Impact of the COVID-19 pandemic on tuberculosis control in Indonesia: a nationwide longitudinal analysis of programme data

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Summary

Background The impact of the COVID-19 pandemic on tuberculosis control in high-burden countries has not been adequately assessed. We aimed to estimate the impact of the COVID-19 pandemic on the national tuberculosis programme in Indonesia, in association with indicators of human development and health-system capacity across all 514 districts in 34 provinces.

Methods We did a nationwide longitudinal analysis to compare tuberculosis case notification, treatment coverage, and mortality rates in Indonesia before (2016–19) and during (2020–21) the COVID-19 pandemic. The following outcomes were assessed: the district-level quarterly reported tuberculosis case notification rate (number of all reported tuberculosis cases per 100 000 population), treatment coverage (proportion of tuberculosis patients who started treatment), and all-cause mortality rate in patients with tuberculosis (number of reported deaths per 100 000 population). District-level data on COVID-19 incidence and deaths, health-system capacity, and human development and sociodemographics were also analysed. Multilevel linear spline regression was done to assess quarterly time trends for the three outcomes.

Findings During the COVID-19 pandemic, the tuberculosis case notification rate declined by 26% (case notification rate ratio 0·74, 95% CI 0·72–0·77) and treatment coverage declined by 11% (treatment coverage ratio 0·89, 95% CI 0·88–0·90), but there was no significant increase in all-cause mortality (all-cause mortality rate ratio 0·97, 95% CI 0·91–1·04) compared with the pre-pandemic period. In the second year of the pandemic, we observed a partial recovery of the case notification rate from Q1 to Q4 of 2021, a persistent decrease in treatment coverage, and a decrease in the all-cause mortality rate from Q2 of 2020 to Q4 of 2021. The multivariable analysis showed that the reduction in the tuberculosis case notification rate was associated with a higher COVID-19 incidence rate (adjusted odds ratio 3·1, 95% CI 1·1–8·6, for the highest compared with the lowest group) and fewer GeneXpert machines for tuberculosis diagnosis (3·1, 1·0–9·4, for the lowest compared with the highest group) per 100 000 population. The reduction in tuberculosis treatment coverage was associated with higher COVID-19 incidence (adjusted odds ratio 11·7, 95% CI 1·5–93·4, for the highest compared with the lowest group), fewer primary health centres (10·6, 4·1–28·0, for the lowest compared with the middle-high group), and a very low number of doctors (0·3, 0·1–0·9, for the low-middle compared with the lowest group) per 100 000 population. No factors were shown to be significantly associated with all-cause mortality.

Interpretation The COVID-19 pandemic adversely and unevenly affected the national tuberculosis programme across Indonesia, with the greatest impacts observed in districts with the lowest health-system capacity. These disruptions could lead to an escalation in tuberculosis transmission in the coming years, warranting the need for intensified efforts to control tuberculosis and strengthen local health systems.

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Introduction

The COVID-19 pandemic caused by SARS-CoV-2 has resulted in more than 6·9 million reported deaths as of July 28, 2023.[1] The COVID-19 pandemic severely disrupted health systems worldwide, affecting the delivery of essential services for other major health conditions such as tuberculosis, the leading cause of death from a single infectious agent other than SARS-CoV-2.[2] Mitigating tuberculosis transmission, morbidity, and mortality involves patient-centred approaches to accessible and high-quality diagnostic and treatment services.[3,4] According to WHO estimates, global tuberculosis case notifications declined from 7·1 million in 2019 to 5·8 million (an 18% decline) in 2020,[5] with pandemic-related disruptions in health services being especially exacerbated in low-income and middle-income countries in sub-Saharan Africa[6,7] and Asia,[8,9] because of health-system vulnerabilities.[2] Only three countries accounted for 67% of the global reduction in tuberculosis case reporting: India, Indonesia, and the Philippines. All three

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For the Bahasa translation of the abstract see **Online** for appendix 1

