophic costs. In the 2019 Global TB report, it was declared that most high burden countries were not on track to meet even the 2020 milestones for the end TB goals. The latest Global TB report shows that while the target was for a 50% reduction in TB incidence rates between the years 2015-2021, worldwide, the cumulative reduction was only 10%.[2,20]

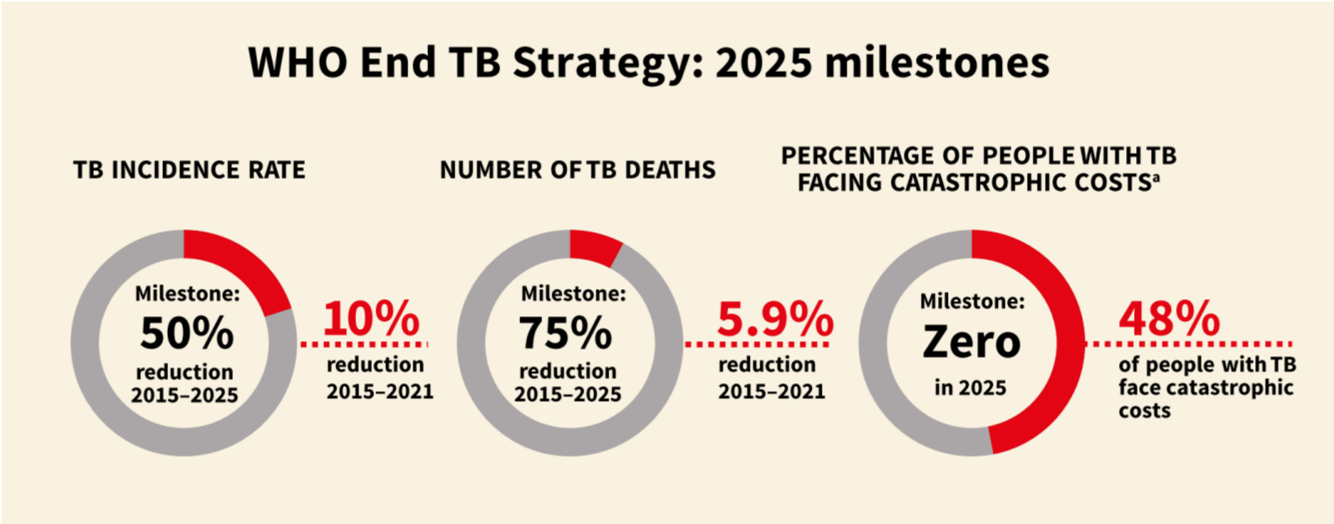


Figure 3.2.2 – Global Tuberculosis Report 2022[2]

3.3 Tuberculosis in Indonesia

It was found in the Global Burden of Disease Study from 2019 that Indonesia faces a double burden of communicable and non-communicable diseases, and this burden is not uniform across the archipelago of islands that make up the country. While non-communicable diseases such as ischaemic heart disease and diabetes have contributed more and more to Indonesia's disability-adjusted life-years (DALYs) over the years, TB has stayed a constant source[21].

Indonesia accounts for 8.4% of estimated incident cases of TB worldwide, making it the third highest burden country with a total TB incidence of 969 000 in 2021, as estimated by the WHO[2]. From the WHO directly, "these estimates are based on annual case notifications, assessments of the quality and coverage of TB notification data, national surveys of the prevalence of TB disease and on information from death (vital) registration systems"[1]. Out of this number, 536 423 cases were missing[2], meaning they remain either undiagnosed, or diagnosed but not notified to the National TB Elimination Program (NTEP). This figure is calculated by comparing the case notifications that are reported from the NTEP. Indonesia also accounts for around 10% of all missing people with TB worldwide[20]. Total TB incidence rate was estimated at 354 per 100 000 population in 2021. The HIV-negative mortality rate in 2021 was 52 per 100 000 population, and the absolute number of deaths due to TB was 144 000. Notifications of people newly diagnosed and relapsed with TB were 570 289 in 2019[20], and only 432 577 in 2021[2]. This decrease in case notifications can be attributed to disruptions in TB diagnostic and treatment services due to the pandemic[1]. Indonesia displayed a steady decline in overall TB incidence before 2020, but it has been since reported that the decline in TB incidence has slowed down since the onset of the pandemic.[22] Multidrug-resistance and rifampicin resistant TB (MDR/RR-TB) is another ongoing epidemic in Indonesia; Indonesia is one of 10 countries that accounts of 70% of the global gap between estimated global incidence of MDR/RR-TB and the number of people enrolled in treatment in 2021. In 2020, out of 7921 laboratory-confirmed cases of MDR/RR-TB, only 5232 (66%) of these individuals were started on treatment[1]. Various factors are associated with non-adherence to TB treatment. From the individual's side, pessimistic knowledge and beliefs about TB treatment, addiction, and side effects of TB treatment could discourage individuals from adhering to TB treatment[23]. From the provider's side, low quality care, failure to follow up, and limited access to all medications required to treat TB (i.e., MDR-TB drugs) contributes to the gap between individuals diagnosed and treated[24]. In 2021, total TB treatment coverage in Indonesia was only 45%[2].

In 2021, it was found that prevalence of TB is higher among men[2], and higher in urban areas than in rural settings[25] (**figure 3.3.1**). These findings are consistent with other high burden settings, where men are found to display a higher burden of TB[26–29], and respondents in urban settings face a higher burden of TB[30]. Prevalence burden was observed to be higher in those aged 55 and above[25,31].

Characteristics	Observed		Chest x-ray		Sputum AFB		Sputum Culture		Sputum Genetic Test	
	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI
Total	759.1	589.7–960.8	725.2	718.1–732.2	256.5	210.1–302.9	545.0	509.5–583.0	894.9	848.7–928.2
Age group (years)										
15–24	360.8	254.3–494.7	783.8	741.2–828.7	137.5	77.3–197.8	414.5	330.7–518.3	851.8	659.6–944.6
25–34	753.4	561.8–995.0	109.1	104.3–114.2	239.9	155.5–324.4	561.4	477.0–659.7	893.6	766.1–955.6
35–44	713.8	527.4–941.0	142.9	137.3–148.7	265.1	170.7–359.4	584.7	503.8–677.5	933.3	809.7–978.7
45–54	835.5	608.9–1,108.3	205.7	198.5–213.2	271.5	166.3–376.7	479.7	408.9–561.8	891.3	761.4–954.6
55–64	1,029.5	734.1–1,398.5	284.7	274.2–295.5	318.6	174.1–463.1	529.6	446.5–627.2	909.1	748.6–971.1
65 or more	1,581.7	1,122.7–2,153.7	373.7	360.9–386.8	527.6	292.0–763.2	678.9	583.6–788.6	875.0	729.5–947.8
Gender										
Male	1,082.7	872.8–1,337.3	200.8	196.4–205.3	392.5	314.5–470.5	607.9	558.6–661.2	896.9	839.9–935.2
Female	460.6	353.6–590.8	133.5	130.1–137.1	131.0	87.6–174.4	463.0	414.2–517.3	890.4	794.4–944.7
Area Classification										
Urban	845.8	678.2–1,047.7	150.1	146.2–154.0	282.2	219.6–344.7	736.6	673.8–804.7	912.0	847.3–950.8
Rural	674.2	511.9–873.6	177.9	174.0–181.9	231.4	163.3–299.5	408.8	369.0–452.7	876.1	800.7–925.6
Region										
Sumatra	913.1	696.7–1,176.7	159.2	154.1–164.3	307.4	208.3–406.5	635.9	564.9–715.1	875.0	775.4–934.2
Java-Bali	593.1	447.2–770.6	152.1	147.9–156.3	216.6	146.5–286.8	487.9	433.6–548.6	838.7	748.4–900.8
Other	842.1	634.7–1,091.8	864.0	809.0–921.4	259.9	184.2–335.6	2,129.8	1,664.0–2,735.6	941.2	663.6–992.3

Data were presented in counts and percentages.
AFB, Acid-fast bacilli; CI, confidence interval; TB, tuberculosis.

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Figure 3.3.1 - Estimated TB prevalence [in Indonesia] per 100,000 population aged 15 years and over according to demographic characteristics and diagnostic approach, figure and caption taken directly from Noviyani et al (2021)[25]

This thesis primarily focuses on adults in an urban city in Indonesia who were seeking care for symptoms indicative of TB and were then diagnosed with pulmonary TB.

3.4 Screening, Diagnostics, and Treatment of TB

Signs and symptoms used by various NTEPs of countries to screen for TB infection are persistent cough, night sweats, weight loss, loss in appetite, fever, coughing up blood, etc. This list is not exhaustive but are most common in people with TB who are past the early stages of infection. Verbal symptom screening is common, but chest x-rays (CXR) are better screening tools. It has been proven to be more sensitive and a more efficient way of indicating whether an individual needs a confirmatory, microbiological diagnostic test.[32] Additionally, ramping up the of CXR could increase the likelihood of correct clinical diagnosis and finding the individuals who are missed by smear microscopy[32].

Verbal symptom screening used to be the primary diagnostic test for TB until more sophisticated methods were developed[17,33]. Acid-fast bacillus (AFB) smear microscopy is a diagnostic tool that uses sputum samples to detect active TB infection using microscopic examination[33–35]. Its sensitivity is 30-40% for a single sample, increasing to 65-75% with repeated tests, meaning that it is correctly able to identify that an individual has active TB disease around 70% of the time, when 2 or more samples collected at different time points are tested. Its specificity is over 98%[34,36]. In 2010, the WHO endorsed a novel rapid test for TB diagnosis - nucleic acid amplification test (NAAT)[37,38]. The Xpert MTB/RIF assay is a cartridge based NAAT (Cepheid, Sunnyvale, CA, USA) and is a fully automated molecular test. Within 2 hours, it is able to detect *M tuberculosis*, as well as rifampin resistance[39]. However, in practice, the duration between an individual depositing their sputum for testing and obtaining a result varies. A study in Indonesia using hospital records from 2015-2016 showed that the median duration between submitting sputum and getting the Xpert result was two days (IQR 1–4).[40] In the 2021 update of the Consolidated Guidelines on Tuberculosis (Module 3: Diagnosis - Rapid diagnostics for tuberculosis detection), the WHO explicitly states that Xpert MTB/RIF should be used as an initial diagnostic test instead of the less sensitive smear microscopy test.

Nevertheless, despite its low sensitivity, many low-resource settings in Indonesia use AFB smears, and chest radiography (Chest X-ray, CXR) as their primary diagnostic tool[41]. Physicians often use CXRs to identify abnormalities in the lung and to complement a smear microscopy test. CXRs are also used to quickly diagnose people living with HIV in low-resource settings[5].

However, in a report in 2016 titled, *Chest Radiography in Tuberculosis: Summary of current WHO recommendations and guidance on programmatic approaches*, the WHO states that CXR cannot be a standalone diagnostic test for detection of TB. It has to be used in addition to other microbiological tests in order to establish a comprehensive TB diagnosis.[42]

The WHO also has published literature to guide treatment plans for individuals with TB. Courses differ depending on whether they are living with HIV, newly infected, being re-treated for TB, or people with drug-resistant or multi-drug resistant TB. New individuals with drug-susceptible pulmonary TB should receive a daily dosing regimen containing 6 months of rifampicin: isoniazid, rifampicin, ethambutol, and pyrazinamide, as recommended by the 2022 WHO consolidated guidelines on tuberculosis[43]. In people with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months as recommended by the 2022 WHO consolidated guidelines on tuberculosis[44]. In 1997, the WHO recommended DOTS – directly observed treatment, short course, containing five main principals[45]:

1) Political and national TB program support
2) Increased and maintained high case detection
3) Provision of adequate supply of the TB drugs
4) Direct monitoring of people with TB on treatment to ensure adherence
5) Systematic monitoring and record keeping of every individual with TB until they are cured

This program was scaled, as between 1995 and 2008, evidence suggests that globally, approximately 6 million deaths were averted, 36 million people were cured, and case fatality dropped from 8% to 4%[9]. DOTS strives for success with the multiple components involved in its implementation, from logistical aspect (recommending a healthcare worker, community volunteer, or religious leader in the form of a caretaker to supervise individuals taking the medication and building a relationship with the individual to ensure adherence and prevent default), to the political aspect, as it is formulated into the policy to ensure government commitment and adequate resource allocation[45].

3.5 The relationship between tuberculosis and the novel coronavirus disease.

SARS-COV-2 is a novel coronavirus that emerged in Wuhan, China, in December 2019. It is highly transmissible, pathogenic, and caused outbreaks globally in the span of a couple of months, much like the two coronavirus disease outbreaks that preceded it, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[46]. A pandemic is defined as an epidemic (widespread occurrence) of an infectious disease that has spread over multiple continents, worldwide. On March 11th, 2020, the COVID-19 outbreak was declared a pandemic, due to its extremely high transmission rate and high likelihood to cause severe infection[47], and this pandemic is still ongoing.

COVID-19 disease and PTB are interrelated. They are both airborne infectious diseases, and both show some similar clinical symptoms. Namely, cough, fever and difficulty breathing. Coinfection of TB and COVID-19 also lead to worse health outcomes for individuals with TB. Mortality is more likely with longer time-to-recovery, and shorter time-to-death[48]. Similarly, preliminary studies have found that both latent and active TB disease leads to a higher susceptibility to COVID-19.[49] The onset of the pandemic and lockdowns also meant that maintaining TB care became difficult (**Figure 3.5.1)**. Individuals had significant difficulty accessing routine healthcare facilities and providers faced closures and had to reallocate resources as priorities shifted[50,51]. According to the WHO, more than 4.2 million people were either not diagnosed or not reported during 2021. Of the estimated 10.6 million new TB cases in 2020, only 6.4 million people were diagnosed and reported, reflecting a large decline as compared to the previous years (**Figure 3.5.2)**. These case notifications have not been this low since 2012. Sixteen countries accounted for 93% of this reduction, with Asian countries (especially India, Indonesia, the Philippines, and China) reflecting the highest fraction. Globally in 2021, there were an estimated 1.4 million deaths among HIV-negative people, and an additional 187 000 deaths among people living with HIV. These numbers represent the second year-on-year increase of TB deaths since 2005[2].

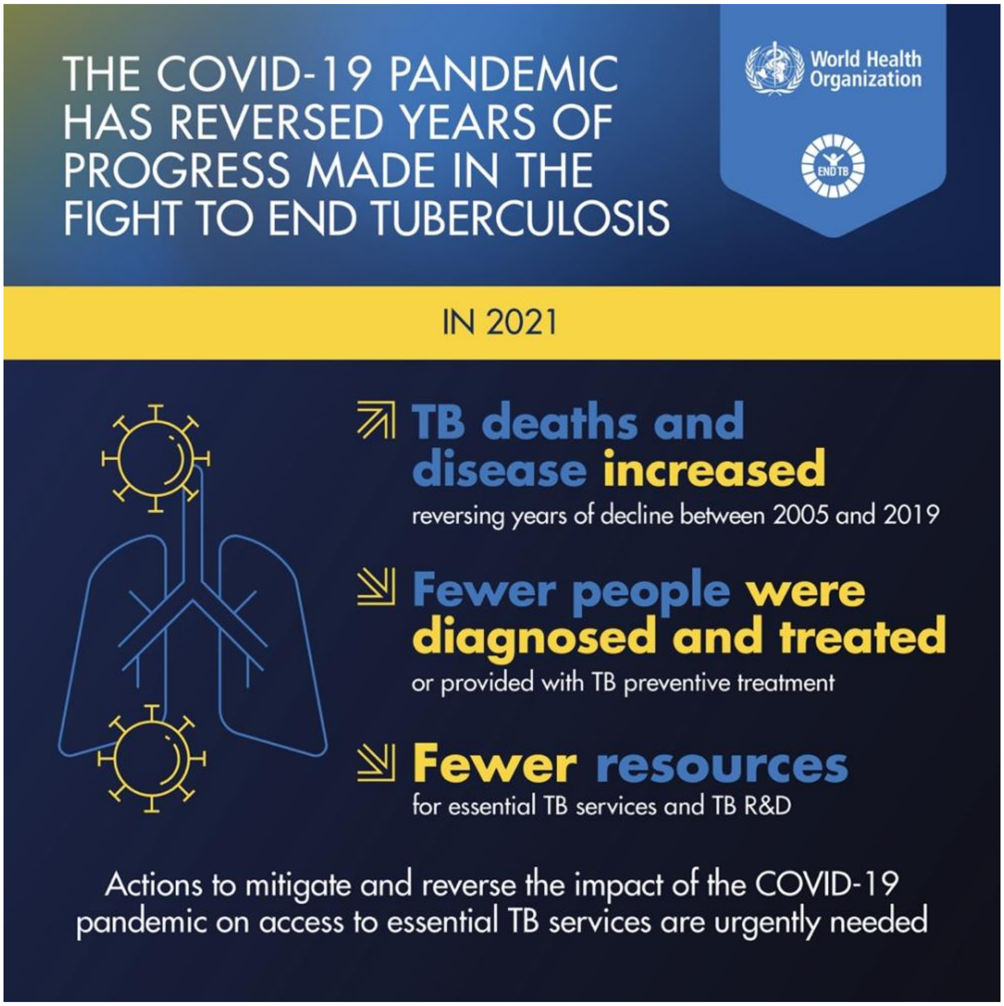

Figure 3.5.1 – The COVID-19 pandemic has reversed years of progress made in the fight to end tuberculosis. Infographic and caption taken from World Health Organization, Tuberculosis and COVID-19[2]

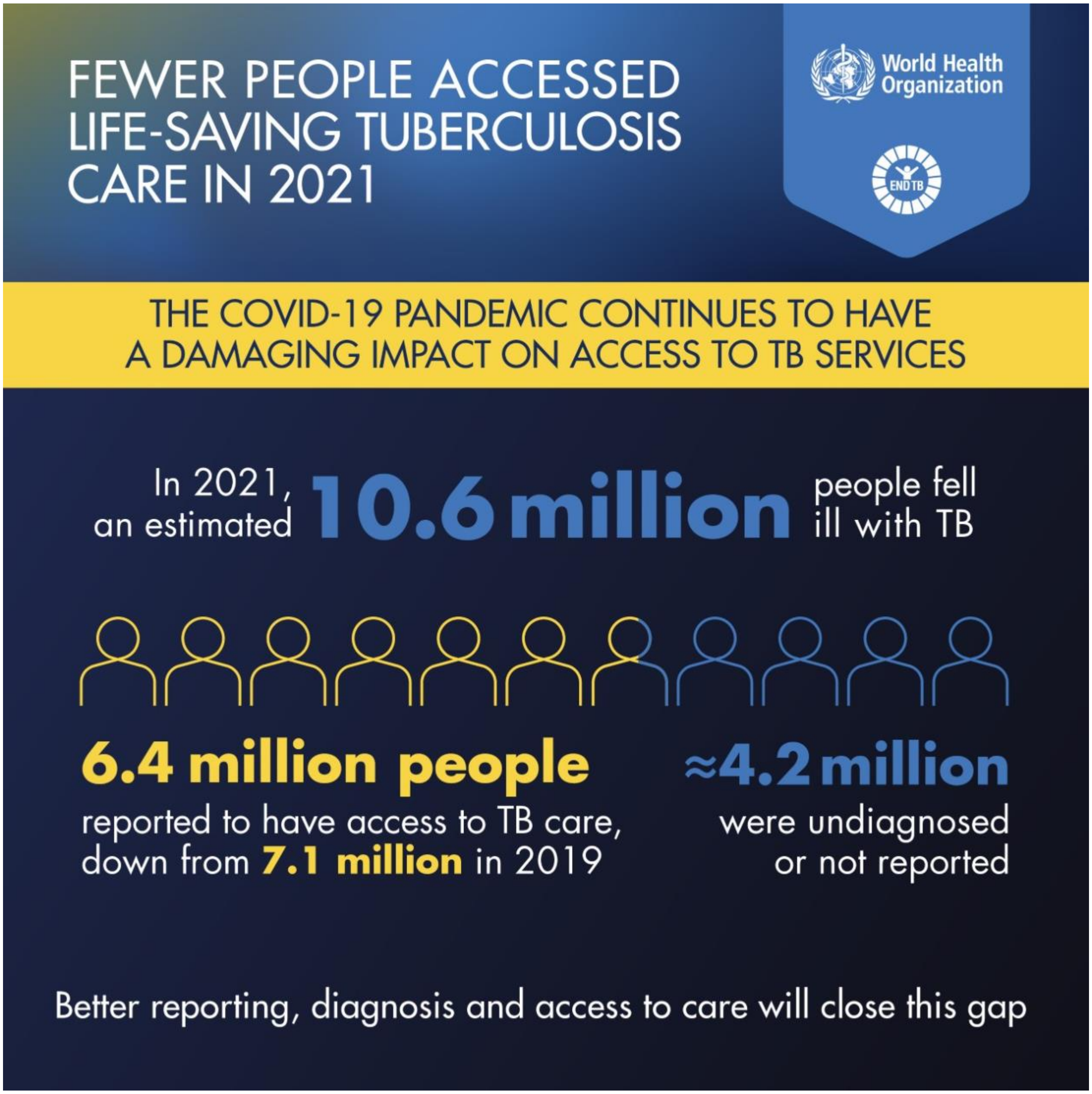

Figure 3.5.2 – An estimated 10.6 million people fell ill with TB. Infographic and caption taken from World Health Organization, Tuberculosis and COVID-19[2]

Disease burden is set to increase significantly, and the Global Plan to End TB predicts through modelling analysis that over the next eight years, if comprehensive financial investment isn't made and interventions that target key objectives aren't scaled up rapidly, an additional 43 million people could develop TB over the next eight years, resulting in 6.6 million additional TB deaths[52].

3.6 Coronavirus Disease

The infection that SARS-CoV-2 causes, COVID-19, manifests on a spectrum, an individual can experience flu-like symptoms to severe respiratory failure[46]. Other common symptoms of COVID-19 disease are fever, dry cough, and fatigue[46,53–55]. Increasing age is associated with more severe infection, higher risk of the development of severe COVID-19, and mortality[46,55–57] (**figure 3.6.1)**, and individuals with underlying conditions (including but not limited to diabetes, cardiovascular disease, hypertension) have a higher risk of developing severe COVID-19[46,54–56,58].

As displayed in **figure 3.6.1**, the incubation period for COVID-19 is around 5 days, after which mild disease may start to develop, and the individual displays symptoms. Around day 8 of infection, severe disease may or may not occur. Critical disease and death usually occur after 11 days of disease onset, or 16 days after exposure[46]. However, since the emergence of new variants and sub-variants, these timelines have changed[59] and continue to evolve with multiple Omicron subvariants emerging.

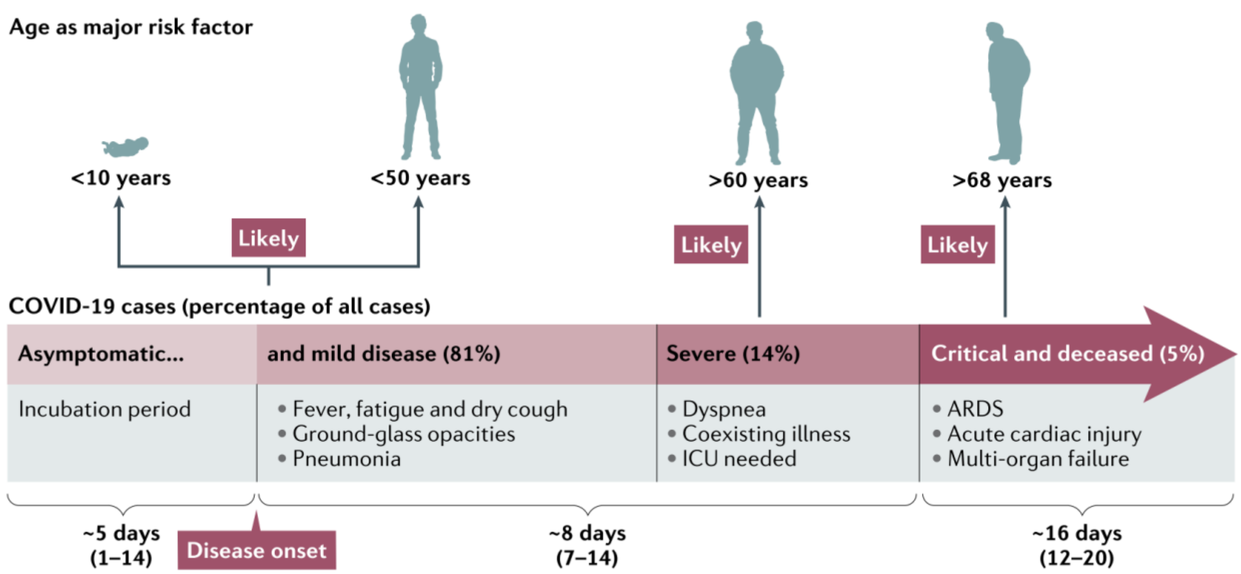

Figure 3.6.1 – COVID-19 development, figure taken from Hu et al (2021)[46]

SARS-CoV-2 has undergone many mutations, resulting in several variants since the detection in human population of the first strain. A variant can be deemed a Variant of Concern (VOC) once it meets one or more of the following conditions[60,61]:

1. Increase in rate of transmission, or drastic change in preceding epidemiology of COVID-19
2. Increase in COVID-19 infection severity, or drastic change in disease presentation

3. Decrease in effectiveness of public health measures, such as diagnostics, vaccinations, or therapeutics

So far, 5 VoCs have been detected (**table 1.5.1),** and their development can be attributed to the failure in deceleration of the spread of the virus.[62,63] The burden of the disease followed the rise and fall of the different dominant variants.