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Research in context

Evidence before this study

We searched PubMed using the search string "("impact") AND ("novel coronavirus" OR "SARS-CoV-2" OR "COVID-19") AND ("tuberculosis" OR "TB")", for research articles published between March 11, 2020 (the date on which WHO declared COVID-19 a pandemic), and June 21, 2023, assessing the impact of the COVID-19 pandemic on national tuberculosis control programmes. According to the WHO global tuberculosis report 2022, global case notifications declined from 7·1 million in 2019 to 5·8 million in 2020 (an 18% decline), with a partial recovery to 6·4 million in 2021. The three countries accounting for most of the global reduction in 2020 were India, Indonesia, and the Philippines (67% of the global total), each of which had major early COVID-19 epidemics. Global tuberculosis mortality increased for the first time in more than a decade, from an estimated 1·4 million deaths in 2019 and 1·5 million deaths in 2020 to 1·6 million deaths in 2021. WHO modelling suggests that the COVID-19 pandemic will have exacerbating effects on tuberculosis incidence and mortality in the coming years. However, most forecasts have applied national-level tuberculosis burden estimates without sub-national patient-level data. A recent nationwide analysis of Indonesia's national tuberculosis programme reported that in the years immediately preceding the COVID-19 pandemic (2017–19), notified cases of drug-susceptible tuberculosis increased, with stable treatment success and mortality rates. To the best of our knowledge, no studies to date have examined the impact of the COVID-19 pandemic on tuberculosis case notification rates, treatment coverage, and mortality rates in Indonesia, in association with health-system factors assessed at the district level.

Added value of this study

This study provides a comprehensive, nationwide analysis of the intertwined COVID-19 and tuberculosis epidemics in Indonesia, a nation with the second highest tuberculosis burden globally and one that experienced the largest COVID-19 epidemic in southeast Asia. One of the key strengths of this study is the use of complete national tuberculosis and COVID-19 surveillance data at the district level, coupled with indicators of human development and health-system capacity for all 514 administrative districts and 34 provinces where more than 275 million people reside. We provide results that are generalisable at the national level and provide an understanding of locally dynamic time trends and associations. This study highlights the immediate impact of the COVID-19 pandemic on national tuberculosis case notification and tuberculosis treatment coverage in Indonesia, as reported for several other resource-limited countries in sub-Saharan Africa and Asia with a high tuberculosis burden. There were early signs of partial recovery in the second year of the pandemic despite significant surges in SARS-CoV-2 infections. The COVID-19 pandemic had the most substantial impact on Indonesia's tuberculosis control programme in districts with the highest COVID-19 incidence rates and fewer numbers of GeneXpert machines, doctors, and primary health centres per 100 000 population; in Indonesia, primary health centres are the principal setting for the management of both tuberculosis and COVID-19 cases.

Implications of all the available evidence

Rigorous large-scale, sub-national analyses of patient databases in countries with a high tuberculosis burden are key to better understand the direct implications of the COVID-19 pandemic on national tuberculosis control programmes. The findings reported here highlight that the greatest needs for improving health-system resilience exist in the most vulnerable and fragile settings.

countries were substantially affected by the COVID-19 pandemic. Global tuberculosis mortality increased for the first time in over a decade, from an estimated 1·4 million deaths in 2019 to 1·5 million in 2020 and 1·6 million in 2021.[10] Reduced case finding and subsequent treatment coverage during the pandemic probably increased transmission rates, forecasting worsening tuberculosis incidence and mortality in the coming years.[5]

The COVID-19 pandemic caught countries unprepared and put health systems under extreme stress, highlighting the need for strengthening health-system resilience, which WHO defines as "the ability of health systems to prepare for, manage (absorb, adapt and transform) and learn from shocks".[11]

Indonesia has the second highest tuberculosis burden in the world[5] and reported the highest number of COVID-19 cases and deaths in southeast Asia.[1] A nationwide analysis of patient-level data from the national tuberculosis programme in Indonesia reported that during the years immediately preceding the COVID-19 pandemic (2017–19), notified cases of drug-susceptible tuberculosis increased from 429 219 to 523 614 (from 167 cases per 100 000 to 196 cases per 100 000), with stable treatment success rates and mortality.[12] Despite considerable progress in reaching universal health coverage,[13,14] access to and quality of health care remains highly variable across Indonesia's decentralised public health system.[14] The 2018 Public Health Development Index (PHDI), a composite indicator constructed by Indonesia's Ministry of Health to measure coverage and equity in health services and health status,[15] ranged from 35% to 75% across the country.