Table 3.6.1 – Variants of concern over the course of the pandemic. Data collected from WHO[60]

Name	Lineage	Status	Earliest documented samples	Date of designation
Alpha	B.1.1.7	No longer a variant of concern	United Kingdom, September 2020	VOC: 18-Dec-2020 Previous VOC: 09-Mar-2022
Beta	B.1.351	No longer a variant of concern	South Africa, May 2020	VOC: 18-Dec-2020 Previous VOC: 09-Mar-2022
Gamma	P.1	No longer a variant of concern	Brazil, November 2020	VOC: 11-Jan-2021 Previous VOC: 09-Mar-2022
Delta	B.1.617.2	No longer a variant of concern	India, October 2020	Variant of Interest: 4-Apr-2021 VOC: 11-May-2021 Previous VOC: 7-Jun-2022
Omicron	B.1.1.529 (Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages. It also includes BA.1/BA.2 circulating recombinant forms such as XE)	Currently the variant of concern, with descendent lineages	Multiple countries, November 2021	Variant under monitoring: 24-Nov-2021 VOC: 26-Nov-2021

3.7 Epidemiology of COVID-19, worldwide and in Indonesia

Worldwide, as of October 2022, 6.5 million deaths due to COVID-19 have been officially reported, and 619 million cases have been reported[64]. According to the WHO, global excess mortality associated with COVID-19 in the first two years of the pandemic (January 2020 – December 2021) was 14.91 million. While this number includes COVID-19 deaths, 9.49 million deaths (64%) were not directly attributable to COVID-19 disease but associated with the pandemic[65]. LMICs (which often have high TB prevalence already[81]) have endured the brunt of the pandemic, as due to poor data early in the pandemic, and poor reasoning regarding classifications of 'burden', the high-income country share of mortality is three times lower. These figures have emerged as burden of COVID-19 is examined in terms of excess mortality as opposed to official estimates of deaths from national data sources[66,67]. It is important to note that the reported number of cases underestimate the true case parameters, as many individuals are asymptomatic and might not be diagnosed and reported, along with limited testing availabilities in low-resource settings.[68] Furthermore, countries have undercounted mortality from COVID-19 as data on all-cause excess mortality is not available. These estimates serve as evidence in showing that the full impact of the pandemic has been much greater than what is indicated by reported COVID-19 disease deaths[66,67,69].

The graph depicted below (**Figure 3.7.1**) shows repeating a rising and falling pattern, which can largely be attributed to the several variants of COVID-19 that developed[70]. For instance, the Beta variant caused the first large spike in cases in all regions in December 2020. The second and third spike can be attributed to the Delta variant, and it caused great devastation in South-East Asia[19], and the spike beginning on December 2021 in incident cases is due to the Omicron variant[71].

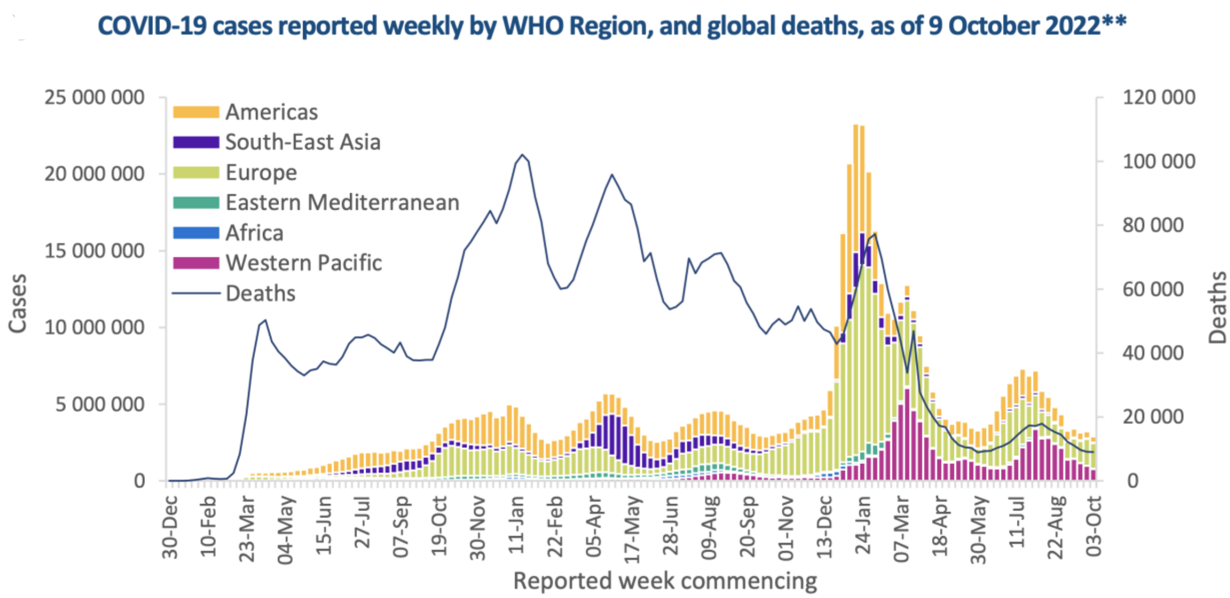

Figure 3.7.1 - COVID-19 cases reported weekly by WHO Region, and global deaths, as of 9th October 2022, figure and caption taken from WHO COVID-19 Weekly Epidemiological Update[70].

In total, there have been 6.45 million infections reported since the pandemic began in Indonesia until October 2022. Additionally, during this time, there have been 158 449 coronavirus-related deaths. Incidence has followed the trend of the rest of the world, and peaks were seen in January 2021, July 2021, and February 2022, with the Beta, Delta, and Omicron variants respectively (**Figure 3.7.2**)[71,72].

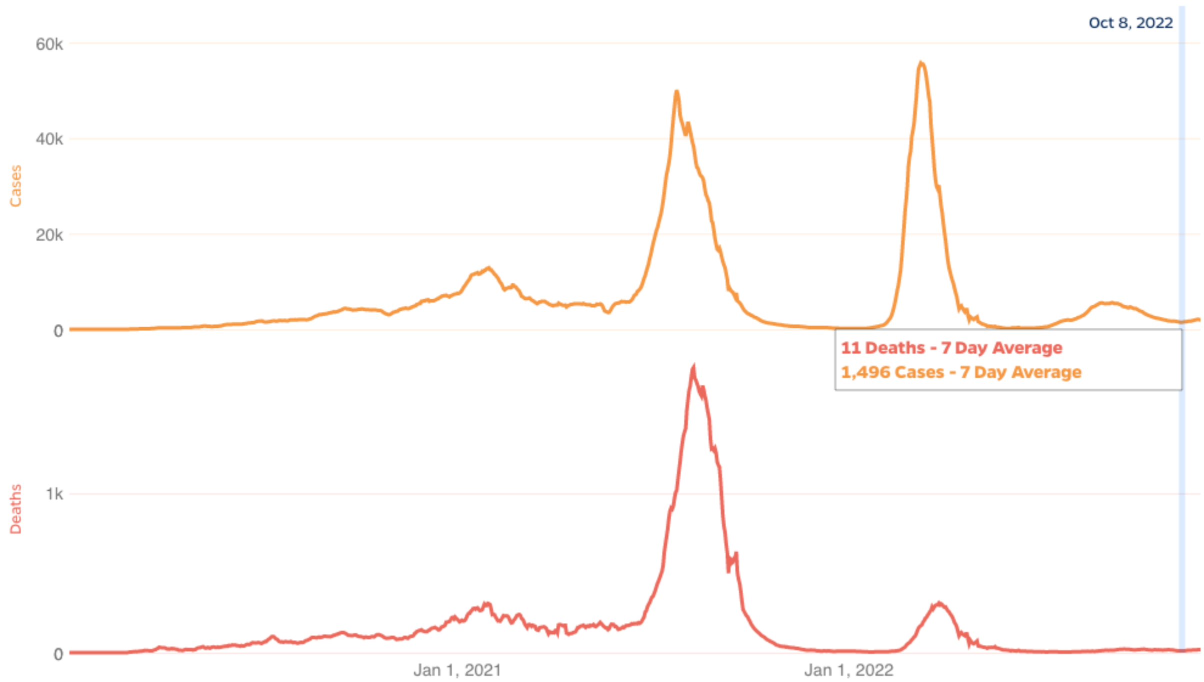

Figure 3.7.2 – All time cases of COVID-19 and deaths. Data Sources: Cases and deaths data from JHU CSSE; testing and vaccine data from JHU CCI; and hospitalization data from the U.S. Department of Health and Human Services. Caption taken from Johns Hopkins University[69]

In February 2022, Indonesia reached a peak with 54,000 incident cases in one day, and deaths followed suit, where the reported number of deaths were at a maximum of 1700. **Figure 3.7.3** shows the distribution of the burden across the country. In February 2022, incident cases reached a new peak of 57,000 in one day, but following deaths stayed around 300 per day [72–74]. However, the estimated excess deaths were estimated by COVID-19 Excess Mortality Collaborators as 736 000, with the ratio between excess mortality rate and reported COVID-19 mortality rate being 5.11 (CI 4.12 – 6.63)[69].

Figure 3.7.3 - Geographic distribution of confirmed COVID-19 cases reported in the last seven days per 100 000 population in Indonesia across provinces, from 10 to 16 February 2022, figure and caption taken from World Health Organization[73]

In February 2022, incidence reached an all-time high, and transmission was mainly due to community transmission. The regions with the highest burden were DKI Jakarta, West Java, East Kalimantan, North Sulawesi, and Papua (**Figure 3.7.3**).[73,75]

Indonesia has been significantly affected by the COVID-19 pandemic and has reversed years of progress in providing essential TB services and reducing TB disease burden. After India, Indonesia had the biggest drop in TB case notifications during the pandemic at 14% in 2020 and increased even further to 18% in 2021 (**Figure 3.7.4**). Disruptions to TB care in Indonesia manifested in the suspension of monitoring, evaluation and surveillance activities, decreased government funding for TB treatment programs, lower quality care for individuals with TB, MDR-TB, and TB-HIV, and decrease in case detection and rapid diagnostic services.[76]

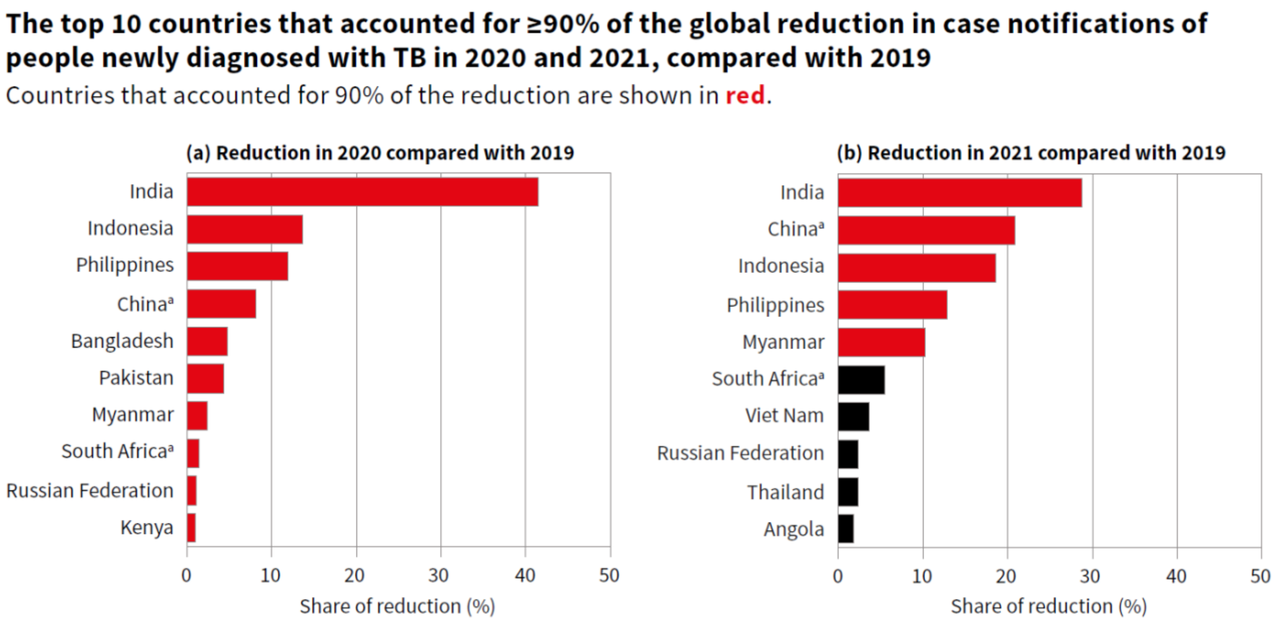

Figure 3.7.4 – Countries with the largest contributions to the global shortfall in TB notifications in 2020 and 2021 compared to 2019, figure and caption taken from World Health Organization [1]

The initial lockdown resulted in limited mobility, where individuals were not freely able to access healthcare. The Indonesia High-Frequency Monitoring of COVID-19 Impact survey found that around 11% of those households who needed medical treatment were unable to access it, citing closures of facilities, lack of money, and unwillingness to seek healthcare due to the COVID-19 pandemic as the main obstacles. Furthermore, 17% of households needing TB treatment were not able to access it in August 2020[77]. The Ministry of Health, Republic of Indonesia also reported that TB Treatment coverage decreased to 47% in 2020[1,78,79]. It is unclear how many TB cases were missed at initial consultation, and how difficult treatment initiation or adherence was for individuals with TB in specific settings, but based on the findings that case notifications decreased, incidence decline slowed down, and treatment coverage decreased, it is evident that the COVID-19 pandemic has undone many years of progress in the fight against TB on the national level.

3.8 TB management within the Indonesian Health System

Indonesia's health system is split into two sectors: the public and the private. The public sector mirrors its decentralized government system and is administered with central, provincial, and district governments[80,81] **(Figure 3.8.1)**. The central Ministry of Health (MoH) runs some tertiary care and specialist hospitals, is responsible for the strategic direction of the overall health system, regulates and sets standards by which all providers must abide, and manages the provision of financial and human resources for infrastructural development[82]. The provincial governments administer provincial level hospitals, oversees technical demands of the district level health services, and manages any health issues that arise across multiple districts within the province. District-level governments manage district level hospitals, sub-district level providers, and the district public health network of community health centres (*puskesmas*, *CHCs*). Therefore, local governments usually fund programmatic operations[82]. Private sector providers are regulated by the MoH, and range from a network of hospitals and health centres run by not-for-profit and charitable organizations to for-profit providers and smaller establishments run by dual role practitioners (doctors who work in the public sector and have simultaneously opened a practice to earn a secondary income)[80,83].

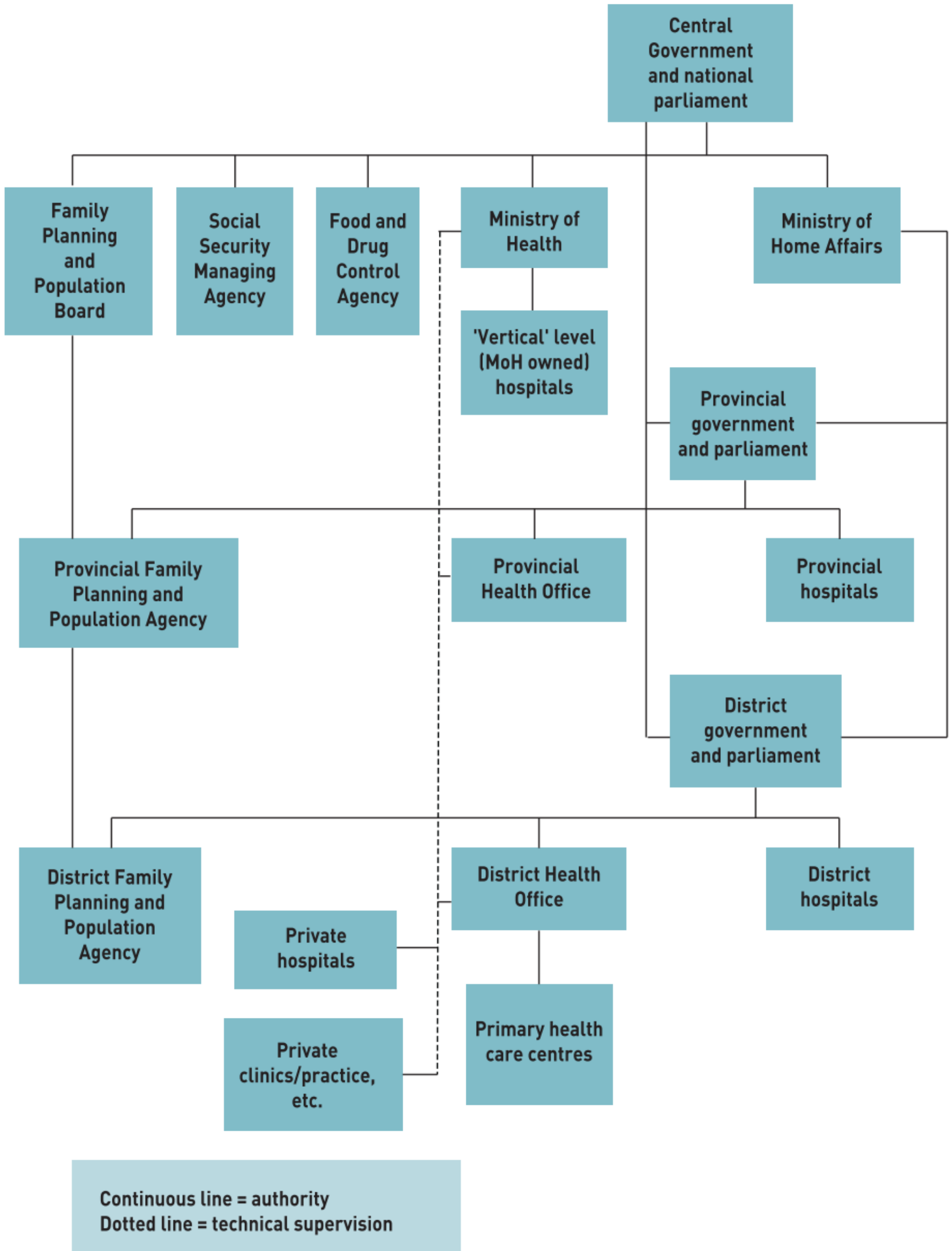

Figure 3.8.1 – Organization of health system in Indonesia, figure taken from Asia Pacific Observatory on Health Systems and Policies, The Republic of Indonesia Health System Review[80]

Healthcare financing is dominated by the private sector; out-of-pocket expenditures, private insurance providers, etc. contribute 62.2% to the total health expenditure, whereas government contribution to health financing is at 37.8%[84]. Indonesia's Universal Social Health Insurance scheme, Jaminan Kesehatan Nasional (JKN), was implemented in 2014 to protect households from catastrophic health spending; the extremely poor and those who could not afford private insurance but were affluent enough to not be eligible for the government's relief programs. However, even after the rollout, the proportion of government contribution to total health expenditure for that year decreased, meaning private sectors mostly financed the health spending[80]. Based on health financing and observational evidence, evidence suggests that care seeking for TB mostly takes place in the private healthcare sector[81,84–86].

The association between the people with TB in high burden countries seeking care primarily in the private sector, and countries with a dominant private healthcare sector has been well-established (**Figure 3.8.2**).[84] Reporting TB notifications has been made mandatory for private clinics and solo practices since 2016, and there are consequences of penalties for providers who fail to comply[87]. However, in Indonesia, despite the high volume of individuals who turn to the private sector for their care-seeking, only 9%[86] of cases that originated from the private sector were reported to the NTEP (2015), and in 2017, this figure only rose to 13%[88]. **Figure 3.8.3** shows that while TB notifications originating from private for-profit agencies have been increasing for Indonesia, they are still below 20% of the total TB notifications.

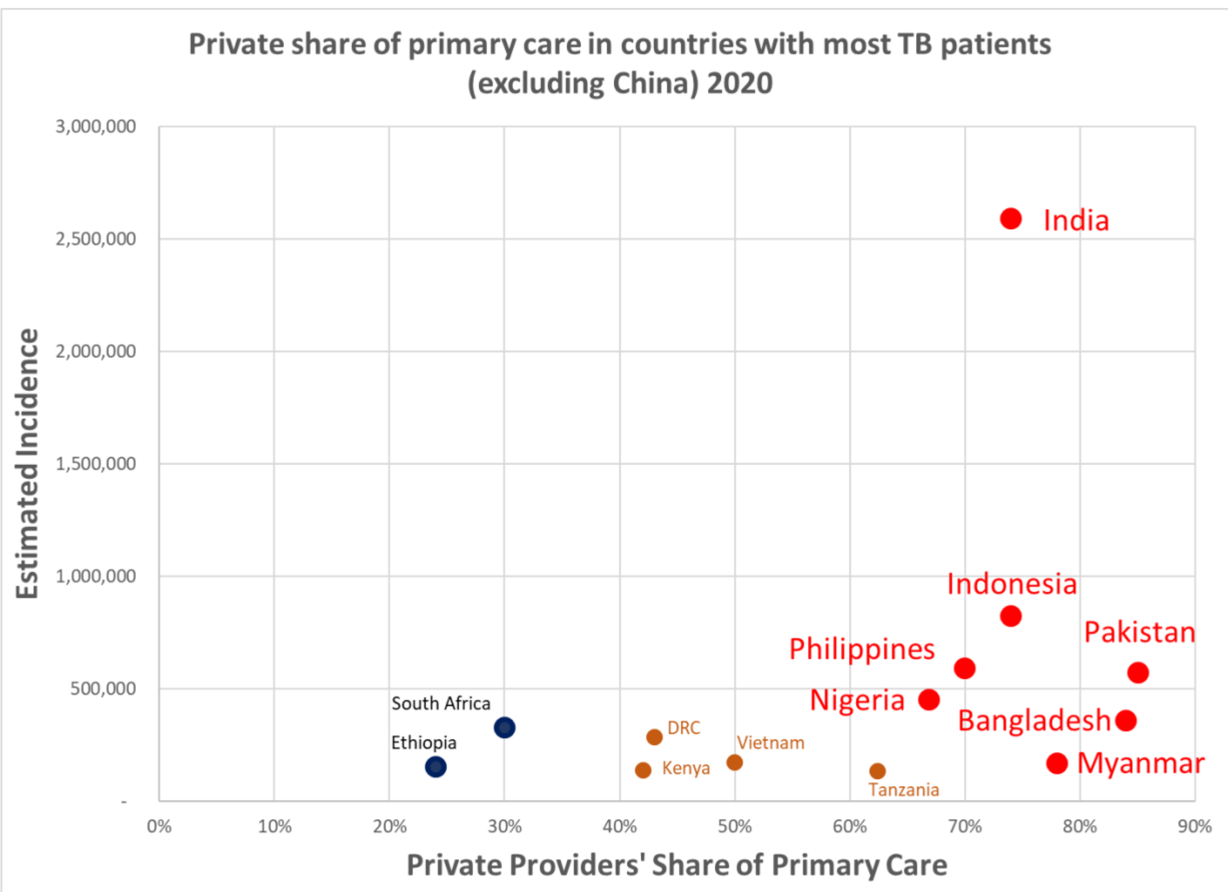

Figure 3.8.2 – Private Share of primary care in countries with most TB patients (2020)[84]

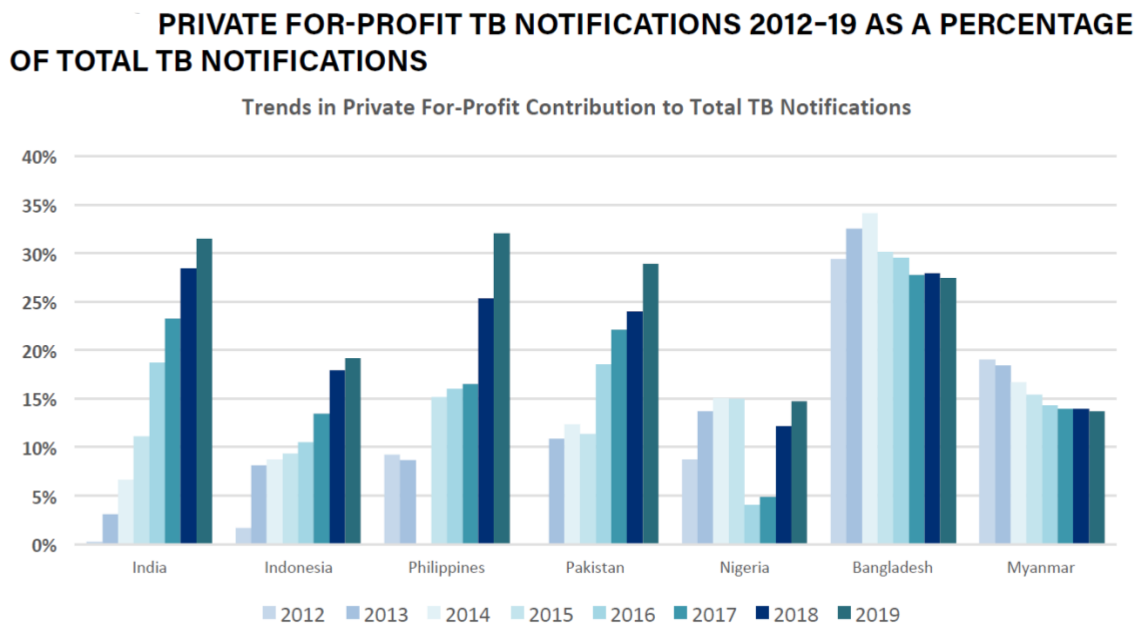

Figure 3.8.3 – Private for profit TB notifications 2012-2019 as a percentage of total TB notifications [89]

In 2001, Uplekar et al. had already predicted this and stated that the private health sector is where people with TB essentially 'go missing'; the low quality of care in the private sector leads to extended delays in diagnosis and treatment initiation[90]. Furthermore, many private providers are not linked to the NTEP, and therefore may not have adequate resources to carry out diagnostics, retention of individual with suspected TB, notify the individual to the NTEP surveillance systems, and oversee treatment provision. Providers that are engaged with the NTEP also have access to TB capacity-building programs, protocols, and guidelines, and are given anti-TB drugs for their clients[91]. The solution Uplekar et al.[90] presented was to achieve full collaboration between public health NTEPs and private practitioners, backed by case studies from New York and the Netherlands, and encouraged that more research should be conducted in the context of private practitioners.[90] There is some evidence to suggest that private providers in Indonesia have limited practical knowledge regarding the correct management of individuals with TB, and inadequate provision of care is common[92–94]. Therefore, the TB public-private mix strategy has been established to increase collaboration between public facilities who are already engaged with the national TB elimination program and private providers who haven't yet been engaged. This, in turn, would progress national level TB control[93].