Previous reports applied extrapolated and modelled tuberculosis burden estimates at national levels.[10,16] However, rigorous large-scale, sub-national analyses of patient databases in countries with a high tuberculosis burden are required to better understand the impact of the COVID-19 pandemic on tuberculosis control,

services, and disease outcomes. We aimed to understand the impact of the COVID-19 pandemic on Indonesia's national tuberculosis programme, by examining tuberculosis case notification, treatment, and mortality rates before (2016–19) and during the pandemic (2020–21), in association with indicators of human development and health-system capacity at the district level, across all 514 districts and 34 provinces.

Methods

Study design and participants

We did a nationwide longitudinal analysis of aggregated data from Indonesia's national tuberculosis programme reported by primary health centres, government hospitals, and private health-care facilities through the national tuberculosis information system (Sistem Informasi Tuberkulosis [SITB]). The SITB is a mandatory case notification system for health-care facilities to inform their district health office. This study is reported as per STROBE guidelines.[17]

Data collection

In accordance with case definitions used by Indonesia's Ministry of Health, we defined the following three study outcomes (per 3-month periods or quarters): the number of newly reported tuberculosis cases, defined as children and adults with clinically diagnosed or microbiologically confirmed tuberculosis and reported as tuberculosis cases; the number of tuberculosis cases initiated on an anti-tuberculosis drug regimen; and the number of reported deaths by any cause, defined as patients with tuberculosis who died for any reason during the course of treatment (all-cause mortality).

We collected district-level data on tuberculosis, COVID-19, health-system capacity, and human development and sociodemographics. For tuberculosis, we collected district-level data on the quarterly number of notified tuberculosis cases, tuberculosis patients who started treatment, and deaths among tuberculosis treatment cases between Jan 1, 2016, and Dec 31, 2021; the number of health facilities with tuberculosis smear microscopy, and the number of health facilities with a TB GeneXpert machine in 2020 and 2021 (from the Ministry of Health's national tuberculosis programme). For COVID-19, we collected district-level data on the number of COVID-19 cases and deaths from March 1, 2020, to Dec 31, 2021 (from the National COVID-19 Task Force Database). To ascertain health-system capacity, we collected data on the number of doctors, nurses, midwives, and primary health centres in 2020 and 2021 (from the Ministry of Health); and the PHDI (from the 2018 PHDI report).[15] To assess human development and sociodemographics, we collected district-level data on annual population numbers between Jan 1, 2016, and Dec 31, 2021 (from Statistics Indonesia),[18] per-capita domestic expenditure, life expectancy at birth, and average length of formal education (from the Human Development Index 2020 report).[19]

Statistical analysis

The following outcomes were assessed: the district-level quarterly reported case notification rate (number of all reported tuberculosis cases per 100 000 population), treatment coverage (proportion of tuberculosis patients who started treatment), and all-cause mortality rate in patients with tuberculosis (number of reported deaths per 100 000 population). Multilevel linear spline regression was used on log-transformed values to assess time trends quarterly for the three outcomes from Jan 1, 2016, to Dec 31, 2021, and to identify the period of impact during the pandemic phase. To visualise the piecewise trends, violin plots of log-transformed quarterly data were overlaid with the fitted linear splines from the multilevel linear spline regression. For linear splines, default knot locations across the studied quarters were based on Harrell's recommended percentiles,[20] and splines with significant slopes in the regression were retained in the models. The final model was informed by likelihood ratio tests. To account for possible seasonal variation in tuberculosis incidence,[21] we assessed pairwise ratios of outcomes by matched quarters that occurred before and during the pandemic period as identified by the splines. We calculated a single average for each of the three study outcomes (ie, case notification rate, treatment coverage, and all-cause mortality rate), as reported during the identified period of impact (quarterly) in the pandemic phase (2020–21). We then compared

	Median (IQR)
COVID-19 burden	
Cumulative incidence rate per 100 000 population*	139 (59–280)
Cumulative mortality rate per 100 000 population*	4 (1–9)
Health-system capacity	
Number of facilities with tuberculosis GeneXpert machine per 100 000 population	0·5 (0·2–0·9)
Number of facilities with tuberculosis microscopy per 100 000 population	4 (3–6)
Number of primary health centres per 100 000 population	5 (3–9)
Number of doctors per 100 000 population	8 (5–18)
Number of nurses per 100 000 population	18 (11–31)
Number of midwives per 100 000 population	18 (12–27)
Public Health Development Index†	0·61 (0·57–0·64)
Human development and sociodemographics	
Per-capita domestic expenditure, US$	675 (574–777)
Number of years of formal education completed, years	8·3 (7·5–9·3)
Life expectancy at birth, years	69·9 (67·4–72·0)
Proportion of population aged ≥60 years	8·7% (7·3–10·4)

*The COVID-19 cumulative incidence and mortality rate per 100 000 population were calculated on the basis of the cumulative number of COVID-19 cases and deaths from March 1, 2020, to Dec 31, 2021, collected from the National COVID-19 Task Force. †Public Health Development Index.[15]

Table 1: **Key characteristics of the 514 districts included in the analysis**

For the **national tuberculosis information system** see http://www.sitb.id/sitb/app

For the **National COVID-19 Task Force Database** see https://data.covid19.go.id/user/login

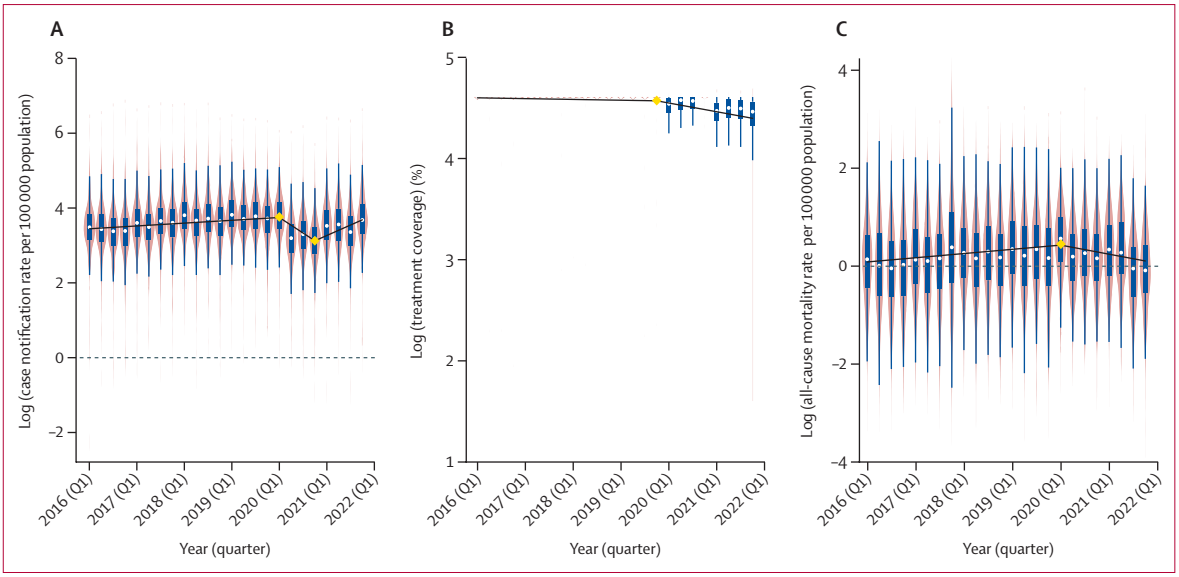

Figure 1: **Time trend analysis of district-level quarterly reported case notification rate (A), treatment coverage (B), and all-cause mortality rate (C)**
Violin plots (shown in pink) show the distribution of the district-level values. The white dots and blue bars represent medians and IQRs, respectively. The black line represents the fitted linear splines, and the yellow diamonds represent the knots identified on the basis of multilevel linear spline regression analysis.

these single average values with a similarly calculated single average for each of the outcomes as reported during the same period (quarterly) in the pre-pandemic phase (2016–19). We expressed the results as case notification rate ratios, treatment coverage ratios, and all-cause mortality rate ratios, with their 95% respective CIs, using the test-based exact method. Three binary response variables (affected *vs* not affected) were created. For each outcome, districts were categorised as affected if at least one of the following criteria were met: a significant decrease in the case notification rate (ie, ratio and 95% CI <1), a significant decrease in treatment coverage (ie, ratio and 95% CI <1), or a significant increase in the all-cause mortality rate (ie, ratio and 95% CI >1). As an additional analysis, we ran the same models without adjusting for seasonality: outcomes were compared between the identified period of impact in the pandemic phase (2020–21) and the immediate preceding period of the same duration in the pre-pandemic phase (2016–19).