3.9 People-centered care

"Integrated, people-centred care and prevention," is the first pillar in the End TB Strategy. The overarching objective is to deliver comprehensive and high-quality care in the form of timely diagnosis and treatment initiation, without the individual incurring catastrophic costs. This approach would also mean that the individual with TB, "is the central figure in the continuum of care," and their specific socioeconomic and personal contexts are taken into consideration when addressing their care, in addition to the immediate medical attention they require[95]. Early detection and provision of treatment for all people affected by TB is the first priority that the WHO recommends countries use to guide their programmatic planning for TB control programs[96]. Ideally, NTEP implementors would actively go out to seek individuals with presumptive TB and connect them to diagnostics, care, and treatment. However, care is often passive, or facility-based, where the onus is on the individual to access care after the onset of symptoms[97].

3.10 Studying care-seeking behaviours, care cascades, and care pathways

To effectively implement people-centred care, the pathways that individuals with TB take to receive diagnosis, treatment, and cure must be studied and analysed. As summarised by Creswell and Sahu (2016)[98], each individual with active TB disease has multiple barriers, options, and costs that they must consider before seeking out care for their symptoms, even before the diagnostic process can begin. Additionally, some variables may be out of the individual's control. However, the variables that are associated with an individual's journey to successful cure and the way that the variables interact can be studied to gain insight on the journeys that haven't yet reached a successful completion and cure.

The care cascade analysis is a methodology that was pioneered by HIV research[99–101], but other diseases have also been analysed using the care-cascade lens in the last decade. Essentially, this analysis lines up the sequential stages that an individual with TB would ideally go through to be cured of the disease and aims to sum up the number of individuals in a country or region who were able to access that step. As illustrated in **Figure 3.10.1** Starting with, "individuals with incident TB," to sum how many individuals in that region were incident cases of TB, to accessing diagnostic tests, being given a definitive diagnosis, being registered with the NTEP, and given treatment, successfully completing treatment, and obtaining the best possible health outcome – recurrence-free survival. The gaps outlined in this analysis (taking the difference between steps) would also potentially allow decision makers at the NTEP to identify where the most individuals are being missed to subsequently clear out bottlenecks or solve problems and find the missing people with TB[99,100]. However, when it comes to tallying the individuals managed in the private sector, without the notifications from private sector providers and/or longitudinal follow-up of privately managed individuals, it would be difficult to account for them.

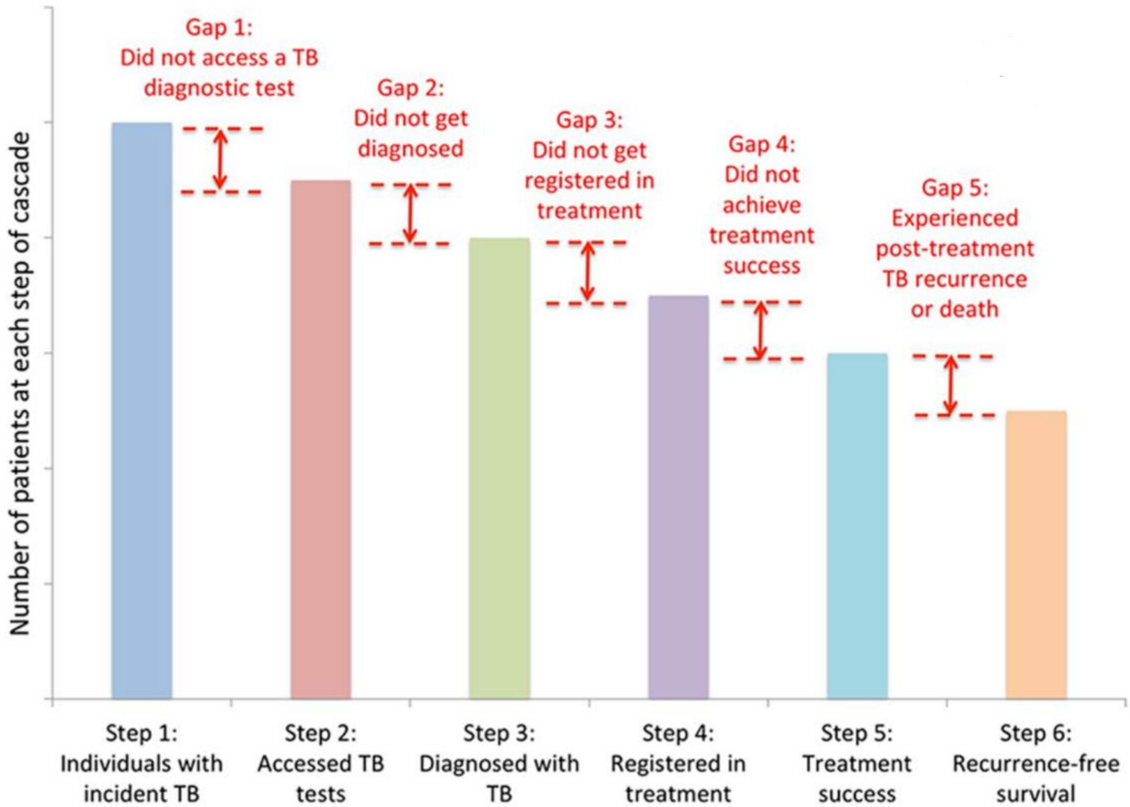

Figure 3.10.1 - A generic model for a care cascade for active TB, figure and caption taken from Subbaraman et al[99]

Figure 3.10.2 illustrates the gaps in TB care in the Indonesian context. In an analysis done at the World Bank, using Optima TB Software, and data and model parameters from 2019, it was found that around 28% of all individuals affected with TB do not get diagnosed. The treatment completion rate seems to be high, as the gap between initiating and completing treatment is small, but up to 48% of all individuals with TB are not connected with treatment[102]. Now, in the wake of the COVID-19 pandemic, it is unclear what the care cascade looks like, and how the gaps have changed. However, it has been well documented that quality of TB care has worsened as a direct cause of the COVID-19 pandemic[19]. Additionally, care cascades describe half the scene. To achieve alignment with people-centred care, it is imperative to look at how many providers there are to deliver high quality service and how accessible those providers are while simultaneously looking at how and where people care[85].

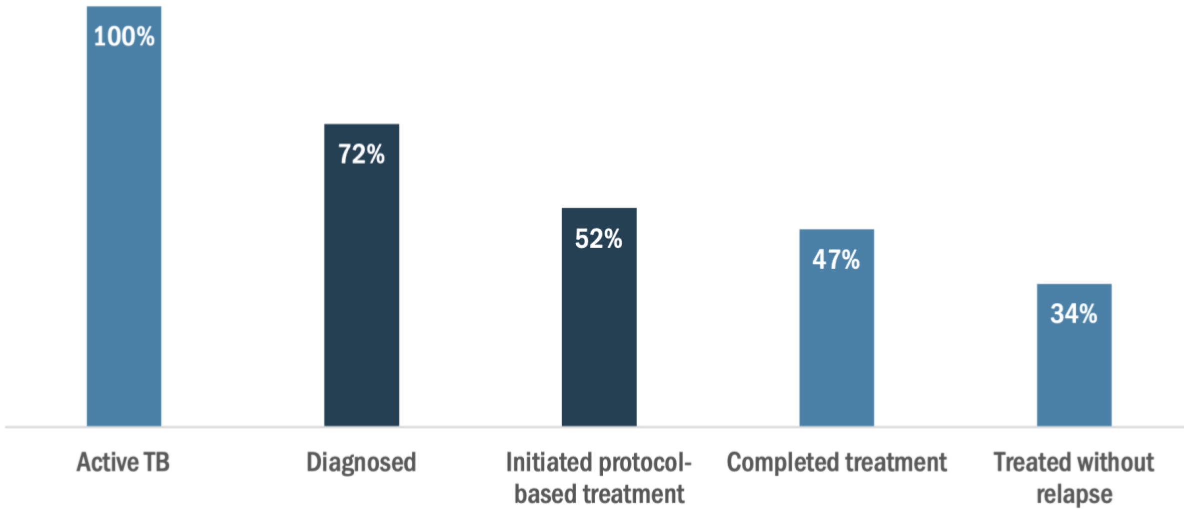

Figure 3.10.2 - The breakdown in the TB care cascade happens early on with delayed or undiagnosed TB and initiation of protocol-based treatment, figure and caption taken directly from Tuberculosis in Indonesia: Epidemic Projections and Opportunities to Accelerate Control. Findings from an Optima TB analysis[102]

"Seldom do tuberculosis programs consider where services should be positioned to meet [people with TB] where they are."[103] To evaluate and further assess this alignment between patient care seeking and service availability, Hanson et al (2017)[103] suggested the patient pathway analysis (PPA). This methodology involves firstly looking at where people seek care for their symptoms (much like the care cascade methodology), along with how many service providers are available and capable of providing care to people with TB. Consequently, estimates of diagnostic coverage and treatment coverage can be calculated - measures to help quantify how well demand and supply for TB care matches up. Through these estimates, the authors can identify gaps to guide decisions and assign priority areas regarding resource allocation. The figure below (**Figure 3.10.3**) is the outcome of a 13-country PPA by Chin, Hanson, and colleagues [104]. In these countries, including Indonesia, a substantial proportion of initial care seeking happens in the private and informal sectors. However, basic diagnostics (smear microscopy) are not available at all primary care facilities, where most people with suspected TB initially seek care. [104]

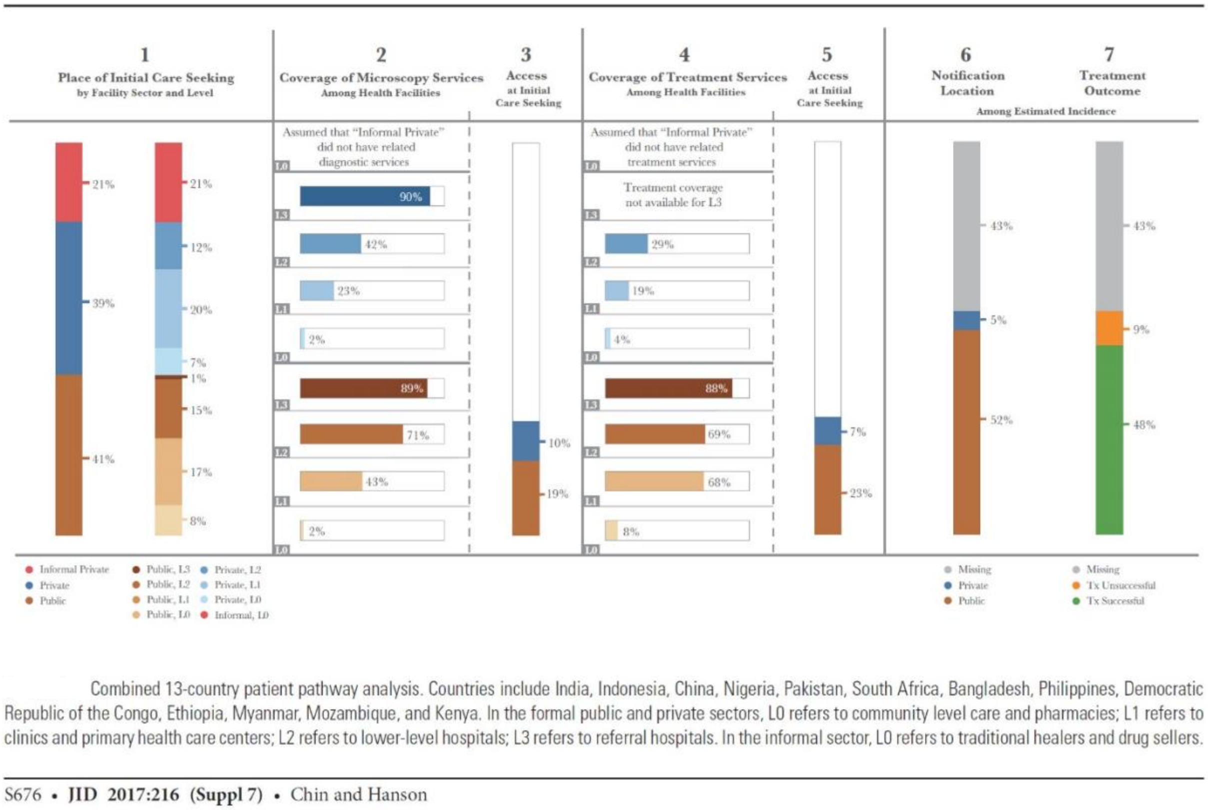

Figure 3.10.3 – A combined 13-country patient pathway analysis. Figure and caption taken from Chin and Hanson (2017)[104]

The authors advise that if a significant portion of individuals are consulting the private providers for their initial care-seeking, but a small proportion of case notifications are originating from the private sector (as is the case in Indonesia) then significant drop out is taking place along the care-seeking pathway[103]. Furthermore, they noted that people are more likely to go missing if the site of their initial care seeking does not have adequate diagnostic and treatment services[104]. Two separate PPAs from Indonesia discovered that individuals primarily sought care private (formal or informal) community-level health facilities, such as drug shops or pharmacies, where diagnostic capacity is limited. Furthermore, these individuals had to transition into either the public sector or higher level private facilities for diagnosis, treatment initiation, and general TB management[81,105]. In general, as individuals with TB transition from one healthcare provider to the next, having multiple encounters, the delays to diagnosis and treatment initiation increase, resulting in worse health outcomes, increased transmission to closed contacts, and higher direct and indirect costs[5,11,13,103,105,106].

There are several limitations of the PPA analysis[103]. First, it requires complete data from the most recent prevalence surveys and service availability surveys. This is unrealistic as this data can be scarce, and secondly, there is low external validity in these data sources due to the national estimates that these datasets usually contain. Even in the Indonesia specific PPAs, Lestari et al. conducted analyses using only using data from the survey that was administered for the study itself, and Surya et al used data sources from different years such as the 2013-2014 National TB prevalence survey, 2017 SITT TB Surveillance Database, etc.; they noted in their own limitations the lack incomplete individual *longitudinal* data. Furthermore, while the PPA might reveal areas of low coverage and suggest where in their journey to successful treatment people with TB aren't fully supported, they also cannot explain what happens to individuals in the gaps identified by the cascade of care analysis. Chin and Hanson therefore suggest conducting an analysis of time delays, patterns of referrals, and investigating the number of visits or encounters with a healthcare provider until a definitive diagnosis was provided[104].

Ideally, a comprehensive analysis of the patient pathway would present three relevant pieces of information: where individuals began seeking care and information regarding the provider, especially the sector and level, how many providers they saw before diagnosis and treatment initiation, and finally, how many encounters they had overall and the timing between these encounters, allowing for delays and bottlenecks to be identified, along with the risk factors for those delays[107]. The first objective addresses the knowledge gap identified in the care cascade methodology. The second and third objective address the knowledge gap identified in the PPA methodology as it takes a deeper dive into the individual care pathways. Taking a people-centred approach to categorise and predict the barriers in a care pathway will not only help allocate resources for the provision of support but achieve justice by identifying which obstacles need to be removed altogether.

3.11 Delays and associated factors to care-seeking, diagnosis, and treatment

Long delays in care seeking, diagnosis, and treatment initiation are often consequences of passive case finding for TB.[108] Delays could be from either side; the care-seeker or the provider. Someone might delay seeking help or go to alternative healthcare providers to self-manage their symptoms, and the health care provider might delay in investigating for TB, try empirical or non-specific, syndromic treatments first, or not be able to provide a definitive diagnosis and refer to other similar-level providers. Exploring and classifying types of delays and their associated factors can also help identify bottlenecks in the care cascade, will facilitate the allocation of attention and resources, and make TB control programs more effective, so that delays can be mitigated and the missing individuals with TB can be found.[108]

To better understand the existing research methodologies and provide an overview of the current knowledge concerning delays, I searched PubMed for existing systematic reviews on TB care delays. Seven reviews were found that systematically quantified estimates for delays that were borne by people with TB and produced pooled measures. Furthermore, eight systematic reviews were found that aimed to synthesize factors associated with delays in TB care.

This section summarises seven systematic reviews (SR) that have synthesized and reported average delays in TB care[108–113]. **Table 3.11.1** shows brief characteristics about the studies. Each SR had an independent way of defining the time points which determined the 'delays' to care. As the earliest SR summarising delays in diagnosis and treatment for tuberculosis, Storla *et al* (2008)[109] noted that definitions of 'diagnostic delay' differed significantly across studies. The reviewers and authors therefore described that some studies took the 'onset of symptoms' to begin at any symptom indicative of TB, while other studies only considered the date that cough started. 'First contact with Healthcare Provider (HCP)' could mean first contact with any healthcare provider, including informal medicine vendors, to first contact with the NTEP of that setting. Similarly, the end of the health system delay could be the date a diagnosis was provided, or it could be the date of treatment initiation. Sreeramareddy *et al* (2009)[108] and Getnet *et al* (2017)[111] excluded studies that didn't fit their specific definition of timepoints so that a comparison could be made across studies. They defined patient delay as the number of days between the date of onset of any symptoms presumptive of TB and the date when any contact was made with a healthcare provider, informal or informal. Health system delay was defined as the number of days between the date of first contact with a healthcare provider and the date of diagnosis. Total delay therefore was the sum of those two measures. Alene *et al* (2020)[114] followed the same definition as the two SRs above[108,111] but only examined the studies which described the patient delay in diagnosis. Sreeramareddy *et al* (2014)[110] followed the same definition for patient delay, but modified diagnostic delay to be the number of days between the date of first contact with a healthcare provider and the date of diagnosis. Additionally, they included treatment delay, which was the time gap between diagnosis provision and treatment initiation, and total delay, which began at date of symptom and ended at date of treatment initiation. Boyd *et al* (2017)[112] described the delays to treatment. More specifically, they wanted to summarise studies that investigated the time delays between date of specimen collection (for diagnosis) to treatment initiation, and the time delays between date of diagnosis and treatment initiation. Bello *et al.* (2019)[113], comparatively, were the most comprehensive in terms of delay measures they included in their analysis; these delays are described further in **figure 3.11.1.** Delays are broken down into patients delay, doctors delay, and treatment delay. Total delay is the sum of all three of these delay types, and diagnostic delay is the sum of the patients delay and doctors delay, while health system delay is the sum of doctors delay and treatment delay[113] (**figure 3.11.1**).

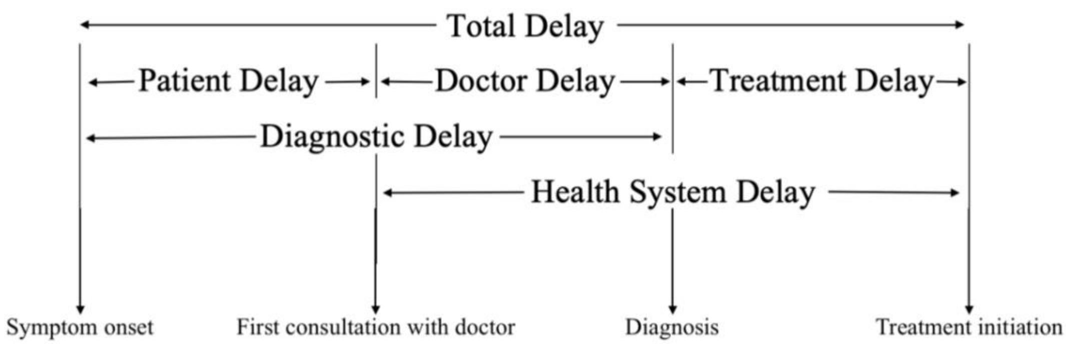

Figure 3.11.1 – Conceptual framework of delays in diagnosis and treatment of pulmonary tuberculosis, figure recreated for clarity, caption taken from Bello et al. 2019 [113]

Table 3.11.1 – Pooled estimates of delays to TB care

Author/Year	Setting	Conceptual Framework	# Studies included in SR	Methodologies of studies in SR	Population	Results	
						Pooled measures reported	**Associated factors for delays**
Storla *et al* (2008)	Global	Diagnostic delay by patient, diagnostic delay by healthcare providers, total diagnostic delay	58	Observational cross-sectional surveys	All ages, pulmonary TB patients and extrapulmonary TB patients	Mean diagnostic delay by the patients: 19.77 days Mean diagnostic delay by the healthcare providers: 20.9 days Mean total diagnostic delay: 71 days	Poverty, low access to healthcare, low education level. Visits to low-level private or public sector healthcare provider. Stigma and false beliefs regarding TB. Morbidities like HIV, or lung disease were both positively and negatively associated with risk of delay.
Sreeramareddy *et al* (2009)	Global	Patient delay, health system delay, total delay	52	Retrospective cohort studies, longitudinal patient recruitment, observational cross-sectional surveys	Pulmonary TB patients, smear/culture-positive tuberculosis patients. Age criteria unclear.	Mean patient delay: 31.03 days Mean health system delay: 27.2 days Mean total delay: 58.23	No such findings reported
Sreeramareddy *et al* (2014)	India	patient delay, diagnostic delay, treatment delay and total delay	23	Observational cross-sectional surveys, prospective cohort, retrospective analysis of medical records	Pulmonary TB patients, 'chest symptomatics' (individuals with cough 2 weeks and presumptive of TB). Age criteria unclear	Median patient delay: 18.4 days (IQR: 14.3-27.0) Median diagnostic delay: 31.0 days (IQR: 24.5-35.4) Median treatment delay: 2.5 days (IQR: 1.9-3.6) Median total delays 55.3 days (IQR: 46.5-61.5)	Poverty, living in rural areas and self-medication (repeated visits to the pharmacist for over-the-counter drugs to manage symptoms). Consultations with multiple providers. Some studies showed that visits to low-level public sector healthcare provider led to positive association with risk, but some studies contradicted this and showed that visits to private sector providers were associated with higher risk of delays.
Getnet *et al* (2017)	LMICs	patient delay, health system delay, total (diagnostic) delay	40	Observational cross-sectional surveys, one retrospective cohort	All ages, regardless of smear type, regardless of treatment category, pulmonary TB patients only	Mean patient delay: 35.5 days (95% CI: 24.4-55.4) Mean health system delay: 28.7 days (95% CI: 19.7-45.8)	Extensive summary of socio-demographic, socioeconomic, behavioural, and clinical risk factors. Initial visit to private providers, informal providers (traditional healers). Long distances to nearest facility, being low income, low education levels. Stigma and false beliefs regarding TB.
Boyd *et al* (2017)	Global	time to treatment from specimen collection, time to treatment from diagnosis	53	Retrospective and prospective cohort studies	All ages, Rifampicin resistant TB patients, multidrug resistant TB patients, extensive drug resistant TB patients	Mean time to treatment from specimen collection: 81 days (95% CI: 70 – 91) Mean time to treatment from diagnosis: 59 days	Molecular testing methods decreased delays, ambulatory second-line treatments lead to decreased delays. Referrals between providers increased delays.

						(95% CI: 50 – 68)	
Bello *et al* (2019)	Global	Patient delay, doctor delay, diagnostic delay, health system delay, treatment delay	198	Observational cross-sectional surveys, patient records, and patient records	All ages, pulmonary TB patients and extrapulmonary TB patients	Mean diagnostic delay*: 61.6 days (95% CI: 53.4 – 69.8) Mean patient delay*: 73 days (95% CI: 67-79) Mean doctor delay*: 32.5 days (95% CI: 27.8–37.1) Mean health system delay*: 41.9 days (95% CI: 37.3–46.4) Mean treatment delay*: 8.4 days (95% CI: 37.3-46.4)	Non-use of chest x-ray was associated with lower risk of delays, and studies in HICs also reported lower delays. Non-use of sputum microscopy was associated with higher risk of delays. Increased proportion of male participants enrolled in the study increased delays, so did increased mean age of patient.
Alene *et al* (2020)	Ethiopia	Patient delay in diagnosis	12	Health facility based observational cross-sectional surveys	All ages, pulmonary TB, smear negative and smear positive	Median patient delay in diagnosis: 24.6 days (95% CI: 20.8–28.4)	Living in rural areas, longer time to reach the nearest health facility, poor knowledge about TB, seeking treatment from non-formal providers, older age, low education levels, and low financial standing.

** Results reported after in-study sensitivity analysis*

Patient delay throughout all the studies ranged from a median of 18.4 days (IQR: 14.3-27.0)[110] to a mean patient delay of 73 days (95% CI: 67-79; after sensitivity analysis)[113]. Doctor delay (including health system delay) ranged from 20.9 days[109] to 32.5 days (95% CI: 27.8–37.1)[113]. Treatment delay was noted in 3 studies: Sreeramareddy et al (2014)[110] who reported a median of 2.5 days (IQR: 1.9-3.6), and Bello et al (2019)[113] who reported 8.4 days (95% CI: 37.3-46.4). Boyd et al (2017)[112] reported a mean treatment delay of 59 days (95% CI: 50 – 68), but it should be kept in mind that only individuals with Rifampicin resistance, multidrug resistance, and/or extensive drug resistance were included, and therefore the mean treatment delay is quite large compared to the other reviews.

Clarifying a clear and definitive conceptual framework, and predetermining definitions for the various delays is imperative[109], as the definitions for symptom onset, consultation with doctor, etc. vary from study to study. This complicates the measurements and comparisons of delays across regions, countries, and even health sectors. It is clear to see that measures of delays are less ambiguous in more recent studies than they were in earlier studies, as evidenced by the recommendation in the Storla et al (2008)[109] review as compared to the more recent Bello et al (2019) review.[113] Additionally, a conceptual framework to classify associated factors can also beneficial in understanding experiences contributing to those delays, as illustrated by Getnet et al.[111]

The objective of the studies in the SRs is not to find a causal relationship, therefore cross-sectional studies are sufficient when trying to measure time delays. Using cross-sectional surveys to measure delays is a quick and inexpensive way to gather information. The researchers administer a survey, and most of the data is self-reported. Poor recall and recall bias has been mentioned as a limitation in some reviews, yet it would be difficult to validate this kind of data.[110,111] Therefore, it would be recommended to recruit individuals early in their treatment journey, or soon after diagnosis.

A few findings are repeated consistently throughout these reviews: individuals who start their journey in a private sector facility seem to be delayed more than their public sector counterparts, seeking care from non-specialized providers multiple times before being diagnosed contributed to longer delays, and once diagnosis was provided, the individual was initiated on treatment in a timely manner.

This next section summarises six SRs that have synthesized and reported factors associated with delays in TB care. Two from the original list of nine were excluded as they were not in English, and no translation was found. **Table 3.11.2** shows brief characteristics about the studies.

Table 3.11.2 – Factors associated with various delays to TB care

Author/Year	Setting	Framework for delays	# Studies included in SR	Population	Methodologies of studies in SR	Results: Framework for factors	Results: Associated factors for delays
Chen et al (2011)	HICs	Healthcare delays, antibiotic delays	9	Extrapulmonary or pulmonary TB patients who were given fluoroquinolone prescription. No mention of age criteria, but generally >14 years of age	Retrospective and prospective cohort studies	N/A	Individuals who were prescribed fluoroquinolone to manage their pneumonia faced significantly longer delays in the correct management for their TB illness, and a 2.7-fold higher risk of developing fluoroquinolone-resistant TB strains.
Finnie et al (2011)	High TB/HIV burden African countries	Patient delay, system delay	20	Individuals with pulmonary or extrapulmonary TB. All ages	Observational cross-sectional surveys, qualitative in-depth interviews, one retrospective cohort study	Predisposing factors, enabling factors, and reinforcing factors	Lack of knowledge about TB. Long travel times and long distances from the health facility. Consulting a traditional healer. Patient preference for private practitioners (classified as traditional healers, religious healers, pharmacists) associated with high risk of delays.
Li et al (2013)	China	Patient delay, diagnostic delay	29	Individuals with pulmonary TB, (including smear positive or negative patients, newly diagnosed cases and those undergoing retreatment). All ages	1 case-control study, 1 cohort study, observational cross-sectional surveys	Individual factors, and structural factors	Classified as individual level and health system factors. Female patients more likely to face higher risk of patient and diagnostic delays. Low education, lack of health insurance, rural residence and therefore long distances to formal healthcare providers, and low income. First visit to an informal provider (traditional healer). Lack of knowledge about TB and high societal stigma. Limited resources for rapid diagnostics at healthcare providers.
Cai et al (2015)	Asia	Patient delay, provider delay	45	Individuals with pulmonary TB. All ages	Observational cross-sectional surveys, 1 cohort study	Socio-demographic, and others	Male participants were at higher risk of delays. Long travel times or large distance to the first healthcare provider. Low-income level. Severe symptoms were preventative against delays.
Scoping review – Barnabishvili et al (2016)	High MDR-TB burden countries	Diagnostic delay	12	Individuals with pulmonary or extrapulmonary TB. All ages	1 case study, observational cross-sectional surveys, qualitative in-depth interviews, cross-sectional secondary data analysis	Three sub-dimensions of acceptability: expectations, attitudes, and health beliefs.	Accessibility barriers; not being treated respectfully, not being communicated with. Doubts about provider efficiency. Privacy was a concern due to the societal stigmatisation of TB. Some evidence for preference for private providers, but this was taken as a risk factor, due to the expected delays in diagnosis and lack of engagement between private providers and National TB Elimination Program.
Sullivan et al (2017)	Sub-Saharan Africa	Treatment delay	47	Children and youth, (0-24 years of age) with TB	Observational cross-sectional surveys, cohort studies	Cost, infrastructure, and health seeking	Cost was a barrier to timely care: indirect cost, direct cost, health system cost, caregiver cost, pre-treatment medical and pre-diagnosis medical costs. Structural barriers: large distance to healthcare provider, limited diagnostic access. In some rural areas, diagnostic

	capacity was enhanced, therefore delays decreased. However, starting at low-level facilities or informal care providers was a risk factor. Loss to follow up after diagnosis and before commencing treatment is a problem for children and youth with TB.

Table 3.11.2 – Factors associated with various delays to TB care

The conceptual frameworks used to classify associated factors in these SRs varied, suggesting that a standardized best practice hasn't been established yet. The need to use a standard definition was highlighted by Finnie et al[115], who claimed it was imperative to for appropriate comparisons across studies. The three SRs investigating factors associated with *patient delays*[115–117] all had the same definition. *Patient delay*; time interval between onset of symptoms and first visit to a healthcare provider. For the definition of *provider delays*, Cai et al[117] included studies that investigated *health system* or *doctor delays*. However, Finnie et al[115] used '*system delay'*. In the review, all studies used first consultation as the starting point of the interval, and all except two used start of treatment as the endpoint (two used diagnosis). While both Li et al[116] and Barnabishvili et al[118] investigated *diagnostic d*elay, they had different starting points in their definition; the former defined *diagnostic delay* as time interval between first visit to healthcare facility and final diagnosis, and the latter defined *diagnostic delay* as interval between symptom onset and final diagnosis. Chen et al[119] were studying a distinct risk factor, and therefore their definitions for the delays do not follow the convention too closely. While the healthcare delay is equivalent to the health system delay defined in the Bello et al[113] model, *antibiotic delays* are the interval from when fluoroquinolones antibiotics were prescribed to the commencement of TB medication. Ambiguity in the definition of the various types of delays was significantly reduced over time. However, it might prove to be beneficial to go a step further and establish a conceptual framework to easily categorise the factors that interact with the outcome of interest in a journey to successful treatment (such as the various types of delays).

Most of the reviews in **Table 3.11.2** are systematic reviews, apart from Barnabishvili et al[118], which is a scoping review, as there was limited research available regarding *acceptability barriers*. Due to the research question and specific association of interest, Chen et al[119] exclusively examined cohort studies for their SR. The most common methodology for the remaining SRs was observational surveys or in-depth interviews.

Sullivan et al[120] concentrated on children and youth with pulmonary TB, while all other studies included people all ages with pulmonary and/or extrapulmonary TB.

After synthesizing findings from both sets of SRs, the implication of these repeated findings is that a bottleneck seems to be at the initial healthcare seeking/pre-diagnostic phase of the care pathway. Once a diagnosis is made, there is limited evidence for loss to follow up for adults. Significant loss to follow up is reported in children and youth (< 24 years of age)[120].

Multiple factors have been identified for the different types of delays: the most common factors associated with patient delays from this round of analyses are lack knowledge about TB, long travel times and distances from the health facility, and societal stigmatisation. Consulting a low-level provider (such as informal providers, traditional healers, or pharmacists and medicine vendors) and lack of resources and rapid diagnostics at these providers are factors associated with doctor delay.

My study consists of data from two cross-sectional surveys collected at two time-points in the same setting with the same sampling procedure. Based on the above analysis, I will aim to categorise the delays in this dataset based on the framework set forward by Bello et al[113] (**figure 3.11.1**).

3.12 Encounters with healthcare providers

While delays have been studied extensively, the practice of mapping the journey of people with TB on a more individual level is relatively recent. Researchers commonly use graphical tools to describe the care trajectory through pre-determined time points. Mistry et al (2016)[121] utilised a flowchart to illustrate provider switching at different stages of the TB care pathway, and found that a large proportion of people approached the private sector as a first point of care. Additionally, for diagnosis and treatment initiation, many transitioned out of the private or informal care sector into the public sector.[121] However, Atre et al[122] (**figure 3.12.1**) were able to add another scale to this same analysis, and were able to illustrate the number of encounters that individuals with TB had with either public or private sector providers until they received a diagnosis and were connected with treatment. This methodology allows for the phenomenon of, "bouncing back," to the private sector after a referral to the NTEP to be recorded and for comparison of complexity against strata of a variable.[122]

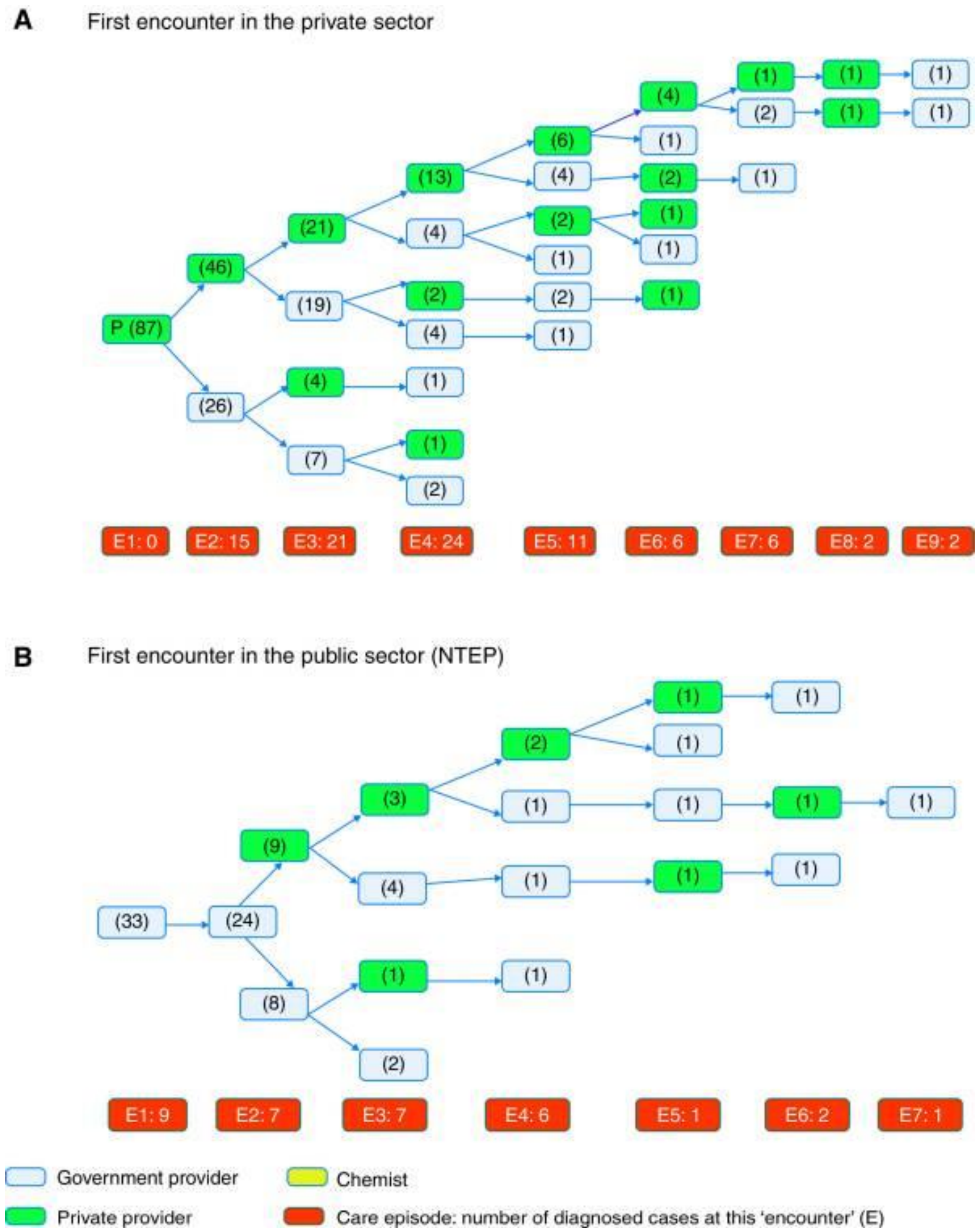

Figure 3.12.1 – Pathways to diagnosis and care among patients with multidrug-resistant tuberculosis. Caption and Figure taken from Atre et all (2022) [122]

Examining the trajectory an individual with TB goes through while accessing TB care has major implications for policy and intervention recommendations. After examining the care-seeking behaviour of individuals who were registered under the Revised National TB control program, researchers in Tamil Nadu, India, were able to advocate, through their findings, for an increased effort in persistent educational campaigns to raise awareness regarding tuberculosis and the need for early diagnosis.[123] A study that used national level health insurance data was able to map individual care pathways of individuals who underwent TB treatment and found that capacity for referrals to diagnostic centres from, “peripheral healthcare facilities,” would streamline access to treatment.[124] From high-level recommendations to formulating strategies for interventions, observing pathways to care can lead to several practical implications for the provision of accessible and high quality TB care[98].

In the context of Indonesia, the patient pathway analysis conducted by Lestari et al[105] utilised Sankey charts to visualise pathways undertaken by people with TB for initial care seeking, diagnosis, and treatment. Sankey charts are a type of flow diagram that, in the context of care pathways, show the flow of a group of people through the steps of the care cascade proportional to the flow quantity. The findings showed that most individuals begin their journey at informal non-public services (such as pharmacies, drug stores, and community-based health centres) or private facilities that provide primary health care (such as privately owned clinics). Additionally, another figure, a stacked bar chart, illustrated the proportion of people that either were diagnosed had a missed diagnosis, over sequential visits, stratified by recruitment site (**Figure 3.12.2**). This allowed the reader to see that people recruited at the primary care level had slightly more visits compared to those recruited at the hospital level, and those recruited in the private sector also had slightly more visits than those recruited in the public sector.[105] These results supported earlier findings by Surya et al[81], showing that the majority of initial care seeking in Indonesia occurred in the private sector, but patients did not encounter diagnostics until they transitioned into a higher level provider, after multiple visits to different providers. However, the readability of these charts is limited, as it is difficult to tell the difference between a proportion of 25% and 30% in charts that are populated this way.

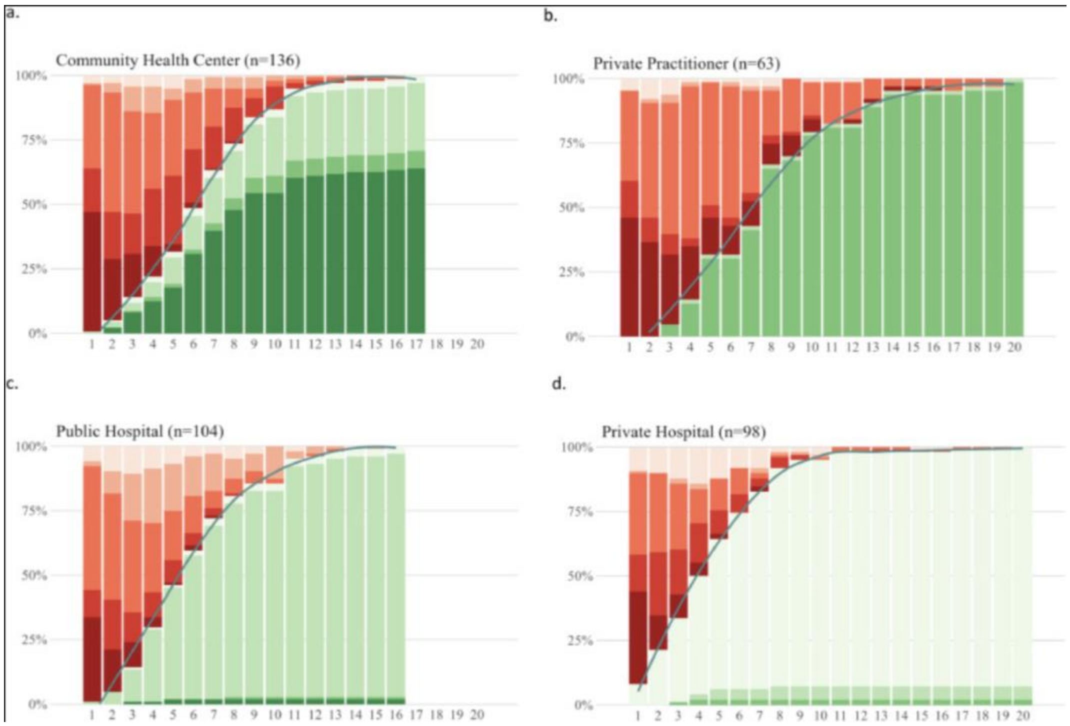

Figure 3.12.2 – Pathways undertaken by tuberculosis patients for diagnosis and treatment according to site of recruitment (N = 401). Caption and Figure taken from Lestari et al (2020)[105]

3.13 The people with TB who went missing during the COVID-19 pandemic

The COVID-19 pandemic added a new layer of complexity on the already convoluted pathway to care. Stay-at-home orders, restrictions in movements, fear of contracting COVID-19, facing mandatory quarantine, and stigmatisation decreased individual's willingness to seek care, and the disruptions in health services due to closure of facilities, reduced hours, shifting of resources from TB to COVID-19, and interruptions in the supply-chain reduced the capacity of providers to be able to provide adequate and high-quality care[19,125,126]. TB is a disease of poverty, meaning that the individuals who are more likely to face worse health outcomes, higher levels of morbidity, catastrophic costs, and substantial loses in productivity and income are those already with low access to high quality care[1,5,90,127,128]. Historically, TB has also been a determinant of a population's descent into poverty[5]. With sub-optimal quality of care even before the onset of the pandemic[1,19], it is unclear to what extent the TB epidemics around the globe in high burden settings have been exacerbated as a direct cause of the pandemic. Those individuals who were at high risk before the pandemic are now at a greater disadvantage and therefore are less likely to be connected with high quality care and successfully be treated of this curable disease, as evidenced in Indonesia by the drop in case notifications, slowing decline of worldwide incidence, increase in mortality, and increase in missing people with TB.[1, 2]

Learning about the pathways to care and the delays that the individuals with TB are facing currently will help illustrate the current landscape and offer insight regarding where individuals with TB are more likely to drop off the pathway[1,18]. The following manuscript proposes using measurements of delays and complexity of pathways to describe the average individual with TB's experience while interacting with these disruptions. The factors that make individuals delayed in a study population can, to some extent, be generalised to a representative population, and indicate factors associated with delays to care in the individuals who haven't yet reached diagnostics or treatment. I aim to answer the following questions:

1. What were the delays, in days, that individuals with TB faced while trying to access care for their symptoms, trying to get a diagnosis, and trying to get treatment, before and after the COVID-19 pandemic?
2. What are the factors associated with a higher number of patient delay, before and after the COVID-19 pandemic? Furthermore, controlling for confounders, was COVID-19 a significant predictor for a higher patient delay?
3. How many different encounters/visits with healthcare providers did individuals with TB have before they were given a diagnosis for TB, before and after the COVID-19 pandemic?
4. What are the factors associated with a higher number of encounters, before and after the COVID-19 pandemic? Furthermore, controlling for confounders, was COVID-19 a significant predictor for a higher number of encounters?

4. Description of Data source

4.1 Secondary data from 2 principal studies

In 2018, the INSTEP study (Investigation of services delivered for TB by external care system, especially the private sector) was conducted by principal investigator Dr. Bachti Alisjahbana (TB-HIV Research Centre, Faculty of Medicine, Universitas Padjadjaran, Bandung) and funded by USAID over a 2-year period, and a cross-sectional survey was disseminated to investigate health care pathways of newly diagnosed people with TB[129]. The study was replicated during 2020-2022 for the as part of the COVID-19 effect on Tuberculosis (COVET) project, led by PI Dr. Madhukar Pai (McGill International TB Centre, Dept. of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal). The COVET project aims to examine the disruptions caused by the COVID-19 pandemic on TB services in private healthcare in 3 countries – India, Indonesia and Nigeria[130]. The study sites are Bandung, Indonesia, Mumbai and Patna, India, and Lagos and Kano, Nigeria, with Dr. Bachti Alisjahbana leading the partnership in Indonesia. The following manuscript is a part of the COVET project, funded by the Bill and Melinda Gates Foundation, and uses secondary datasets from the cross-sectional surveys conducted in Bandung, Indonesia, as part of the INSTEP and COVET projects.

The pre-COVID-19 dataset comes from the INSTEP study conducted from 2017-2019, housed at and administered by the Universitas Padjadjaran[105]. The primary study utilised a hierarchical sampling methodology. First, 36 sub-districts in Bandung were randomly sampled. Then from all the healthcare providers in those areas, 10 community health centres (CHCs) were randomly sampled, and 2 public and 3 private hospitals were purposely sampled based on their willingness to participate and provide a patient list for recruitment. Smaller, lower-level health care providers in the private sector (PPs) were approached separately, and 145 out of 282 private practitioners expressed willingness to participate. From Bandung Municipal Health Office's TB report, the researchers mapped the distribution of case notifications against type of provider who notified the national TB program, and proportionately sampled people from those providers. Therefore, they recruited 30% of the sample from CHCs, 40% from hospitals and 30% from PPs. The dataset is anonymized and does not contain any identifying variables regarding the participants. The primary study was done by Lestari et al[105] under PI Dr. Bachti Alisjahbana, and it was found that most commonly, individuals with TB approached private practitioners or informal providers such as pharmacists for their initial symptoms.

The during-COVID-19 dataset comes from the COVET study conducted from 2020-2022, administered by the McGill International TB Centre at McGill University (MITBC) and Padjadjaran University TB Working Group (Principal Investigator Dr. Bachti Alisjahbana, Senior Researcher Dr Bony Weim Lestari, and research assistants Eka Saptiningrum, Auliya Ramanda Fikri, Kuuni Ulfah Naila El Muna, and Rodiah Widarna). Our team at MITBC (Principal Investigator Dr. Madhukar Pai, postdoctoral candidate Charity Omenka, and master's research students Lavanya Huria and Angelina Sassi, and research assistant Nathaly Aguilera Vasquez) in partnership with team in Indonesia, aims to better understand (and subsequently model) the impact of COVID-19 on the supply and demand of TB services and care in the private sector. In Indonesia, the INSTEP study from 2017 was essentially repeated, following a similar protocol for data collection and surveying methods, so that the newer dataset and the baseline were comparable. However, since the purpose of the COVET project was to examine the private healthcare sector, sampling was prioritized in private hospitals and clinics.

The manuscript will utilise these two secondary datasets to compare the effect of COVID-19 on patient pathways and delays. We will compare the time delays to first consultation, diagnosis, and treatment initiation after the onset of the COVID-19 pandemic to the baseline findings from 2019 and examine potential predictors of an increase in delays using regression analysis. **Figure 4.1.1** illustrates the merging of the two datasets for the purposes of this research study. Additionally, we will assess predictors of a more complex pathways and investigate the role of COVID-19 on changes to an individual with TB's pathway by using regression analysis.

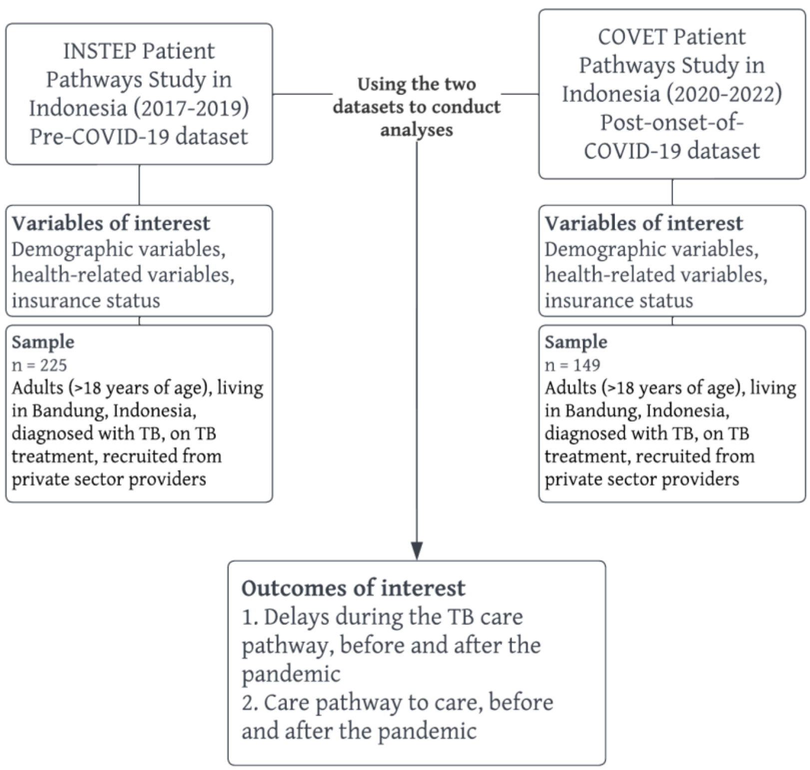

Figure 4.1.1 – Flowchart depicting the two datasets

4.2 Study population

All individuals in the baseline dataset are adults (>18 years of age), living in Bandung, West Java, Indonesia, diagnosed with TB, and on TB treatment. Enrolment into the primary study depended on the individual being a patient in one of the sampled public hospitals, community health centres, private hospitals, or private providers. Individuals who had previous history of being on TB treatment, extrapulmonary TB, and those outside the study site (Bandung) were excluded.