The district-level COVID-19 incidence and mortality rate, numbers per 100 000 population of facilities with a GeneXpert machine, facilities with a tuberculosis microscopy smear service, primary health centres, doctors, nurses, and midwives, per-capita domestic expenditure (US$ per capita), and mean duration of formal education in the general population (years) were calculated as explanatory variables and categorised into four groups (ie, lowest, low-middle, middle-high, and highest) on the basis of restricted cubic splines construction. The range of each category as identified by the restricted cubic splines construction is presented in appendix 2 (p 1).

See Online for appendix 2

Descriptive statistics included summaries of medians (IQRs), proportions, and geographical maps showing spatial heterogeneity of the study outcomes. We used bivariable and multivariable mixed-effects logistic regression models to assess factors associated with a significant decrease in the tuberculosis case notification rate, decrease in treatment coverage, and increase in all-cause mortality rate, expressed as odds ratios (ORs) with 95% CIs. Province was treated as the random-effect variable to adjust for clustering of observations within provinces. The null model analysis, wherein no predictor was added, revealed that the province level accounted for 70% of the variance for case notification and 60% of the variance for treatment coverage, and the likelihood ratio test confirmed the use of mixed-effects logistic regression models ($p<0·0001$ for all). However, the null model accounted for 0% of the variance for all-cause mortality rate, and the likelihood ratio test suggested that logistic regression was better than mixed-effects logistic regression. All independent variables with a p value less than 0·20 in the bivariable analysis were assessed in the multivariable models. Final model selection was based on forward selection informed by the likelihood ratio test. We set statistical significance at p values less than 0·05, and all tests were two sided. All analyses were done in Stata/IC15.1.

Ethics

This study was approved by the Health Research Ethics Committee of the National Institute of Health Research and Development, Ministry of Health of Indonesia (LB.02.01/2/KE.486/2021). The requirement for patient consent was waived as this was a secondary analysis of aggregated routine programme data with no personal identifiers.