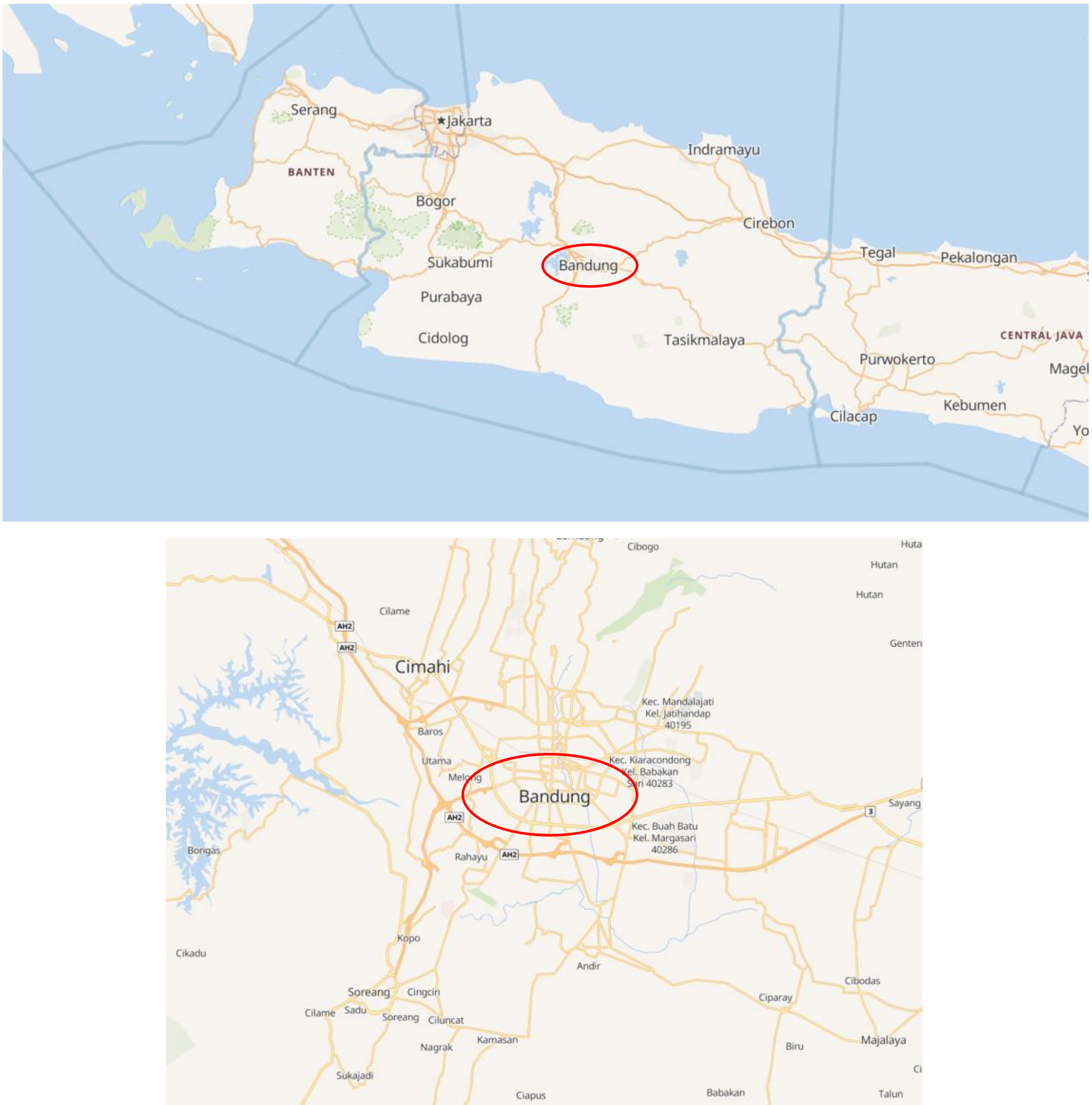

Figure 4.2.1 – Maps of Bandung, West Java, Indonesia

Enrolment into the primary during-COVID-19 also depended on the individual being a patient in one of the sampled private hospitals or clinics. However, some public hospitals and community health centres were sampled due to non-response from individuals in the original sampling frame.

Comparing the pre- and during-COVID-19 outcomes will provide interesting insight on the TB care landscape in an urban setting in Indonesia. Since the COVET study is primarily including individuals from the private sector, participants from the public sector in the baseline study will be excluded from the dataset for the purposes of my thesis. Additionally, only TB-positive participants recruited from the private sector TB-positive individuals will be included for comparable analysis therefore TB-negative individuals and individuals sampled from community health centres and public sector hospitals will be excluded. The sample size of the pre-COVID-19 dataset from the INSTEP study is 225 (after exclusion of participants from the public sector). The sample size of the during-COVID-19 dataset from the COVET study is 149. A more detailed explanation of the sampling techniques is in Chapter 6 (Manuscript) of this thesis.

4.3 Variables of interest and power from resulting analysis

The secondary datasets consist of variables such as date of birth, sex, employment status, education history, marital status, health insurance status and usage during their TB care, date of symptom onset, date of first consultation with healthcare provider, date of diagnosis, date of treatment initiation, and number and order of visits to a healthcare provider. After merging the datasets, a binary variable for 'status of COVID-19' will also be created.

Variables of interest will include the dates of symptom onset, first consultation, diagnosis, and treatment initiation will be utilised to calculate the time interval in days between these events and we will quantify the delays before and after the onset of COVID-19, and if COVID-19 is a significant predictor of a change in delays, adjusting for other relevant predictors such as age, sex, marital status, etc. The question asking participants about their journey to treatment initiation will also be utilised. The variables describe all the providers the participant accessed throughout their TB care journey, in chronological order.

For this study, sample sizes were already fixed and could not be changed. The pre-COVID-19 sample size was fixed at 225 after excluding participants recruited in the public sector. The during-COVID-19 sample size was fixed at 149 participants as recruitment numbers were decided across 3-countries and limited by the grant budget. With these two fixed sample sizes, we had a power of 93.8% to detect our main outcome - difference in patient delay due to the pandemic (Cohen's *d*, estimated at 0.37), at the 5% alpha level. For the secondary outcome of number of encounters before diagnosis, we had a power of 99.7%, at the 5% level, to detect *d* of 0.5.

5. Manuscript

Care pathways of individuals with TB, before and during the COVID-19 pandemic in Bandung, Indonesia

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5.1 Introduction

Indonesia has the third highest global tuberculosis (TB) burden. While estimated incidence was 969 000 in 2021, approximately 536 423 people (55.3%)[2] people remain undiagnosed, or diagnosed but not notified to the National TB Program (NTP), otherwise referred to as, 'missing people with TB.' Locating the missing people with TB has remained a challenge for decades[85], and has been deemed the single biggest barrier to TB control in Indonesia[86]. In 2013, the Indonesian National TB Prevalence Survey indicated that two-thirds of treated individuals with TB were not reported to the NTP[104]. Furthermore, Indonesia is one of three countries that account for over 46% of all missing people with TB[89]. The COVID-19 pandemic has only widened this gap, and Indonesia saw the second biggest drop in TB notifications; between 25-30% fewer cases were notified in the first six months of 2020 as compared to 2019[18]. This was repeated once again in 2021, and Indonesia contributed to 18% of the reduction in TB case notifications[2].

The Indonesia High-Frequency Monitoring of COVID-19 Impact Survey, conducted from May-August 2020, found that 11% of households that needed medical treatment were unable to access it, citing closures of facilities, lack of money, and unwillingness to seek healthcare due to the COVID-19 pandemic as the main obstacles. Furthermore, 17% of households needing TB treatment were unable to access it in August 2020[77,131]. The Ministry of Health, Republic of Indonesia also reported that TB Treatment coverage decreased to 47% in 2020[1,78,79], and 45% in 2021[2]. The partial recovery for case notifications that was seen in 2021 was overshadowed by the increase in incidence[2]. It is unclear how many TB cases were missed by primary care providers, and how difficult diagnosis, initiating or adhering to treatment was for individuals with TB in specific settings. However, based on the findings that case notifications decreased and treatment coverage decreased, it is evident that COVID-19 pandemic has undone many years of progress in the fight against TB.

In the context of the Indonesian health system, 74% of initial care-seeking for TB takes place in the private healthcare sector[86]. Care in the private sector can be more personalised, quickly accessible, and more affordable, and since TB is a disease of poverty[13,109,110,128], it is not surprising that poor individuals with TB turn to private clinics or private pharmacies for primary care. While under-reporting to the National TB programs in the secondary public health facilities is a cause of concern, it is evident that the private sector is where linkages to the public health system and the

NTP need to be strengthened and financing needs to increase so that high quality, affordable, and timely care is provided to all those affected by TB[86,88,132].

To implement and guide interventions that promote the early diagnosis of TB, retention, and encourage adherence to care, healthcare seeking behaviours need to be studied. The care cascade analysis is one such methodology. This analysis lines up the sequential stages that an individual with TB would ideally go through to be cured of the disease and aims to sum up the number of individuals in a country or region who were able to access that step. The care cascade for individuals with TB is therefore accessing care for the first time, diagnosis, initiation of treatment, adherence to treatment, and post-treatment outcome[133,134]. Another methodology, the patient pathway analysis (PPA), goes a step further, as it outlines each step of the care cascade, summarises how many individuals with TB reached each consecutive stage, and simultaneously examines service delivery by measuring the quantity, sector, and level of providers were present to meet the individuals where they were[85]. Two separate pre-pandemic PPAs from Indonesia discovered that individuals sought care at private (formal and informal) primary-level health facilities, such as drug shops or pharmacies, where diagnostic capacity is limited. Furthermore, these individuals had to transition into either the public sector or higher-level private facilities for diagnosis, treatment initiation, and general TB management[81,105]. In general, as individuals with TB transition from one healthcare provider to the next, and have multiple encounters, the delays to diagnosis and treatment initiation increase, resulting in worse health outcomes, increased transmission to closed contacts, and higher direct and indirect costs[5,11,13,103,105,106] However, among others, one limitation of the PPA is that it cannot measure the duration of delays that individuals face while navigating the journey towards their recovery, it simplifies the individual's journey to fit the care cascade model when in reality the pathway is possibly more complex, nor capture the factors associated with higher delays or complex pathways without cross-referencing individual-level data. Moreover, the COVID-19 pandemic has added a layer of complexity, as the effects of the restrictions and lockdown protocols on delays and care pathways have not yet been fully studied. These are the knowledge gaps that the following study aims to fill.

We aimed to quantify the delays that individuals with TB faced while trying to access care for their illness, before and during the COVID-19 pandemic, their journey through the care cascade, the encounters individuals had with healthcare providers before they for a TB diagnosis, and examine the factors associated with patient delay and the number of encounters.

6.2 Methods

Datasets

In 2018, the INSTEP study (Investigation of services delivered for TB by external care system, especially the private sector) was conducted in Bandung, Indonesia, over a 2-year period. The study was funded by the Partnerships for Enhanced Engagement in Research, which is a USAID-funded competitive grants program that was awarded to the TB-HIV Research Center, Faculty of Medicine, Universitas Padjadjaran, in Bandung. It aimed to cover a comprehensive assessment of TB services delivered in the private sector, comprising of three studies. One of these three studies was a cross-sectional survey conducted to investigate health care pathways of newly diagnosed individuals with TB[129]. A follow-up study was done in 2020-2022 as part of the COVID-19 effect on Tuberculosis (COVET) project. The COVET project aimed to examine the disruptions caused by the COVID-19 pandemic on TB services in private healthcare in 3 countries – India, Indonesia and Nigeria[130] and is funded by the Bill and Melinda Gates Foundation. The study sites were Bandung in Indonesia, Mumbai, and Patna in India, as well as Lagos and Kano in Nigeria. The scope of the present study encompasses findings from Bandung.

Study setting, population, and COVID-19 wave

The surveys were conducted in Bandung, West Java province, Indonesia. All individuals in the baseline dataset are adults (>18 years of age), living in Bandung, West Java, Indonesia, diagnosed with TB, and on TB treatment at the time of recruitment. Bandung is an urban city, the third largest in the country, located southeast of Jakarta. In 2018, during the INSTEP project recruitment, Bandung's population was 2,537,934. In 2021, during the COVET project recruitment, Bandung's population was 2,606,850, showing a 2.71% increase. Bandung has several universities and professional schools, and is known for its small enterprises in tourism, hospitality, manufacturing, technology, and retail. In 2021, 443 235 TB cases were notified to the NTP nationwide. Whereas in 2018, this number was 570 289.

Demand for initial care is higher in pharmacies, informal healthcare providers, and primary level providers. However, since these providers are rarely equipped with diagnostics required for a definitive TB diagnosis, individuals usually have an iterative process of going to healthcare providers for their persistent symptoms until they get a diagnosis and are subsequently connected with treatment[105]. Individuals delay healthcare seeking as they are often in denial about the severity of their illness due to the stigma surrounding TB[135–137].

TB services are supplied through both public sector and private sector providers all throughout the country. In Bandung, there are 80 community health centres (CHCs), 358 clinics, 22 secondary level hospitals, 15 tertiary level hospitals. Of these services, 106 (22.3%) are publicly funded. Only 6 CHCs 5 hospitals, and 1 public laboratory have Xpert/MTB-RIF as a molecular test for TB diagnosis, which is the diagnostic test primarily recommended by the National TB Elimination Program (NTP) for diagnosing clinical TB. It is unclear how many private clinics and practitioners have diagnostic facilities.

Respondents were recruited between July 2021 and February 2022. **Figure 3** shows the levels of restrictions during the period of interest, daily COVID-19 cases, daily recruitment, and the dates that our respondents sought care and got a diagnosis. Recruitment was slower during periods of high COVID-19 burden, and the most active between the months of September and January. During this period, restriction levels ranged from Level 4 (rules allowed non-essential establishments to operate at a maximum of 10% capacity on-site, whereas essential businesses operated at just under 100%), to Level 2, (hotels, supermarkets, restaurants, and theaters could still operate up to a maximum of 75% of the total capacity and had to be closed by 9 pm).

Sampling and enrolment for pre-COVID-19 dataset

A more detailed description of the sampling procedure for the INSTEP project is given in the article by Lestari et al[105]. The researchers used hierarchical sampling, starting from sub-districts of Bandung. Bandung contains 151 sub-districts, from which 30 were randomly selected in proportion to population size. These sub-districts contained 282 private practitioners, 30 community health centres (CHCs), 7 public hospitals, and 10 private hospitals. From this frame, 10 CHCs were randomly chosen, and 2 public hospitals and 3 private hospitals were chosen according to their high TB case density and their willingness to participate in the study. Out of 282 PPs, 145 PPs were willing to participate in the study, and they were deemed eligible if they were able to diagnose TB in people. Enrolment into the primary INSTEP study depended on the individual being a patient in one of the sampled public hospitals, community health centres, private hospitals, or private practitioners. A sampling frame from patient records was obtained, and consenting individuals were enrolled from 1st October 2017 till 31 January 2019, until the desired sample size was met. Aiming for 80% power, 5% error, and a design effect of 1, adjusting for a non-response rate of 10%, a sample size of 396 participants was calculated[105]. Written consent was obtained at the time of interview by the interviewer. This study includes 225 respondents from this dataset, 80 individuals from private hospitals, and 145 individuals from private clinics. Individuals who had previous history of being on TB treatment, extrapulmonary TB, and those outside the study site (Bandung) were excluded.

Sampling and enrolment for during-COVID-19 dataset

Sampling for the COVET project was designed to closely replicate the INSTEP project. The researchers used hierarchical sampling, starting from sub-districts of Bandung. 30 sub-districts were randomly sampled. From the corresponding area, 59 private practitioners, and 4 private hospitals were selected. A sampling frame from patient records was obtained, and consenting patients were enrolled from 7th July 2021 until 28th February 2022, until the desired sample size was met. Some public hospitals and community health centres were also sampled due to a high non-response rate from the individuals in the original sampling frame. However, this study only analyses data from respondents recruited from private sector facilities. Information regarding the sample from the two datasets is described further in **Figure 1.**

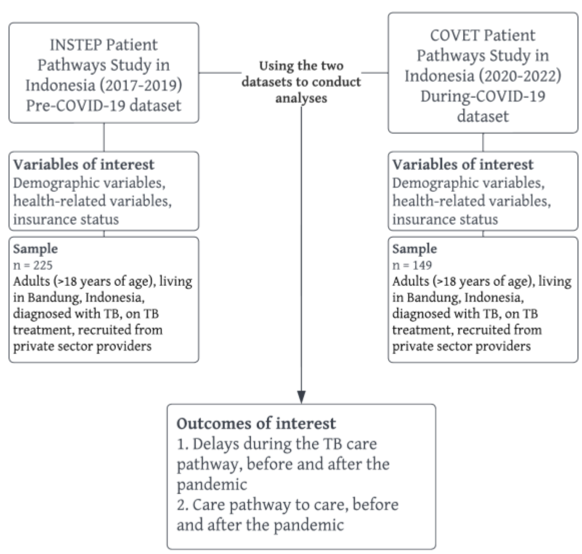

Figure 1. Flowchart depicting pre- and during-COVID-19 datasets

For this study, sample sizes were already fixed and could not be changed. The pre-COVID-19 sample size was fixed at 225 after excluding participants recruited in the public sector. The during-COVID-19 sample size was fixed at 149 participants as recruitment numbers were decided across 3-countries and limited by the grant budget. With these two fixed sample sizes, we had a power of 93.8% to detect our main outcome - difference in patient delay due to the pandemic

(Cohen's *d*, estimated at 0.37), at the 5% alpha level. For the secondary outcome of number of encounters before diagnosis, we had a power of 99.7%, at the 5% level, to detect *d* of 0.5.

Statistical Analysis

All data cleaning, visualisation, and statistical analysis was performed on R[138]. COVID-19 cases in Bandung were presented to contextualise the time point at which recruitment occurred, as the effects of COVID-19 were not constant throughout the pandemic. The two samples (pre-COVID-19 and during-COVID-19) were described by median and interquartile range (IQR) for age and average household monthly income, and categorical variables were described by proportion (percentage). As individuals were from several healthcare providers across Bandung, no clustering at specific healthcare facilities was suspected, and to limit recall bias, all individuals were surveyed within 6 months of their treatment initiation.

Univariable regression was used to first investigate factors associated with patient delay and numbers of encounters until diagnosis, and then a multivariate model was fitted to control for confounders and investigate the effect of the COVID-19 pandemic on the outcomes of interest.

The associated factors for the patient delay model were chosen based on the previous manuscript by Lestari et al[105] and after reviewing literature regarding the most common factors associated with patient delays (**Chapter 3**). Age, gender, education level, employment status, average household income, insurance status, comorbidities were taken from the previous manuscript[20], and minutes to nearest CHC was included as a variable as the association between patient delay and long distances from a healthcare facility has been proven in multiple systematic reviews summarising the risk factors of delays in TB[111,115,116,120]. An additional two variables were added that might have confounded the relationship between COVID-19 and TB: the symptoms of cough and fever prompting the initial visit to a healthcare provider. We hypothesized that having a fever or a cough can be associated with patient delay, as these the presence of these symptoms can prompt an immediate visit to a primary health care provider[139], or can be treated as non-severe symptoms and increase delays/number of encounters to informal providers[109,111,115,117].

Due to the outliers in the data and the skewed but unimodal underlying distribution of the continuous outcome variables, quantile regression (*tau* = 0.5) was utilised to examine the association between the outcome of interest (patient delay, number of encounters) and their associated factors. Additionally, no parametric assumptions are required in the quantile regression[140,141]. The benefit of using a median regression also allows us to simply characterize the distributions of health outcomes in a well-defined population as they exist during this time and record how the distribution is changing over time[142]. The change is median delays or median number of pre-diagnostic encounters based on specific factors is therefore worth investigating. The explorations of other quantiles are expressed in the Appendix (**Appendix I and Appendix II**)

Therefore, we performed two quantile regressions with *tau* = 0.5 each for both outcome variables, to examine whether the onset of the pandemic increased delays or pre-diagnostic encounters. The variables we controlled for the patient delay model were age at treatment initiation, sex, highest education level, minutes to closest health centre, employment status, insurance enrollment (binary variable; yes or no), average monthly household income (changed to USD), any comorbidities (binary variable; none, 1 or more), cough (binary variable; yes or no), fever (binary variable; yes or no). The variables we controlled for the number of encounters model were age at treatment initiation, sex, highest education level, minutes to closest health centre, employment status, insurance enrollment (binary variable; yes or no), average monthly household income (changed to USD), any comorbidities (binary variable; none, 1 or more), cough (binary variable; yes or no), fever (binary variable; yes or no), and provider at first encounter.

Sensitivity analyses were performed by using logistic regression for the same models. A cut-off of 30 days was used to indicate patient delay, and a cut-off of 6 encounters was used to indicate a high number of encounters, with all the same predictors as mentioned above. These cut-off values for patient delay were taken from Lestari et al[105]. The cut-off for 6 encounters was chosen as it is the median for both samples. The motivation for not changing the parameters/quantiles in the original model but changing the outcome variable itself and fitting a new model as the quantile regression has the flexibility of testing first if a given exposure differs by a percentile of the outcome. Once this has been disproven, we can go ahead with a traditional logistic regression. Furthermore, this regression will validate the findings from the primary analysis. Multicollinearity was checked using the package car, and results for model diagnostics are presented in the Appendix (Appendix III).

5.3 Outcomes of interests and definitions

The main outcomes of interest were participant's date of symptom onset, date of first consultation with a healthcare provider, date of diagnosis, and date of treatment initiation to calculate *delays* at each step of the TB care cascade. Additionally, we inquired about all the *encounters* the individual had with various healthcare providers leading up to their diagnosis.

Specifically, the purpose of the visit, the type of provider, and the provider's sector. These outcome variables serve as indication of the participant's complex care pathway, as the main objective is to discern whether the onset of the COVID-19 pandemic is a significant predictor in more complex TB care pathway with longer TB diagnostic and treatment delays. Socio-demographic variables were also collected to ensure that they were controlled for when examining factors associated with delays and number of encounters.

The various types of delays are presented in the **Figure 2**. *Patient delay* is defined as the number of days between the onset of symptoms and first consultation with healthcare provider, *doctor delay* is defined as the number of days from that first consultation until the participant was given a diagnosis for their TB, and *treatment delay* is the number of days between the date of diagnosis and date of TB treatment initiation. *Encounter* is defined as a visit to a healthcare provider (of any level, from community pharmacist to specialist at a tertiary care hospital). The different kinds of healthcare providers that individuals visited during their care pathway are private clinics, private hospitals, public hospitals, community pharmacies, CHCs, *puskesmas* traditional healers and medicine shops, and public and private laboratories. Community pharmacies are defined as stand-alone shops, with registered pharmacists present, and traditional healers and medicine shops are informal healthcare providers, more locally known.

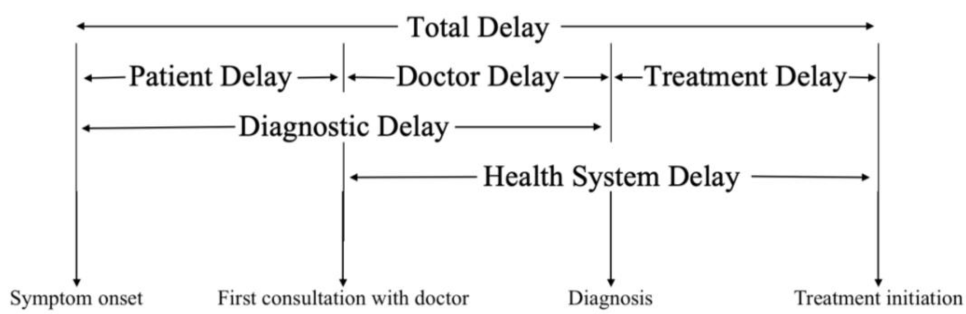

Figure 2. Conceptual framework of delays in diagnosis and treatment of pulmonary tuberculosis, figure recreated for clarity, caption taken from Bello et al. (2019) [113]

5.4 Ethics

Ethical clearance for this manuscript study was provided by the McGill University Faculty of Medicine and Health Sciences Institutional Review Board (IRB Internal Study Number: A04-M43-22A), Research Institute of McGill University Health Centre (Covid BMGF / 2021-7197), and Universitas Padjadjaran Research Ethics Committee (166/UN6.KEP/EC/2021). As this study will use data from two primary studies conducted at Universitas Padjadjaran, Bandung, Indonesia, this study only uses secondary data. Ethics and scientific approval by the institution at the local study site had already been obtained at the time of analysis.

5.5 Results

COVID-19 and recruitment

Respondents were recruited between July 2021 and February 2022, and **Figure 3** shows that care seeking followed the distribution of the recruitment quite closely. **Figure 3** shows the daily COVID-19 cases, daily recruitment, the dates that our respondents went to seek care and got a diagnosis, and the restrictions level in place for that period in Bandung. Recruitment was slower during periods of high COVID-19 burden, and the most active between the months of September 2021 and January 2022. Our sample represents care seeking throughout the year, from January 2021 till the end of February 2022. Before the spike in cases due to the delta wave, Bandung had micro-restrictions in place, meaning that markets, malls, shopping centres, restaurants, and cafes were limited to a 25% capacity and operational until 8:00 pm. Other essential services such as groceries, pharmacies, and healthcare facilities were operating at full capacity[143]. COVID-19 cases displayed a cyclical pattern of rise and fall every couple of months, with the largest rise in cases at the end of recruitment, and the second highest peak in July 2021. However, as the data suggests, care seeking was still ongoing as restrictions did not affect healthcare facilities[143], and individuals were also being diagnosed during these times of heightened burden and recovery. Therefore, the COVID-19 variable was treated as a binary variable, either present or not-present.

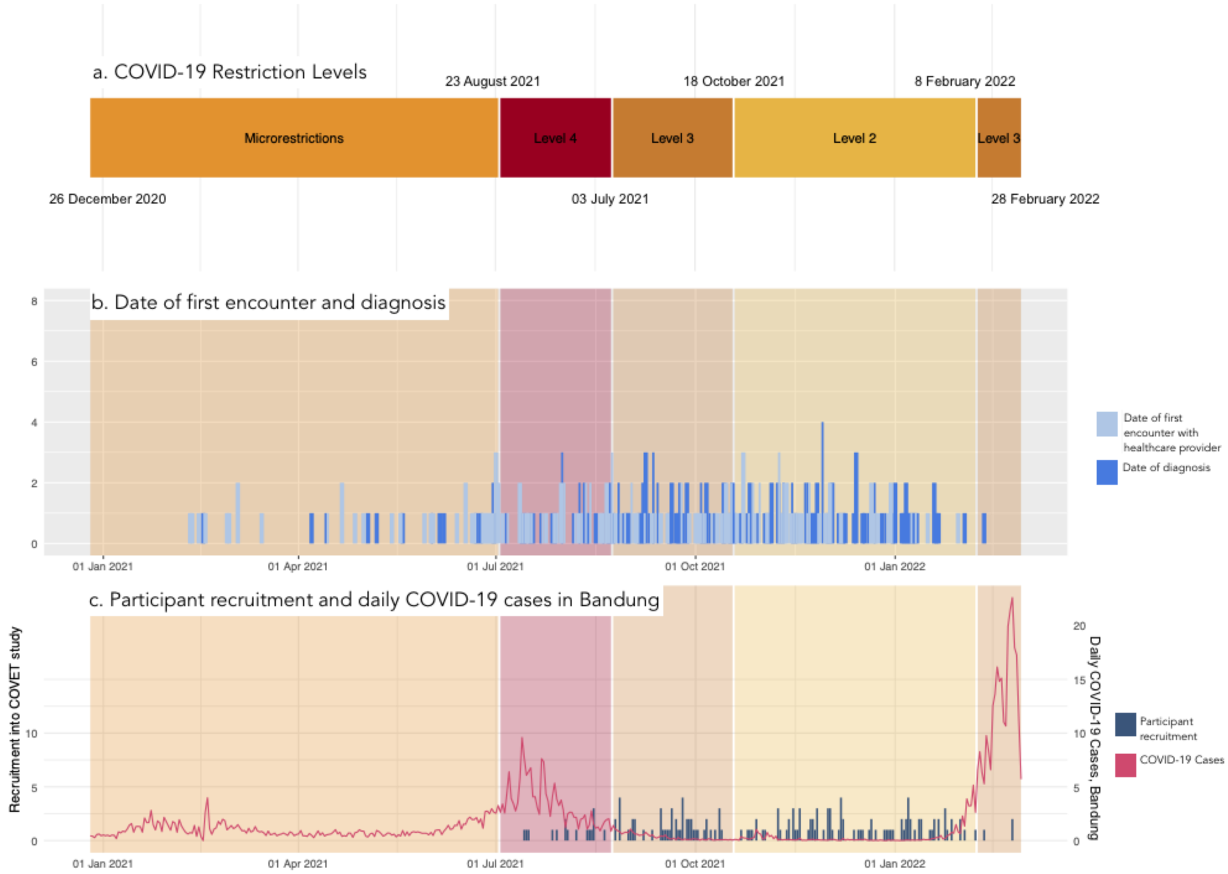

Figure 3. COVID-19 restriction levels in Bandung, relevant dates in participant care pathway, and participant recruitment and daily COVID-19 cases in Bandung

Baseline characteristics

The following table presents the baseline characteristics of the sample. A chi-squared test of homogeneity was conducted to test how different the two samples are (**Table 1).** The median age of the participants was 35 years and 36 years, before and during COVID-19, respectively. One hundred and twenty-four (55.1%) participants from the pre-COVID-19 sample were male, whereas 79 (53%) participants from the during COVID-19 sample were male. In the pre-COVID-19 sample, 52 participants (23.1%) had primary school or less schooling, while 55 participants (36.9%) in the during-COVID-19 sample had primary school or less schooling. 144 participants (64.0%) had completed high school while 72 participants (48.0%) had completed high school. A higher number of participants, 71, as well as a higher proportion of participants (47.7%) were unemployed in the during-COVID-19 sample whereas only 64 (28.4%) participants were unemployed in the pre-COVID-19 sample. Median monthly household income was higher for the during-COVID-19 sample as compared to the pre-COVID-19 sample (193USD vs. 163USD). A higher proportion of participants were enrolled in an insurance scheme (either the national insurance scheme or a private insurance scheme) during COVID-19 as compared to (85.9% vs. 74.7%). Around the same proportions of participants from the pre-COVID-19 sample and the during COVID-19 sample had smoked in the past year (41.8% vs. 38.3% respectively), 17% of the participants in the pre-COVID-19 sample had 1 or more comorbidities, whereas 21% of the sample in the during COVID-19 sample had 1 or more comorbidities. All participants from the during COVID-19 sample suffered from symptoms that prompted them to visit a healthcare provider to get a diagnosis for their illness, which included, persistent cough (92.6%), night sweats (50.3%), coughing blood (23.5%), weight loss (64.4%), and fever (47.7%). There were 9 participants (4%) in the pre-COVID-19 sample that were able to get a diagnosis from a referral without suffering any symptoms. However, 83.6% of the sample suffered from persistent cough, 55.1% suffered from night sweats, 20.9% were coughing blood, 65.8% suffered from weight loss, and 61.8% had fever.

The providers most often seen at first encounter by both samples were informal providers, namely pharmacies, traditional healers, midwives. Most participants (53.5%) in the pre-COVID-19 sample obtained diagnosis at private practitioners, whereas 58.4% of the sample in the during-COVID-19 sample obtained their diagnosis at private hospitals. Finally, treatment was managed by community health centres (24.4%), private practitioners (29.3%), and private hospitals (46.2%) for the pre-COVID-19 sample. For participants in the during COVID-19 sample, treatment was managed by community health centres (36.2%), private practitioners (2.0%), public hospitals (1.3%), and private hospitals (60.4%). A higher proportion of individuals in the during-COVID-19 sample were given a diagnosis at the same place as their first visit (42.3% vs. 32%), but a lower proportion of individuals were connected with treatment at the same place as their diagnosis in the during-COVID-19 sample (59.1% vs. 66.2%).

Table 1 – Baseline Characteristics. Pre-COVID-19 sample and during COVID-19 sample

	Pre-COVID-19 (Years: 2017-2019) n (%)	**During COVID-19 (Years: 2021-2022) n (%)**	**p-value**
	(N=225)	(N=149)	
Age at treatment initiation			
Median (IQR)	35.0 (24.0 to 50.0)	36.0 (25.0 to 58.0)	0.159
Sex			
Male	124 (55.1)	79 (53.0)	0.771
Female	101 (44.9)	70 (47.0)	
Highest Education Level			
No formal schooling/less than primary school	52 (23.1)	55 (36.9)	0.007
High school completed	144 (64.0)	72 (48.3)	
College/university completed	29 (12.9)	22 (14.8)	

Employment Status			
Unemployed	64 (28.4)	71 (47.7)	0.001
Employed	108 (48.0)	42 (28.2)	
Student at school/university	11 (4.9)	15 (10.1)	
Other (housewife/husband, retired, etc.)	42 (18.7)	21 (14.1)	
Avg. monthly household income (USD)*			
Median (IQR)	163.3 (100.0 to 214.2)	193.3 (102.7 to 333.3)	0.049
Enrolled in an insurance scheme (private or government)			
No insurance	57 (25.3)	21 (14.1)	0.013
Has insurance	168 (74.7)	128 (85.9)	
Smoked in the past year			
No	131 (58.2)	92 (61.7)	0.567
Yes	94 (41.8)	57 (38.3)	
Any comorbidities			
No comorbidities	187 (83.1)	117 (78.5)	0.328
1 or more comorbidities	38 (16.9)	32 (21.5)	
Symptoms that prompted visit to healthcare provider			
Cough	188 (83.6)	138 (92.6)	0.016
Night sweats	124 (55.1)	75 (50.3)	0.424
Coughing Blood	47 (20.9)	35 (23.5)	0.640
Weight Loss	148 (65.8)	96 (64.4)	0.875
Fever	139 (61.8)	71 (47.7)	0.010
No symptoms			
No symptoms	9 (4.0)	0 (0.0)	0.033
Symptoms present	216 (96.0)	149 (100.0)	
Sector of provider at first encounter			
Private Sector	197 (87.6)	141 (94.6)	0.036
Public Sector	28 (12.4)	8 (5.4)	
Provider at first encounter			
Informal Provider	88 (39.1)	72 (48.3)	0.137
Community Health Centre	26 (11.6)	8 (5.4)	
Private Practitioner	81 (36.0)	52 (34.9)	
Private Hospital	28 (12.4)	17 (11.4)	
Public Hospital	2 (0.9)	0 (0.0)	
Location of diagnosis			
Community Health Centre	0 (0.0)	1 (0.7)	0.005
Private Practitioner	120 (53.3)	61 (40.9)	
Public Hospital	7 (3.1)	0 (0.0)	
Private Hospital	98 (43.6)	87 (58.4)	
Location of treatment provision			
Community Health Centre	55 (24.4)	54 (36.2)	0.001
Private Practitioner	66 (29.3)	3 (2.0)	
Public Hospital	0 (0.0)	2 (1.3)	
Private Hospital	104 (46.2)	90 (60.4)	
Diagnosis given in the same location as the first encounter			
Yes	72 (32.0)	63 (42.3)	0.055
No	153 (68.0)	86 (57.7)	
Treatment given in the same location as the site of diagnosis			
Yes	149 (66.2)	88 (59.1)	0.194
No	76 (33.8)	61 (40.9)	

**** Exchange rate of 1 USD = 15 000 IDR***

Distribution of delays, pre-COVID-19 and during-COVID-19

Figure 4 shows the distribution of the number of days for each type of delay. Compared to the pre-COVID-19 sample, the participants in the during COVID-19 sample faced higher patient and doctor delays. While it took median 28 days for a participant in the pre-COVID-19 sample with symptoms to visit a healthcare provider, it took median 32 days for a participant in the during COVID-19 sample. The IQR for patient delay has increased significantly for participants in the during COVID-19 sample, ranging from 14-90 days, whereas the IQR of patient delay for participants in the pre-COVID-19 sample is 10-31 days. This might be due to the maximum of 582 days of patient delay in the duing-COVID-19 sample. The pre-COVID-19 sample follows a bi-modal distribution. The distribution starts at day 0, which shows the participants who displayed no symptoms; therefore, they did not have any patient delay. The right tail of this distribution shows that a few participants had large delays, as compared to the rest of the sample. For participants in the during COVID-19 sample, the distribution is right skewed, looks a little more normal, but has a large spread. The distributions of doctor delays are quite similar, with the pre-COVID-19 median doctor delay of 15 days, and the median doctor delay during COVID-19 as 18 days. Treatment delay stayed relatively unchanged, from 1 day (IQR 0-4 days) in the pre-COVID-19 sample to 1 day (IQR 0-3 days). The box and whisker plots (boxplots) illustrate the median and IQR of the delays (**Figure 4**). For patient delay, the boxplot is skewed, with the median approaching the right third quartile, but is still quite narrow. The boxplot for the during COVID-19 sample is wider, skewing towards the first quartile. The boxplots for the doctor delays for the two samples are quite similar, with the during COVID-19 sample displaying a higher maximum. The boxplot for treatment delay is also quite similar for both samples.

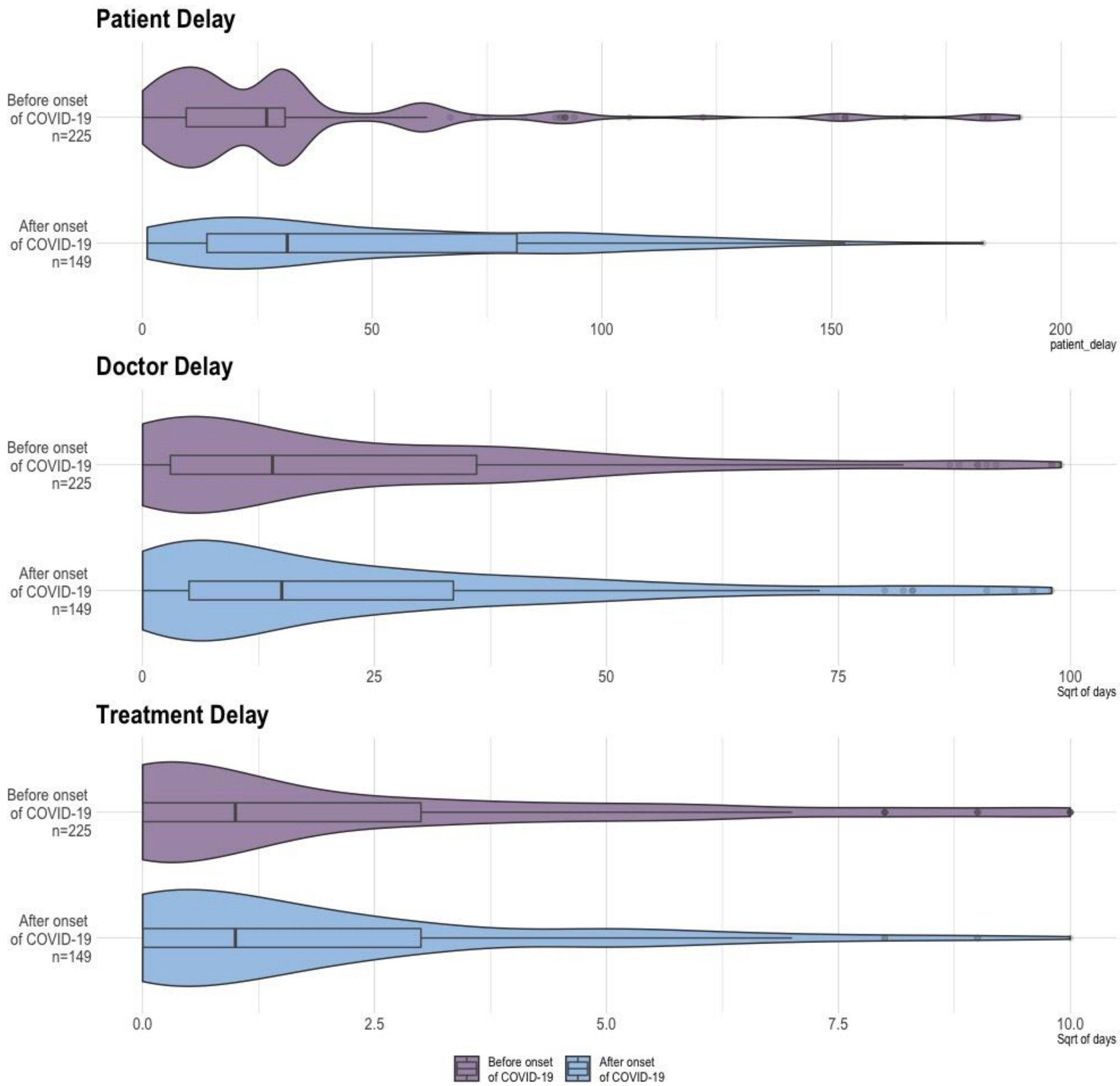

Figure 4. Distribution of delays, pre-COVID-19 and during COVID-19

Table 2 – Delays throughout the care cascade

Delay	Time point	Median (days)	IQR	95% CI*	Min, Max	p-value**
Patient Delay	Pre-COVID-19	28	10 to 31	(16, 30)	0, 304	0.001
	During-COVID-19	32	14 to 90	(31, 55)	1, 585	
Doctor Delay	Pre-COVID-19	15	4 to 41	(12, 22)	0, 362	0.253
	During-COVID-19	18	5 to 48	(14, 26)	0, 288	
Treatment Delay	Pre-COVID-19	1	0 to 4	(1, 2)	0, 40	0.774
	During-COVID-19	1	0 to 3	(1, 2)	0, 37	

** Method = "exact"*
*** Chi-squared test to test difference of medians between the two time-points*

Care pathway for individuals with TB, pre-COVID-19 and during COVID-19

Figure 5 shows the care pathways for individuals with TB in both samples. For initial presentation, a higher proportion of participants went to informal providers in the during-COVID-19 sample (48.3%) as compared to the pre-COVID-19 sample (39.1%). The proportion of participants who went to community health centres decreased during COVID-19 (from 11.6% to 5.4%), and no participants went to a public hospital for initial care seeking. More diagnoses happened at private hospitals during COVID-19 (58.4% during-COVID-19 as compared to 43.6% pre-COVID-19) and no diagnoses happened at public hospitals, as compared to 3.1% in the pre-COVID-19 sample. A larger number of individuals with TB got their treatment initiated by community health centres during COVID-19 as compared to before. In the pre-COVID-19 sample, out of the 120 indiviuals diagnosed at private practitioners, 55 (45.8%) individuals were referred to community health centres for treatment management and 65 (55.2%) of individuals stayed with private practitioners. However, in the during-COVID-19 sample, out of 61 individuals, 53 (86.9%) went to CHCs or their treatment, 3 (4.9%) stayed with private practitioners, 2 (3.3%) went to public hospitals, and 3 (4.9%) went to private hospitals. However, like the pre-COVID-19 sample, most individuals who were diagnosed at private hospitals in the during COVID-19 sample stayed with private hospitals for their treatment management.

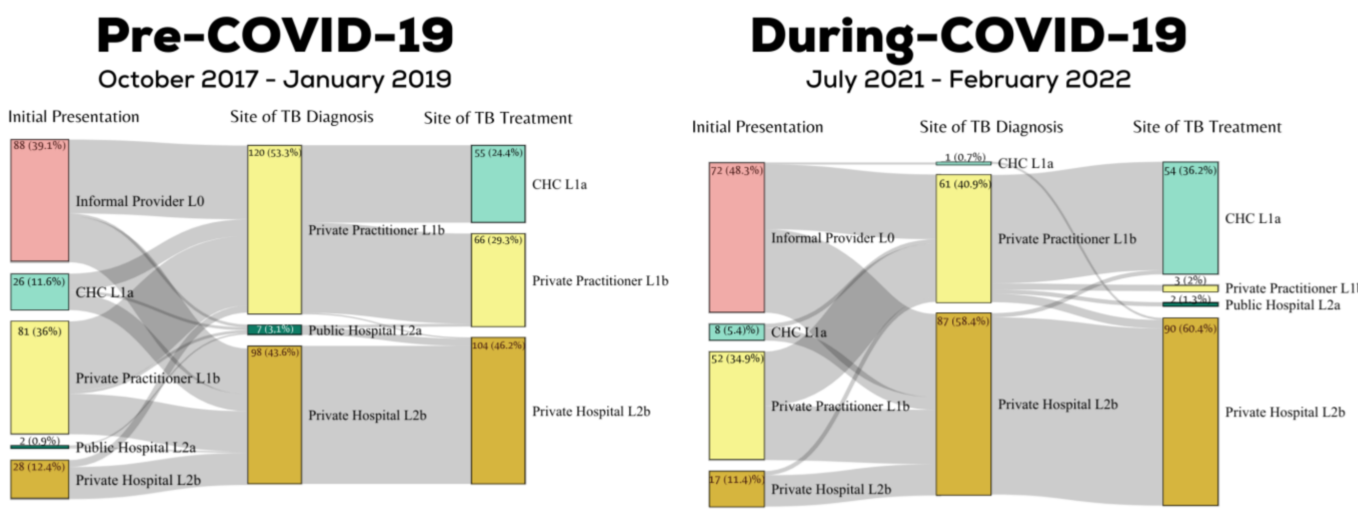

Figure 5. Sankey Chart showing individuals with TB in the pre-COVID-19 and during-COVID-19 sample moving through the care pathway

Encounters with health care providers and site of diagnosis provision and misses for individuals with TB, pre-COVID-19 and during COVID-19

Figure 6 shows the proportion of individuals who were either given a diagnosis or missed a diagnosis, over sequential encounters. The dark green line separates the individuals already diagnosed from the individuals who haven't been diagnosed yet. This line is steeper for the pre-COVID-19 sample as compared to the during COVID-19 sample, meaning individuals in this sample were diagnosed after a fewer number of encounters as compared to during COVID-19. Median encounters until diagnosis was 5 for participants in the pre-COVID-19 sample, and it was 7 in the during-COVID-19 sample. 75% of the sample was diagnosed at encounter 7 in the pre-COVID-19 sample, whereas 75% of the sample was diagnosed at encounter 11. Informal providers were also visited until later encounters during COVID-19, and by a higher proportion of participants. There were more missed opportunities to be diagnosed at private practitioners in the pre-COVID-19 sample, but there were more missed opportunities to be diagnosed at private hospitals during COVID-19.

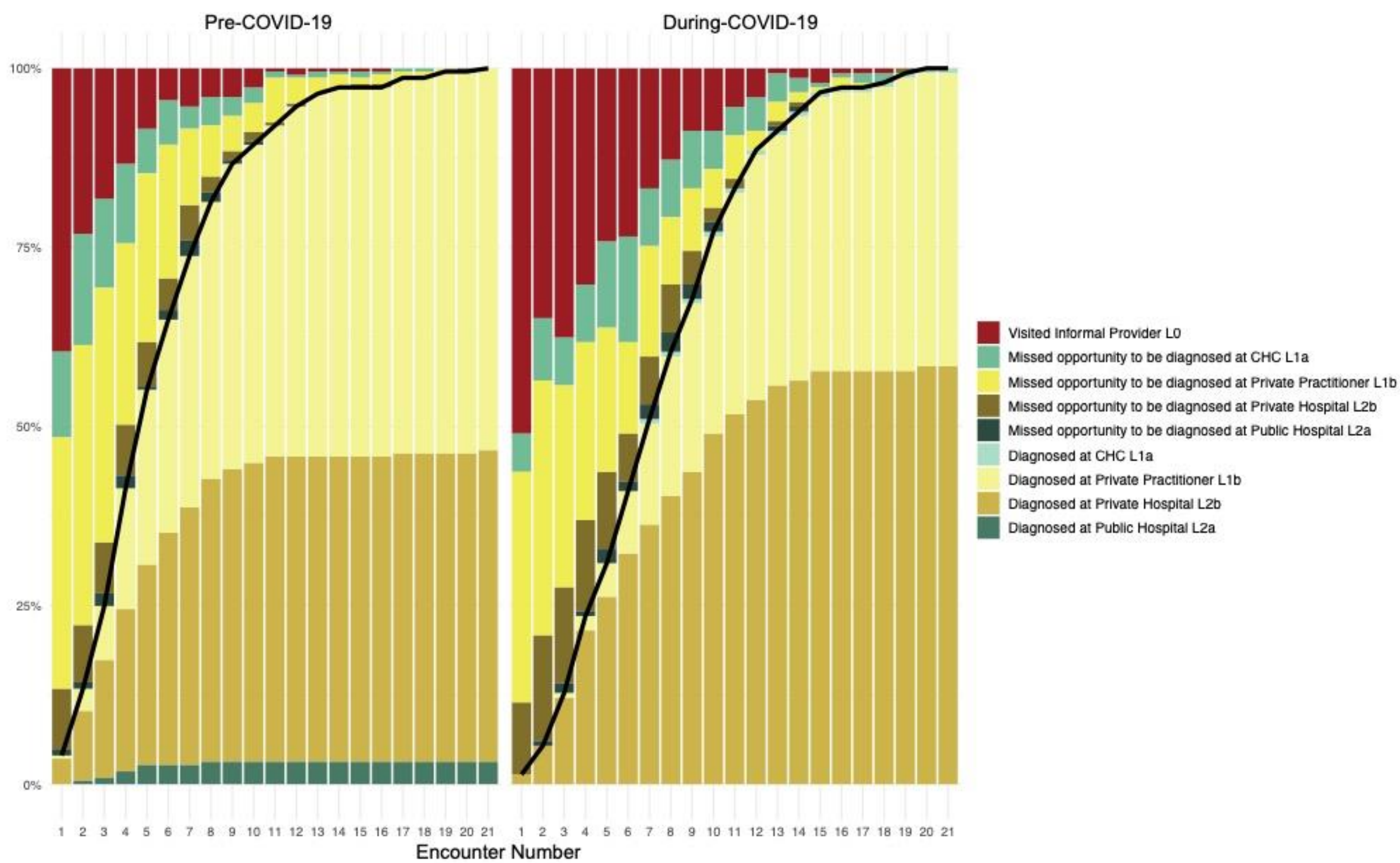

Figure 6. Encounters with health care providers and site of diagnosis provision and misses for individuals with TB, pre-COVID-19 sample and during COVID-19 sample

Pathway matrix of individuals with TB, pre-COVID-19 and during COVID-19

This figure shows the unique pathways that individuals with TB followed before they were diagnosed with TB. Each coloured cell represents an encounter, and each row represents a unique pathway. The pre-COVID-19 sample size was 225 and there were 155 unique pathways, and 131 unique pathways in the during-COVID-19 sample. In both matrices, we can see that there are more red cells higher up, indicating visits to informal providers with participants with a higher number of encounters. Visits to informal providers were repeated, during both time points. The penultimate visits for the pre-COVID-19 sample took place more often in the private sector, but there were more penultimate visits with CHCs for the during COVID-19 sample. Participants in the post-COVID-19 sample seemed to be switching into the public sector from the private sector more often, as evidenced by the prevalence of green cells near the right-side of the matrix.