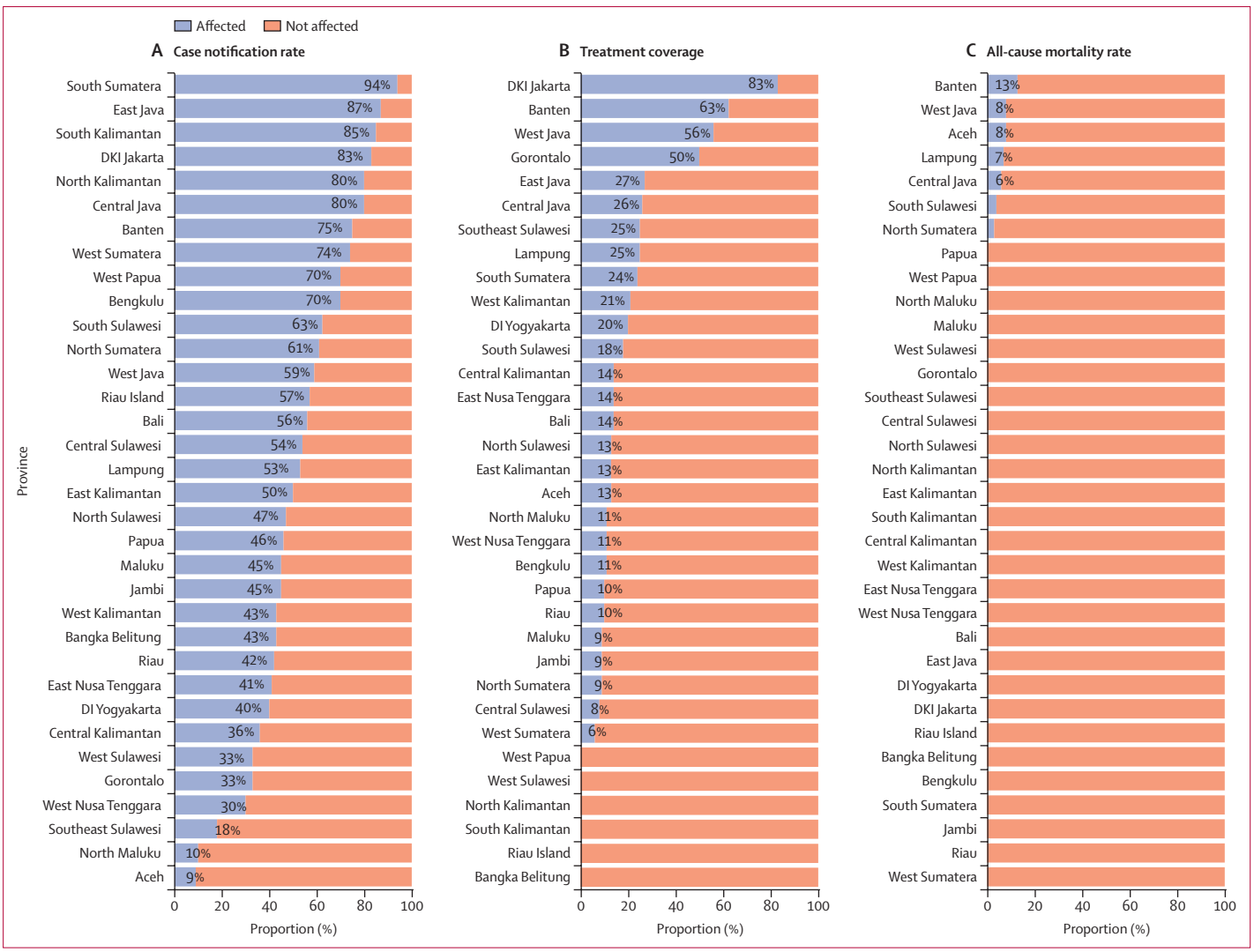

Figure 2: **Proportion of affected districts within each province during the COVID-19 pandemic years 2020–21, compared with the pre-pandemic year 2018–19**
(A) Decrease in case notification rate. (B) Decrease in treatment coverage. (C) Increase in all-cause mortality rate. Three binary response variables (affected *vs* not affected) were created. For each outcome, districts were categorised as affected if at least one of the following criteria were met: a significant decrease in the case notification rate (ie, ratio and 95% CI <1), a significant decrease in treatment coverage (ie, ratio and 95% CI <1), or a significant increase in the all-cause mortality rate (ie, ratio and 95% CI >1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The annual number of new tuberculosis cases in Indonesia increased from 360 565 in 2016 to 565 669 in 2019 (before the pandemic), then decreased to 393 323 in 2020 and 473 006 in 2021 (during the pandemic). The annual number of all-cause deaths among patients with tuberculosis increased from 9049 in 2016 to 13 059 in 2019 (pre-pandemic), and to 14 148 in 2020, and decreased to 12 016 in 2021 (during the pandemic; appendix 2 p 3). The characteristics of the 514 districts included in this study are summarised in table 1.

Based on multilevel linear spline regression (figure 1A–C), we defined Q2 of 2020 to Q4 of 2021 as the pandemic impact period for the case notification rate, treatment coverage, and all-cause mortality rate, and Q2 of 2018 to Q4 of 2019 as the pre-pandemic period.

The quarterly case notification rate gradually increased from Q1 of 2016 to Q1 of 2020, sharply decreased from Q2 (the pandemic in Indonesia officially started in early March, 2020) to Q4 of 2020, and then increased from Q1 to Q4 of 2021 (figure 1A). The overall case notification rate ratio was 0·74 (95% CI 0·72–0·77), suggesting a 26% decline in the case notification rate during the pandemic. 289 (56%) districts reported a significant decline in the tuberculosis case notification rate, with the highest