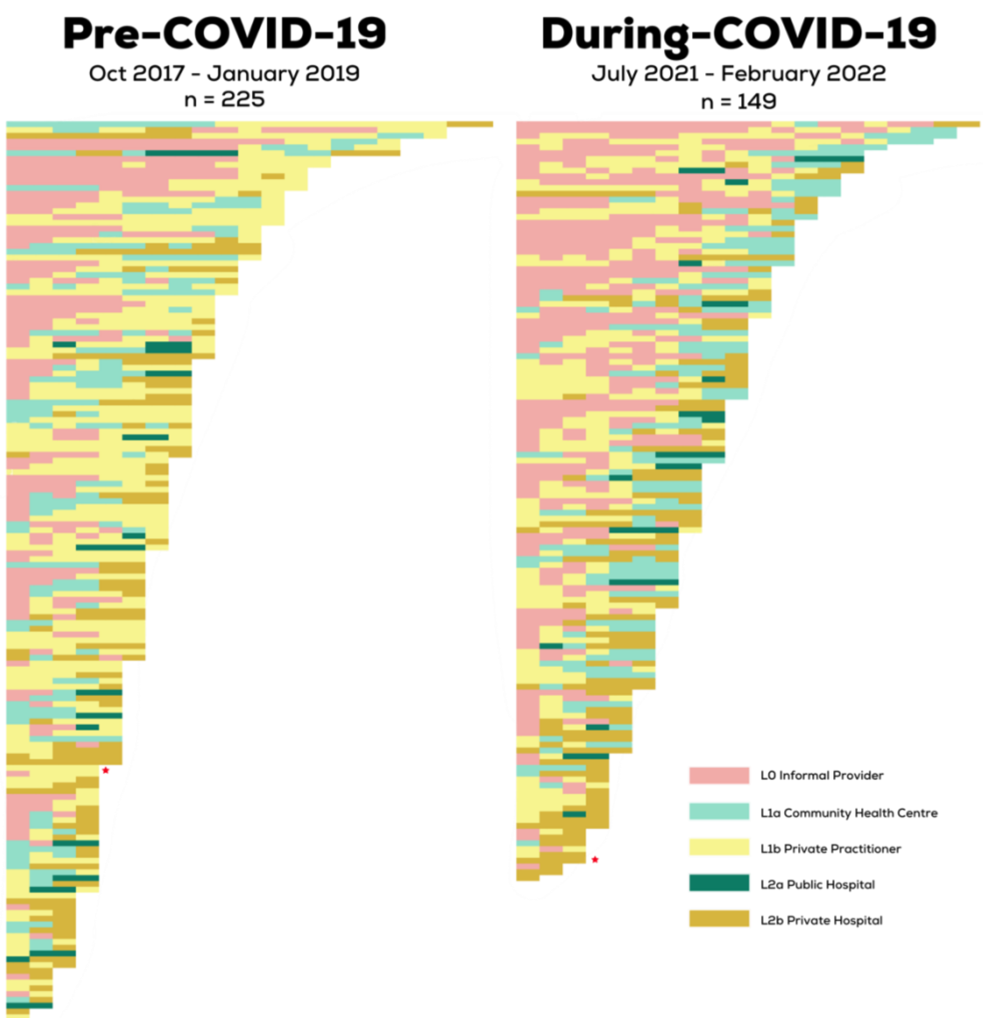

Figure 7. Pathway matrix showing individual encounters with different providers in unique pathways, pre-COVID-19 sample and during COVID-19 sample

Factors associated with patient delay

The regression coefficients in **Table 3** show the median change in patient delay (measured in days). The variables age, gender, education level, minutes to closest health center, employment status, insurance status, average monthly household income, smoking history, comorbidities, coughing, and fever symptoms were fitted in the median regression equation and controlled for. The median change in patient delays in the adjusted model was found to be 2.75 days higher for the during-COVID-19 sample as compared to the pre-COVID-19 sample (adj. median = 4.42, 95% CI: -7.20, 16.03, p value: 0.457). Individuals who were employed faced lower patient delays compared to individuals who were unemployed (adj. median = -20.13, 95% CI: -39.14, -1.12, p value: 0.039).

Table 3 – Median regression; factors associated with patient delay

	Unadjusted		Adjusted	
Outcome: Patient Delay				
Variable	Coefficient (CI)	p-value	Coefficient (CI)	p-value
COVID-19 Status				
Pre COVID-19				
During COVID-19	4.00 (-10.91, 18.91)	.599	4.42 (-7.20, 16.03)	.457
Age at Treatment Initiation	0.03 (-0.10, .15)	.658	-0.21 (-0.59, .17)	.280
Gender				
Male				
Female	1.00 (-5.55, 7.55)	.765	8.32 (-3.57, 20.20)	.172
Highest Education Level Completed				
Primary School or less				
High School Completed	-2.00 (-17.14, 13.14)	.796	-6.54 (-20.50, 7.42)	.360
College/University Completed	-1.00 (-12.95, 10.95)	.870	-7.18 (-23.46, 9.09)	.388
Employment Status				
Unemployed				
Employed	-3.00 (-14.19, 8.19)	.600	-20.13 (-39.14, -1.12)	.039
Student at school/university	-12.00 (-23.46, -.54)	.041	-28.31 (-60.92, 4.29)	.090
Other (housewife/husband, retired)	0.00 (-10.07, 10.07)	1.000	15.78 (-23.55, 55.10)	.433
Insurance Status				
Doesn't have insurance				
Has insurance	-1.00 (-5.62, 3.62)	.672	0.82 (-11.27, 12.91)	.895
Minutes to Nearest CHC	0.05 (-0.22, .32)	.716	-0.19 (-0.96, .57)	.625
Average Monthly Household Income	0.00 (-0.03, .03)	1.000	0.01 (-0.03, .05)	.674
Any comorbidities				
No				
Yes, 1 or more	0.00 (-11.07, 11.07)	1.000	0.80 (-17.14, 18.75)	.930
Symptom that prompted visit: Cough				
Cough not present				
Cough present	10.00 (-5.03, 25.03)	.193	4.94 (-10.46, 20.34)	.530
Symptom that prompted visit: Fever				
Fever not present				
Fever present	0.00 (-3.98, 3.98)	1.000	2.74 (-7.78, 13.27)	.610

Factors associated with number of encounters before diagnosis

The regression coefficients in **Table 4** show the median change in encounters. Participants in the during COVID-19 sample underwent a median of 2 more encounters before they were diagnosed with TB as compared to the pre-COVID-19 sample (unadjusted median = 2, 95% CI: 0.829, 3.171, p-value 0.001). The variables COVID-19 status, age, gender, education level, minutes to closest health center, employment status, insurance status, average monthly household income, smoking history, comorbidities, coughing and fever symptoms, and provider at first encounter were fitted in the median regression equation and controlled for in the multivariate regression. After adjusting for relevant confounders, participants in the during COVID-19 sample underwent a median of 1.72 more encounters before they were diagnosed with TB as compared to the pre-COVID-19 sample (adjusted median = 1.59, 95% CI: -0.18, 3.36 p-value 0.080). However, for individuals who visited a private hospital as compared to community health centres for their initial visit underwent a smaller number of encounters (adjusted median = -4.29, 95% CI: -6.76, -- 1.881, p-value 0.001).

	Unadjusted		Adjusted	
Outcome: Number of encounters				
Variable	Coefficient (CI)	p-value	Coefficient (CI)	p-value
COVID-19 Status				
Pre COVID-19				
During COVID-19	2.00 (0.91, 3.09)	0.001	1.59 (-0.18, 3.36)	.080
Age at Treatment Initiation	0.00 (-0.03, .03)	1.000	0.02 (-0.03, .07)	.480
Gender				
Male				
Female	2.00 (0.58, 3.42)	.006	0.08 (-1.44, 1.59)	.921
Highest Education Level Completed				
Primary School or less				
High School Completed	-2.00 (-3.29, -.71)	.003	0.19 (-1.56, 1.94)	.834
College/University Completed	1.00 (-1.04, 3.04)	.337	1.20 (-0.87, 3.26)	.258
Employment Status				
Unemployed				
Employed	-1.00 (-2.52, .52)	.198	-1.09 (-2.93, .74)	.243
Student at school/university	-1.00 (-3.08, 1.08)	.346	-0.11 (-5.87, 5.65)	.970
Other (housewife/husband, retired)	-1.00 (-2.71, .71)	.251	0.86 (-2.30, 4.02)	.594
Insurance Status				
Doesn't have insurance				
Has insurance	0.00 (-1.29, 1.29)	1.000	0.28 (-1.60, 2.15)	.772
Minutes to Nearest CHC	0.00 (-0.06, .06)	1.000	0.03 (-0.07, .13)	.542
Average Monthly Household Income	0.00 (0.00, .01)	.260	0.00 (0.00, .01)	.356
Any comorbidities				
No				
Yes, 1 or more	0.00 (-1.27, 1.27)	1.000	-0.82 (-2.51, .87)	.341

Symptom that prompted visit: Cough				
Cough not present				
Cough present	2.00 (0.74, 3.26)	.002	0.68 (-0.90, 2.27)	.398
Symptom that prompted visit: Fever				
Fever not present				
Fever present	0.00 (-1.16, 1.16)	1.000	0.00 (-1.23, 1.23)	.999
Provider at first encounter				
Community Health Centre				
Informal Provider	2.00 (0.19, 3.81)	.031	0.68 (-1.56, 2.92)	.552
Private Practitioner	-1.00 (-2.55, .55)	.206	-1.29 (-3.30, .73)	.212
Private Hospital	-3.00 (-4.70, -1.30)	.001	-4.29 (-6.76, -1.81)	0.001
Public Hospital	-3.00 (-5.91, -.09)	.044	-2.58 (-5.85, .69)	.123

Table 3 – Median regression; factors associated with number of encounters before diagnosis

Sensitivity Analysis

The sensitivity analysis consisted of fitting a univariate and multivariate logistic regression. For the patient delay outcome, the variables COVID-19 status, age, gender, education level, minutes to closest health center, employment status, insurance status, average monthly household income, smoking history, comorbidities, coughing, and fever symptoms were fitted into the model. The logistic regression was in concordance with the non-parametric model and shows that regarding patient delays (with the cut-off being 30 days), employment status is a significant predictor of a decrease in delays (adjusted odds ratio: 0.29, 95% CI: 0.12, 0.71, p-value 0.008), meaning an individual who is employed is 71% less likely to be delayed more than 30 days in seeking care for their TB symptoms as compared to an individual who is unemployed, controlling for all the aforementioned confounders. Being a student is also protective against being delayed in seeking care for symptoms (adjusted odds ratio: 0.13, 95% CI: 0.02, 0.71, p-value 0.025), as a student is 87% less likely to be delayed more than 30 days.

For the outcome of number of encounters before diagnosis, a cut-off of 6 encounters was chosen. The logistic regression found that the odds of having more than 6 encounters was 2.97 times higher for the during COVID-19 sample as compared to the pre-COVID-19 sample (adjusted odds ratio: 2.97, 95% CI: 1.16, 7.92, p-value 0.025). Being a female participant as compared to a male participant also meant that the odds of having more than 6 encounters was 2.95 times higher (adjusted odds ratio: 2.95, 95% CI: 1.42, 6.32, p-value 0.004). Visiting a private hospital for the initial consultation was seen to be protective (adjusted odds ratio: 0.03, 95% CI: 0.00, 0.18, p-value 0.001).

Table 5 – Logistic regression; factors associated with patient delay, cut-off 30 days

	Unadjusted		Adjusted	
Outcome: Patient Delay greater than 30 days				
Variable	Coefficient (CI)	p-value	Coefficient (CI)	p-value

COVID-19 Status				
Pre COVID-19				
During COVID-19	2.22 (1.46, 3.41)	0.001	1.55 (0.67, 3.57)	0.297
Age at Treatment Initiation	1.01 (1.00, 1.02)	0.234	0.98 (0.95, 1.01)	0.162
Gender				
Male				
Female	1.42 (0.95, 2.14	0.090	1.51 (0.78, 2.97)	0.226
Highest Education Level Completed				
Primary School or less				
High School Completed	0.47 (0.29, 0.75)	0.002	0.65 (0.29, 1.47)	0.304
College/University Completed	0.53 (0.27, 1.04)	0.066	0.57 (0.20, 1.59)	0.285
Employment Status				
Unemployed				
Employed	0.45 (0.28, 0.72)	0.001	0.29 (0.12, 0.71)	0.008
Student at school/university	0.39 (0.15, 0.91)	0.034	0.13 (0.02, 0.71)	0.025
Other (housewife/husband, retired)	0.91 (0.50, 1.68)	0.769	2.21 (0.43, 17.07)	0.38
Insurance Status				
Doesn't have insurance				
Has insurance	0.74 (0.45, 1.22)	0.235	0.61 (0.28, 1.33)	0.215
Minutes to Nearest CHC	1.01 (0.98, 1.04)	0.552	0.96 (0.90, 1.01)	0.102
Average Monthly Household Income	1.00 (1.00, 1.00)	0.688		
Any comorbidities				
No				
Yes, 1 or more	0.84 (0.49, 1.41)	0.507	0.72 (0.25, 2.03)	0.537
Symptom that prompted visit: Cough				
Cough not present				
Cough present	1.33 (0.73, 2.49)	0.359	1.10 (0.44, 2.83)	0.836
Symptom that prompted visit: Fever				
Fever not present				
Fever present	1.07 (0.71, 1.61)	0.756	1.45 (0.75, 2.82)	0.269

Table 6 – Logistic regression; factors associated number of encounters before diagnosis, cut off 6 encounters

	Unadjusted		Adjusted	
Outcome: More than 6 encounters				
Variable	Coefficient (CI)	p-value	Coefficient (CI)	p-value
COVID-19 Status				
Pre COVID-19				
During COVID-19	2.67 (1.75, 4.10)	0.001	2.97 (1.16, 7.92)	0.025
Age at Treatment Initiation	1.01 (0.99, 1.02)	0.335	1.01 (0.98, 1.04)	0.591
Gender				
Male				
Female	1.66 (1.10, 2.52)	0.015	2.95 (1.42, 6.32)	0.004
Highest Education Level Completed				
Primary School or less				
High School Completed	0.65 (0.41, 1.04)	0.070	0.65 (0.27, 1.58)	0.347
College/University Completed	1.10 (0.57, 2.16)	0.771	1.05 (0.34, 3.22)	0.936
Employment Status				
Unemployed				
Employed	0.69 (0.43, 1.11)	0.127	0.74 (0.28, 2.00)	0.555
Student at school/university	0.72 (0.30, 1.68)	0.453	0.72 (0.11, 4.52)	0.716
Other (housewife/husband, retired)	0.69 (0.38, 1.26)	0.233	0.98 (0.16, 7.94)	0.983
Insurance Status				

Doesn't have insurance				
Has insurance	1.21 (0.73, 2.01)	0.469	0.89 (0.37, 2.15)	0.797
Minutes to Nearest CHC	0.99 (0.96, 1.02)	0.504	1.03 (0.98, 1.09)	0.301
Average Monthly Household Income	1.00 (1.00, 1.00)	0.459	1.00 (1.00, 1.00)	0.614
Any comorbidities				
No				
Yes, 1 or more	0.91 (0.54, 1.54)	0.738	0.95 (0.29, 3.13)	0.935
Symptom that prompted visit: Cough				
Cough not present				
Cough present	2.72 (1.40, 5.62)	0.004	1.26 (0.43, 3.84)	0.671
Symptom that prompted visit: Fever				
Fever not present				
Fever present	1.10 (0.73, 1.67)	0.640	0.84 (0.40, 1.77)	0.651
Provider at first encounter				
Community Health Centre				
Informal Provider	1.83 (0.87, 3.88)	0.113	1.05 (0.30, 3.54)	0.940
Private Practitioner	0.64 (0.30, 1.37)	0.242	0.36 (0.11, 1.18)	0.097
Private Hospital	0.11 (0.03, 0.35)	0.001	0.03 (0.00, 0.18)	0.001
Public Hospital*	NA	NA	NA	NA

** Not enough observations for model fitting*

5.6 Discussion

The objective of this manuscript was to describe the care pathways for individuals with TB in an urban setting in Indonesia before and after the onset of the COVID-19 pandemic. Segregating by the two time points, we graphed the distribution of delays that individuals with TB faced at each step of the care cascade (**Figure 4**). Using a Sankey chart, we then illustrated where individuals went for each step of the care cascade (**Figure 5**). Next, we examined the period from symptom onset to diagnosis and examined the encounters that our samples had with healthcare providers until they were diagnosed with having TB using a bar chart (**Figure 6**) and a pathway matrix (**Figure 7**). Using a median regression, we then examined the factors associated with patient delays (**Table 3**) and number of encounters (**Table 4**) and conducted a sensitivity analysis using logistic regression (**Tables 5 and 6**).

Our findings agree with two separate PPAs from Indonesia, that discovered that individuals primarily sought care private (formal or informal) community-level health facilities, such as drug shops or pharmacies, where diagnostic capacity is limited. Furthermore, these individuals had to transition into either the public sector or higher level private facilities for diagnosis, treatment initiation, and general TB management[81,105].

The participant demographics were different for the two samples (**Table 1**). Education levels changed, and a greater proportion of participants had no formal schooling or less than primary school level. The average monthly household income was higher for the during-COVID-

19 sample, but this was due to a few outliers rather than a full shift in participant demographic. A greater proportion of individuals were also enrolled in an insurance scheme. We hypothesized that being enrolled in an insurance scheme may provide incentive to consult more doctors for second or third opinions on their illness, but lack of insurance has also been found to be associated with higher delays[116]. However, our results do not show an association between insurance enrolment and delays or number of encounters. A greater proportion of participants were unemployed in the during-COVID-19 sample. Unemployment was on the rise nationwide, but particularly affected urban settings in Indonesia, and our sample reflected this change[144,145]. The health inequities between unemployed and employed individuals have been studied extensively, and being unemployed puts a financial strain on an individual, leading to adverse health effects[146–149]. Poverty exacerbates TB[52,86,128], and in our study, we can see the direct impact unemployment has on care-seeking outcomes. Furthermore, while the socio-economic well-being of participants in our study beyond treatment completion is unknown, a mixed-method study from an urban setting in Malawi found that TB-affected households remain vulnerable after treatment completion[150]. Ensuring that the inequity faced by individuals who are unemployed is reduced could accelerate TB prevention efforts, improve access to timely care for individuals with TB, and prevent TB-related catastrophic costs.

While Indonesians have been known to regularly self-medicate[151], the proportion of pre-diagnostic visits to informal providers increased during COVID-19 as compared to before the pandemic. Most reasons cited for using the informal sector is convenience, affordability, and social and cultural effects[152]. In the context of COVID-19, a pharmacy that is closer and more accessible might be even more appealing than publicly administered free clinics when transportation and other non-medical costs are considered. Moreover, COVID-19 disease and TB are interrelated. They are both airborne infectious diseases, and both show similar clinical symptoms. Namely, cough, fever and difficulty breathing[46,153]. The perceived stigmatization from having either disease, or denial regarding severity of the symptoms could have prevented individuals from visiting a formal healthcare provider, resulting in a greater average number of encounters. The increased number of visits to informal providers also translated in a higher proportion of missed opportunities to be diagnosed at private practitioners or private hospitals (**Figure 6**).

On the other hand, post-diagnosis delays in the during-COVID-19 sample were comparable to the pre-COVID-19 sample, where median doctor delays showed a 3 day increase in doctor delay, and treatment delay remained unchanged. Disruptions have been noted in the screening and pre-diagnostic algorithm, but not in the logistics of patient management. Our findings of a 1-day treatment delay are shorter than the pooled estimates of treatment delay found in systematic reviews from several countries[110,113]. Most of the individuals diagnosed at private practitioners transitioned to CHCs for their treatment management in the during-COVID-19 sample. Treatment is free at DOTs centres, which are mostly at CHCs, which could be the reason for more participants opting for care at CHCs rather than with the private practitioners they obtained a diagnosis at amidst COVID-19.

There are several implications of our results that can be translated into recommendations for moving forward and mitigating the consequences that arose from the COVID-19 disruptions. Advertising and raising awareness regarding the quick referral from diagnosis to treatment initiation might build faith in the formal health sector and incentivise individuals to stick with their care-seeking journey. It has been found in various settings that some individuals were not aware that TB treatment is free through the NTP, or the public health sector[154–156]. Scaling up educational interventions might be beneficial in encouraging individuals to visit CHCs that are linked to the NTP for quick and efficient diagnosis and consequent linkage to care. A second recommendation would be to meet the individuals where they are and conduct more pharmacy engagement strategies. Visits to informal providers have increased, but if a referral algorithm that connects individuals with presumptive TB from pharmacies to diagnostic facilities was strengthened, then delays and number of encounters before diagnosis could decrease, leading to identify some of the missing people with TB[157]. Finally, a recommendation would be to invest and finance more active case finding (ACF) projects. The World Health Organization defines ACF as systematic screening for active TB, normally outside of health facilities. ACF projects lead to an increase in case notifications, shrinking the pool of missing people with TB, a decrease in the patient delay, reduces the total cost and the prevalence of catastrophic costs, and mitigates inequities that would otherwise be faced by vulnerable populations[97]. In Indonesia's context, an ACF intervention conducted in 3 phases from 2014 to 2018 screened 377,304 individuals of whom 1547 tested positive, and 95% were initiated on treatment. The authors noted that by combining community-based education and outreach with training and infrastructure support to health services, large numbers of people with TB can be reached[158]. Taking the onus for care-seeking from the individual to the health system might mitigate the long delays that individuals are now facing amidst the COVID-19 pandemic and reduce the repeated visits to informal healthcare providers.

This research builds on previously collected data to create unique pre- and during-COVID-19 descriptions on care pathways of individuals with TB, exclusively recruiting participants from private sector records. Nevertheless, there are several limitations to our study. Recruiting only from private providers is a limitation, as it would have been insightful to also describe the landscape of the public sector. However, to complement previous TB pathway analyses[81,105,159], as well as collect information on the dominant health sector in Bandung, we decided to exclusively study those individuals currently being looked after by the private sector. Another limitation of our methodology is that we were unable to conduct an attrition analysis. Differences between non-respondents and participants could have contributed to biased results in either direction. Perhaps individuals who refused to participate had even more complex journeys and therefore did not want to share due to fatigue related to their illness or could have had an unremarkable journey and therefore did not see the need to contribute to the research study. Recall bias was another cause of concern in our study; due to poor recall, participants could have underestimated or overestimated their wait-times. However, we tried to mitigate it by ensuring to recruit participants who had recently been diagnosed with TB (in the past 6 months). Finally, our study takes place in an urban setting in Bandung, Indonesia, meaning that the results might not be representative of all individuals with TB in Indonesia.

Our study is the first to report on TB care pathways in Indonesia since the onset of the pandemic. While delays to TB care have been extensively researched and studied, there was uncertainty regarding the effect of the pandemic on TB care service delivery and care uptake. Our results enrich our understanding of the impact of the COVID-19 pandemic on the demands of private healthcare markets and studying care-seeking for TB also informs subjects outside of TB. Recommendations from our study can also advise stakeholders on how to restore services regarding public-private mix. Another strength is that we were able to study multiple outcomes using one comprehensive survey tool.

5.7 Conclusion

The care-seeking of individuals with TB did become more complex during the COVID-19 pandemic as compared to before the pandemic. The care-seeking delays were longer, and on average, more visits to healthcare providers before diagnosis were taking place. More missed opportunities mean worse health outcomes; the reduction of the overall mortality and morbidity among a population becomes more challenging as care seeking is delayed. Individuals with TB could potentially see poorer prognosis of their disease and could increase transmission with their close contacts[109,135,159]. Our study examines the individuals with TB that were found. People with TB that have yet to be diagnosed might have experienced even more complex pathways. Identifying the issues in the TB care pathways, assessing the effect of the COVID-19 pandemic on these care pathways, and providing recommendations on addressing the gaps in care will aid in determining how to deliver people-centered care[85].

5.8 Acknowledgements

This study was done by the TB working group at Universitas Padjadjaran, and we express our sincere gratitude to the research staff for data collection and management. We also acknowledge the contribution of the healthcare workers and TB officers that were instrumental in the organisation and administration of the primary studies. I wish to acknowledge BWL for her support and inspiration while creating the visualisations for this manuscript. I would like to thank ES and ARF for helping collect the data, clean and validate the data, and also help inform the analysis.

5.9 Funding

The primary study received support from the Bill & Melinda Gates Foundation, and the secondary analysis was supported by master’s level funding from the same grant.

6. Discussion

6.1 Literature Review

The aim of the literature review was to situate the reader on the most up-to-date knowledge on the epidemiology of TB worldwide and in Indonesia, the epidemiology of COVID-19 worldwide and in Indonesia, and management of TB with regards to screening, diagnostics, and treatment regiments. This was followed by a discussion regarding the management of TB in the context of the Indonesian health system. I provided justification regarding the care pathways methodology and the health outcomes discussed in the manuscript; delays to care in TB and the encounters with healthcare providers. To better understand the existing research methodologies and provide an overview of the current knowledge concerning delays, I searched PubMed for existing systematic reviews on TB care delays. The reviews resulted in gathering pooled estimates of delays, and the most common factors associated with an increase in delays. To ascertain the best ways to illustrate the care pathways of individuals with TB, several graphical representations of care pathways were presented. I was therefore able to recreate some graphics, as well as create an innovative approach (**Figure 7**) to illustrate care seeking pathways of individuals with TB.

6.2 Manuscript

The objective of the manuscript was to describe the care pathways for individuals with TB in an urban setting in Indonesia before and after the onset of the COVID-19 pandemic. Segregating by the two time points, we graphed the distribution of delays that individuals with TB faced at each step of the care cascade (**Figure 3**). Using a Sankey chart, we then illustrated where individuals went for each step of the care cascade (**Figure 4**). Next, we examined the period from symptom onset to diagnosis and examined the encounters that our samples had with healthcare providers until they were diagnosed with having TB using a bar chart (**Figure 5**) and a pathway matrix (**Figure 7**). Using a median regression, we then examined the factors associated with patient delays (**Table 2**) and number of encounters (**Table 3**) and conducted a sensitivity analysis using logistic regression (**Tables 4 and 5**).

The participant demographics were different for the two samples (**Table 1**). Education levels changed, and a greater proportion of participants had no formal schooling or less than primary school level. The average monthly household income was higher for the during-COVID-19 sample, but this was due to a few outliers rather than a full shift in participant demographic. A greater proportion of individuals were also enrolled in an insurance scheme. We hypothesized that being enrolled in an insurance scheme may provide incentive to consult more doctors for second or third opinions on their illness, but lack of insurance has also been found to be associated with higher delays[116]. However, our results do not show an association between insurance enrolment and delays or number of encounters. A greater proportion of participants were unemployed. Unemployment was on the rise nationwide, but particularly affected urban settings in Indonesia, and our sample reflected this change[144,145]. The health inequities between unemployed and employed individuals have been studied extensively, and being unemployed puts a financial strain on an individual, leading to adverse health effects[146–149]. Poverty exacerbates TB[52,86,128], and in our study, we can see the direct impact unemployment has on care-seeking outcomes. Furthermore, while the socio-economic well-being of participants in our study beyond treatment completion is unknown, a mixed-method study from an urban setting in Malawi found that TB-affected households remain vulnerable after treatment completion[150]. Ensuring that the inequity faced by individuals who are unemployed is reduced could accelerate TB prevention efforts, improve access to timely care for individuals with TB, and prevent TB-related catastrophic costs.

While Indonesians have been known to regularly self-medicate[151], the proportion of pre-diagnostic visits to informal providers increased during COVID-19 as compared to before the pandemic. Most reasons cited for using the informal sector is convenience, affordability, and social and cultural effects[152]. In the context of COVID-19, a pharmacy that is closer and more accessible might be even more appealing than publicly administered free clinics when transportation and other non-medical costs are considered. Moreover, COVID-19 disease and TB are interrelated. They are both airborne infectious diseases, and both show similar clinical symptoms. Namely, cough, fever and difficulty breathing[46,153]. The perceived stigmatization from having either disease, or denial regarding severity of the symptoms could have prevented individuals from visiting a formal healthcare provider, resulting in a greater average number of encounters. The increased number of visits to informal providers also translated in a higher proportion of missed opportunities to be diagnosed at private practitioners or private hospitals (**Figure 6**).

On the other hand, post-diagnosis delays in the during-COVID-19 sample were comparable to the pre-COVID-19 sample, where median doctor delays showed a 3 day increase in doctor delay, and treatment delay remained unchanged. Our findings of a 1-day treatment delay are shorter than the pooled estimates of treatment delay found in systematic reviews from several countries[110,113]. While treatment success rate for Indonesia has been falling over the past decade, from 89% in

2010 to 83% in 2019[160], our findings still suggest that once the individual with TB has been identified, they are looked after by the formal healthcare system. Disruptions have been noted in the screening and pre-diagnostic algorithm, but not in the logistics of patient management. The site of diagnosis remained similar for both the samples, but no participants were diagnosed at public sector providers in the during COVID-19 sample. However, there was a higher proportion of public sector involvement during the treatment initiation for our participants. Most of the individuals diagnosed at private practitioners transitioned to CHCs for their treatment management in the during-COVID-19 sample. Treatment is free at DOTs centres, which are mostly at CHCs, which could be the reason for more participants opting for care at CHCs rather than with the private practitioners they obtained a diagnosis at amidst COVID-19.

There are several implications of our results that can be translated into recommendations for moving forward and mitigating the consequences that arose from the COVID-19 disruptions. Advertising and raising awareness regarding the quick referral from diagnosis to treatment initiation might build faith in the formal health sector and incentivise individuals to stick with their care-seeking journey. It has been found in various settings that some individuals were not aware that TB treatment is free through the NTP, or the public health sector[154–156]. Scaling up educational interventions might be beneficial in encouraging individuals to visit CHCs that are linked to the NTP for quick and efficient diagnosis and consequent linkage to care. A second recommendation would be to meet the individuals where they are and conduct more pharmacy engagement strategies. Visits to informal providers have increased, but if a referral algorithm that connects individuals with presumptive TB from pharmacies to diagnostic facilities was strengthened, then delays and number of encounters before diagnosis could decrease, leading to identify some of the missing people with TB[157]. One example in Indonesia was the campaign set forward by mClinca which utilised SwipeRx (a pharmacy-focused, multifunctional app designed to improve the effectiveness and efficiency of pharmacy operations) to disseminate messages, posters, and teaching materials to promote routine TB screening amongst pharmacists. Using such methods, lower-level providers could be empowered to take part in the NTP's efforts to reduce patient delays, improve linkages to diagnostics, connect individuals with treatment, and find the missing people with TB. A USAID report from 2009 described that the Indonesian Pharmacists Association trained 50 pharmacists to screen and refer individuals with presumptive TB. The program was not monitored due to resource and personnel constraints and therefore tapered off.

Regardless, this provides evidence that drug sellers and pharmacies were willing to collaborate on projects from the NTP even without external financial incentive or compensation[151]. Finally, a recommendation would be to invest and finance more active case finding (ACF) projects. The World Health Organization defines ACF as systematic screening for active TB, normally outside of health facilities. This could be in the form of door-to-door visits by community volunteers screening for symptoms, collecting, and transporting sputum[161], or community mobilisation in the form of diagnostic outreach clinics and sputum collection or transport from health posts to diagnostic centres[162]. The objectives of ACF are targeted case-finding and prompt initiation of treatment to rapidly render the individual non-infectious[97]. ACF projects lead to an increase in case notifications, shrinking the pool of missing people with TB, a decrease in the patient delay, reduces the total cost and the prevalence of catastrophic costs, and mitigates inequities that would otherwise be faced by vulnerable populations[97]. In Indonesia's context, an ACF intervention conducted in 3 phases from 2014 to 2018 screened 377,304 individuals of whom 1547 tested positive, and 95% were initiated on treatment. The authors noted that by combining community-based education and outreach with training and infrastructure support to health services, large numbers of people with TB can be reached[158]. A feasibility study regarding an ACF intervention in Bandung from 2017 showed that CHWs were able to undertake screening effectively, and almost all householders were willing to participate[163]. While no individuals with TB were found during the intervention, taking the onus for care-seeking from the individual to the health system might mitigate the long delays that individuals are now facing amidst the COVID-19 pandemic and reduce the repeated visits to informal healthcare providers.

This research builds on previously collected data to create unique pre- and during-COVID-19 descriptions on care pathways of individuals with TB, exclusively recruiting participants from private sector records. Nevertheless, there are several limitations to our study. Recruiting only from private providers is a limitation, as it would have been insightful to also describe the landscape of the public sector. However, to complement previous TB pathway analyses[81,105,159], as well as collect information on the dominant health sector in Bandung, we decided to exclusively study those individuals currently being looked after by the private sector. Another limitation of our methodology is that we were unable to conduct an attrition analysis. Differences between non-respondents and participants could have contributed to biased results in either direction. Perhaps individuals who refused to participate had even more complex journeys and therefore did not want to share due to fatigue related to their illness or could have had an unremarkable journey and therefore did not see the need to contribute to the research study. Recall bias was another cause of concern in our study, but we tried to mitigate it by ensuring to recruit participants who had recently been diagnosed with TB (in the past 6 months). Our sample was not proportional to the full number of patients treated in the recruitment facilities. Finally, our study takes place in an urban setting in Bandung, Indonesia, meaning that the results might not be representative of all individuals with TB in Indonesia.

Our study is the first to report on TB care pathways in Indonesia since the onset of the pandemic. While delays to TB care have been extensively researched and studied, there was uncertainty regarding the effect of the pandemic on TB care service delivery and care uptake. Our results enrich our understanding of the impact of the COVID-19 pandemic on the functioning of private healthcare markets and studying care-seeking for TB also informs subjects outside of TB. Recommendations from our study can also advise stakeholders on how to restore services regarding public-private mix. Another strength is that we were able to study multiple outcomes using one comprehensive survey tool. The pathway map is a new methodology that can be used to study the patterns of referrals and visits to different levels and types of healthcare providers. The individual level data can provide insight on what is happening between the steps of the care cascade, a limitation that was set forth by Chin and Hanson[104]. A recommendation for further research is to try and create the pathway matrix for the encounters after diagnosis. Mapping the referral pattern from treatment initiation to treatment completion may also provide insight on TB treatment default.

6.3 Conclusion

In conclusion, the care-seeking of individuals with TB did become more complex during the COVID-19 pandemic as compared to before the pandemic. The care-seeking delays were longer, and on average, more visits to healthcare providers before diagnosis were taking place. More missed opportunities mean worse health outcomes; the reduction of the overall mortality and morbidity among a population becomes more challenging as care seeking is delayed. Individuals with TB could see poorer prognosis of their disease and could increase transmission with their close contacts[109,135,159]. Our study examines the individuals with TB that were found. People with TB that have yet to be diagnosed might have experienced even more complex pathways. Identifying the issues in the TB care pathways, assessing the effect of the COVID-19 pandemic on these care pathways, and providing recommendations on addressing the gaps in care will aid in determining how to deliver people-centered care[85].

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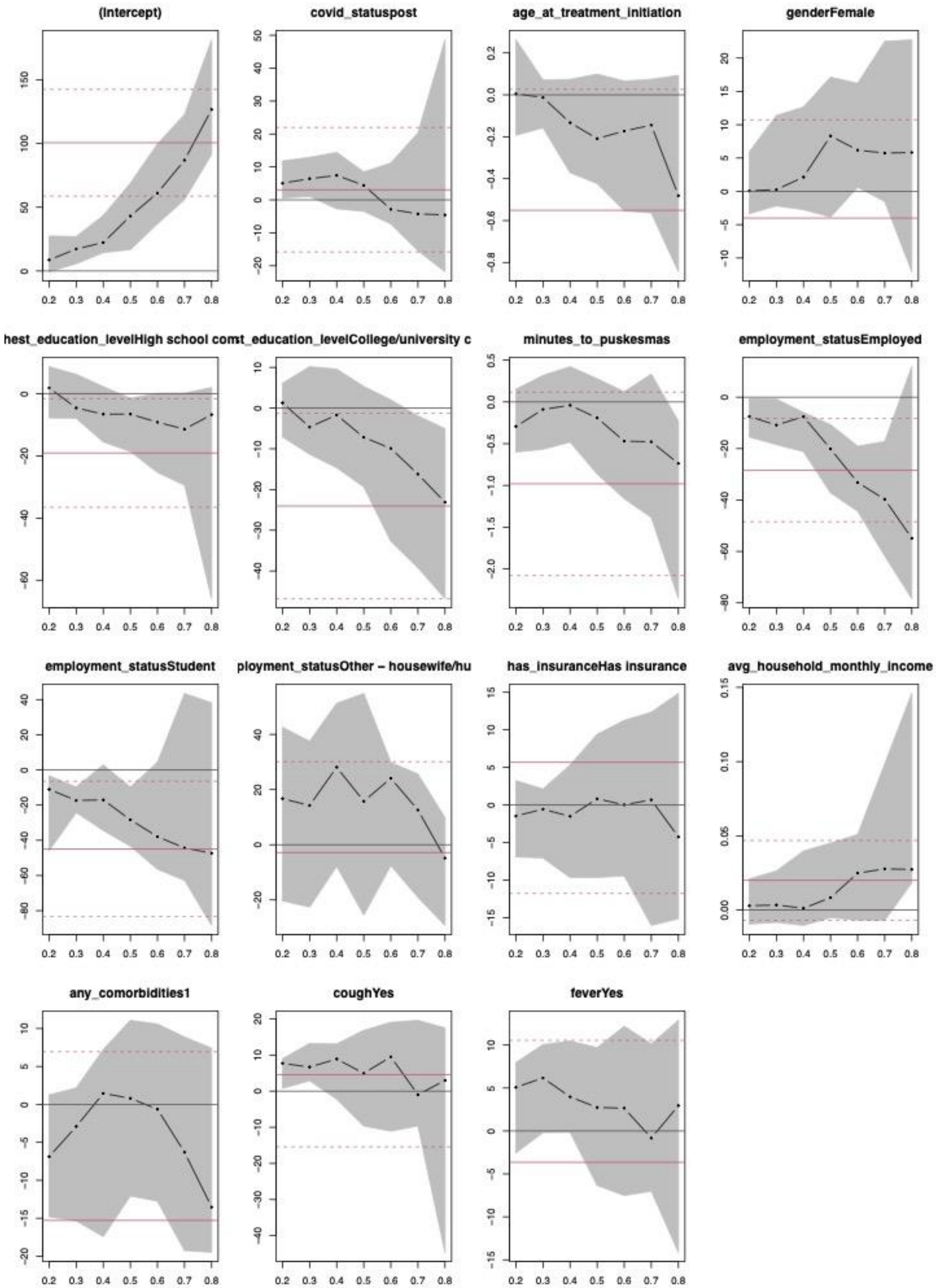
8. Appendices

Appendix I - Coefficient Plot for Patient Delay Model

These plots show the estimated coefficients as a function of quantile. The x-axis represents the different quantiles of the data, from 0.2 to 0.8, and the y-axis represents all the coefficients of the variable. Namely, the change in median patient delay for a category of a variable as compared to the reference category. The straight solid red line shows the ordinary least squares (OLS) coefficient.

Taking a closer look at the most relevant variable, COVID-19 status, we can see that for lower quantiles the data suggest that the coefficient is above 0, while lower quantiles are below 0. This means that for lower quantiles of the patient delay data, the during COVID-19 sample has a greater delay than the pre-COVID-19 sample. however, for higher quantiles (60% and above) the during-COVID-19 sample has lower patient delay than the pre-COVID-19 sample. Most of the other variables follow a similar pattern across all quantiles. The variables age at treatment initiation, high school completed, college/university completed, minutes to puskesmas, employed, students, and fever follow a decreasing trend, meaning that their coefficient gets more negative for higher quantiles (for higher patient delays). This means that when more extreme cases of patient delay are included, then the effect gets stronger, and more negative as compared to the reference category. The has insurance variable does not move around from 0 too much, suggesting that participants at all quantiles faced more/less delays whether they had insurance or not. For average monthly household income, lower quantiles of patient delay do not suggest a strong relationship, but at higher quantiles of patient delays, the delay has increased. This coefficient is extremely close to 0, therefore we cannot interpret a strong relationship. Finally, for having comorbidities as compared to none, there is a u-shaped curve present. Lower quantiles of patient delay show that comorbidities are protective, and the coefficient is negative, and so do higher quantiles of patient delay.

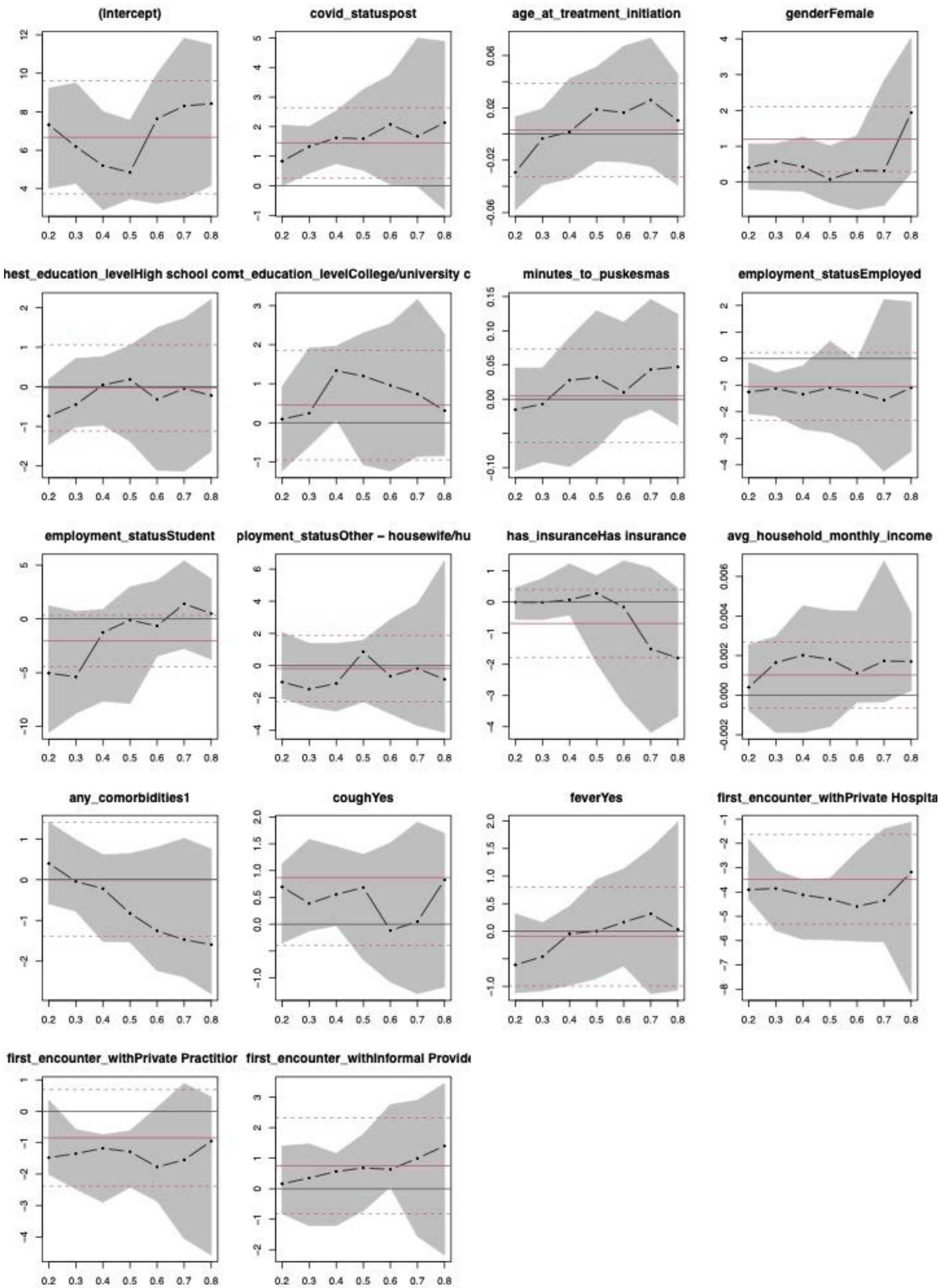
Comparisons to the OLS coefficient are quite helpful. For the variables COVID-19 status, insurance status, average monthly household income, any comorbidities and cough, the 0.5 quantile coefficient (coefficient reported in manuscript) and the OLS coefficient are quite close. Almost the variables are also captured between the dotted red lines, which are the OLS estimate's confidence intervals, apart from the tail ends of employment status and education level (high school completed and college/university completed). This means that a simple linear regression could have also been conducted for similar results.



Appendix II – Coefficient plot for Encounters model

For this model, the effect of COVID-19 is more noticeable, and as quantiles get higher, the coefficient increases from 1 to 2, meaning that for the highest numbers of encounters, the encounters for the during-COVID-19 sample are on 2 median encounters higher than for the pre-COVID-19 sample. It is interesting to see that for all quantiles, female participants also have positive coefficients, with a stark rise at the highest quantile (0.8). This means that for the highest numbers of encounters, women have higher median encounters. Most variables' 0.5 quantile coefficient lies quite close to the OLS estimate, namely, COVID-19 status, age at treatment initiation, gender, high school completed, college/university completed, minutes to puskesmas, employed, student, housewife, average monthly household income, cough, fever, first visit to private hospital, first visit to private practitioner, and first visit to informal provider. This means that a linear regression could have also been used. However, a quantile regression was chosen since it is evident that the outliers do cause a strong effect. Consequently, the normality assumption could be contested.

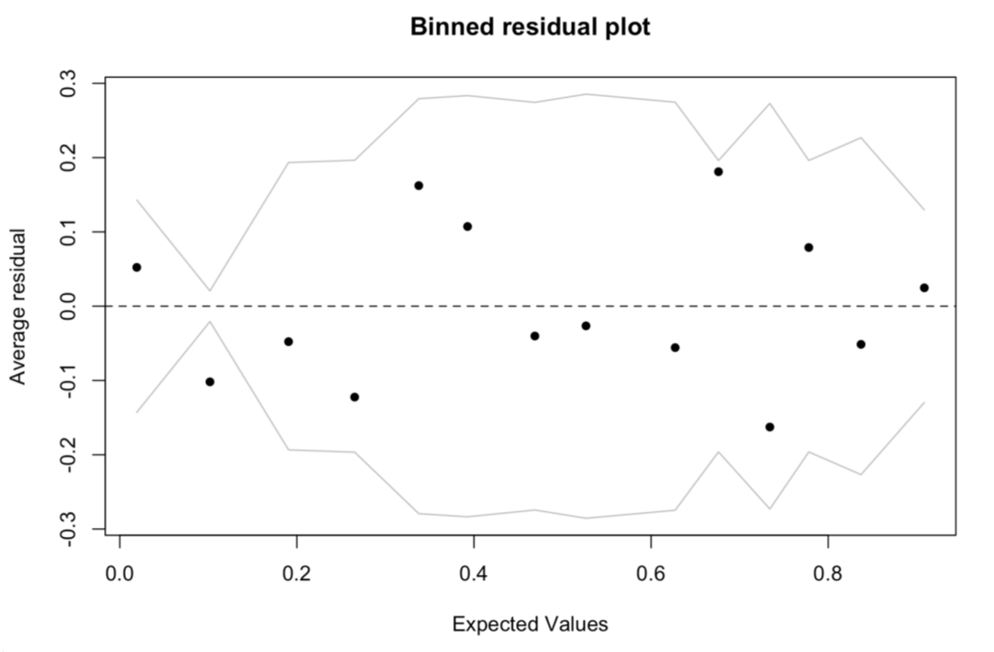
For example, taking a closer look at the student variable, the low quantiles show that being a student (as compared to an unemployed individual) can result in 5 less median encounters. A median regression therefore allows for such outliers to sway the coefficient to provide a more accurate coefficient. Another such variable is the insurance status variable. For higher quantiles of encounters, the encounters are lower for individuals with insurance as compared to none. In other words, not having insurance for those individuals who have already made higher than average visits to healthcare providers will result in even more visits before a diagnosis is given.


(Intercept)
covid_statuspost
age_at_treatment_initiation
genderFemale
hest_education_levelHigh school comt_education_levelCollege/university c
minutes_to_puskesmas
employment_statusEmployed
employment_statusStudent
ployment_statusOther – housewife/hu
has_insuranceHas insurance
avg_household_monthly_income
any_comorbidities1
coughYes
feverYes
first_encounter_withPrivate Hospita
first_encounter_withPrivate Practitior
first_encounter_withInformal Provid
0.2 0.3 0.4 0.5 0.6 0.7 0.8

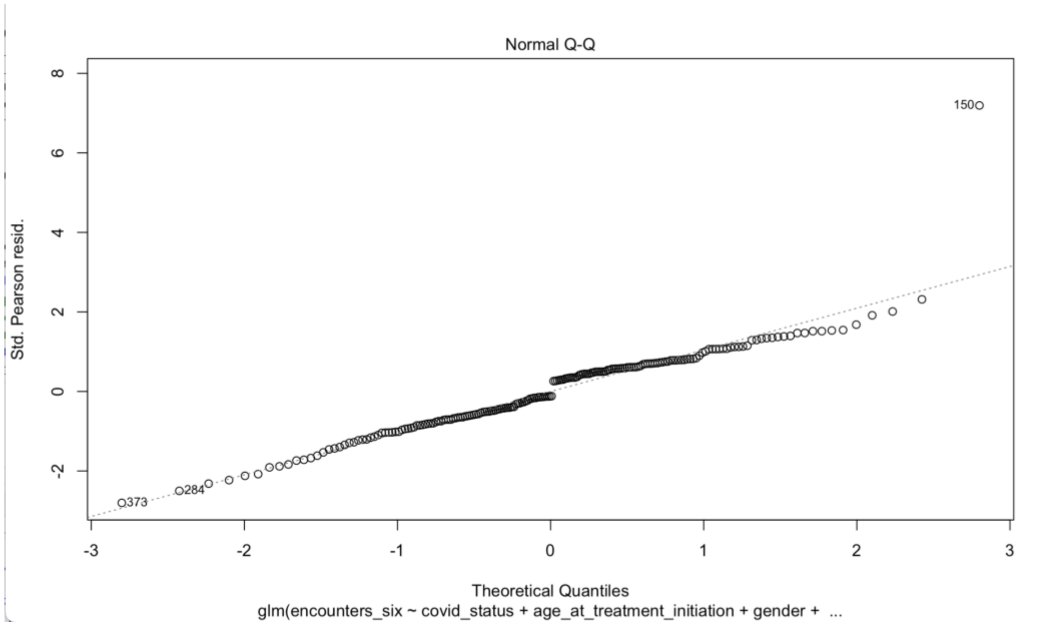
Appendix III - Colinearity

```
> car::vif(model)
                                GVIF Df GVIF^(1/(2*Df))
covid_status                1.969002  1        1.403211
age_at_treatment_initiation 1.512714  1        1.229924
gender                      1.180419  1        1.086471
highest_education_level     1.443053  2        1.096025
minutes_to_puskesmas        1.102144  1        1.049831
employment_status           2.799374  3        1.187162
has_insurance               1.193971  1        1.092690
avg_household_monthly_income 1.271677  1        1.127687
any_comorbidities           1.421437  1        1.192240
cough                       1.136359  1        1.066001
fever                       1.124335  1        1.060346
first_encounter_with        1.444919  4        1.047081
```

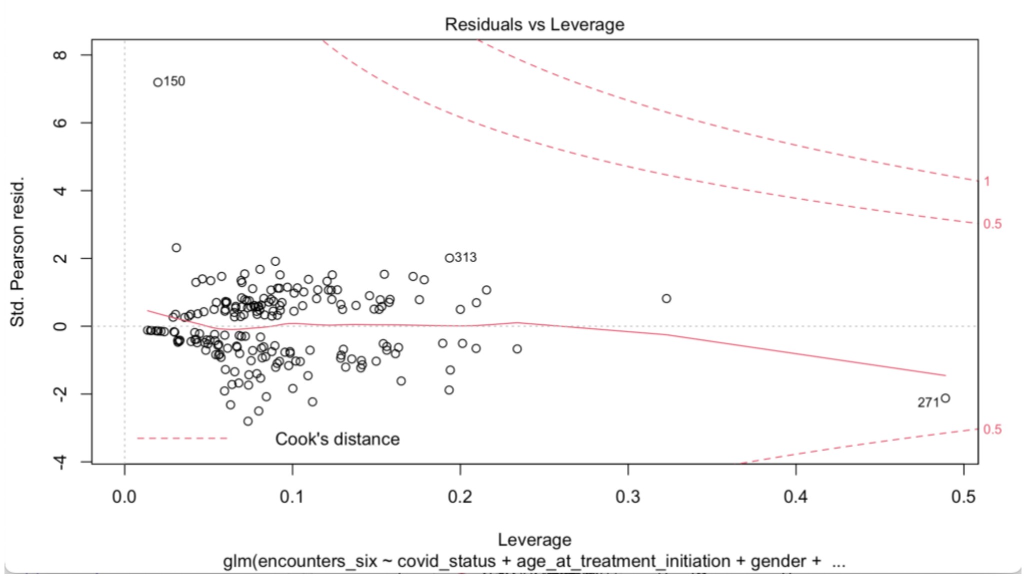
As a score below 5 for the variance inflation factor (VIF) is not a cause of concern, all our variables are independent and not collinear[66]. This is helpful for both the quantile regression models and the logistic regression models.



Most of the data is within the grey lines, which are the standard error bands for the model. The model assumption of linearity is met as the data does not look non-linear across the binned expected values.



The normality assumption is also met as the Q-Q plot shows that the data follows the dotted line closely.



Finally, we can see that only point #271 and #150 are outliers but still do not fall outside the dashed lines. This means that there are no influential points in our regression model and the fit is sufficient.