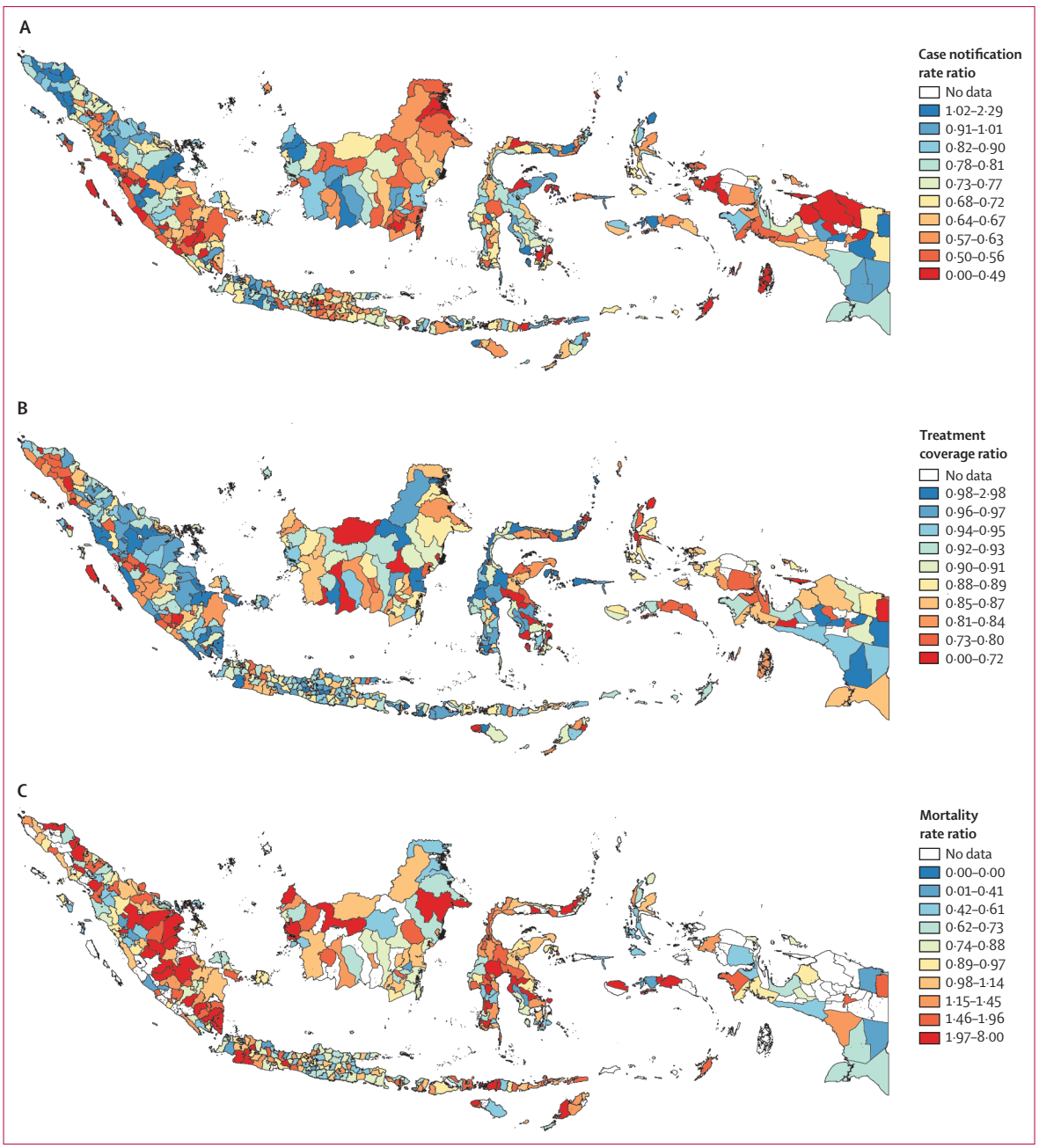

Figure 3: **Case notification rate ratio (A), treatment coverage ratio (B), and all-cause mortality rate ratio (C) by district**
(A) A small case notification rate ratio (ie, closer to 0) indicates that fewer tuberculosis cases have been notified during the pandemic compared with before the pandemic (ie, the greatest negative impact of the COVID-19 pandemic on the national tuberculosis programme), whereas a high case notification rate ratio (ie, >1) indicates that more tuberculosis cases have been notified during the pandemic compared with before the pandemic (ie, the smallest negative impact of the COVID-19 pandemic on the national tuberculosis programme). (B) A small treatment coverage ratio (ie, closer to 0) indicates that fewer tuberculosis cases have been treated during the pandemic compared with before the pandemic (ie, greatest negative impact of the COVID-19 pandemic on the national tuberculosis programme), whereas a high treatment coverage ratio (ie, >1) indicates that more tuberculosis cases have been treated during the pandemic compared with before the pandemic (ie, the smallest negative impact of the COVID-19 pandemic on the national tuberculosis programme). (C) A high all-cause mortality rate ratio (ie, >1) indicates more reported deaths during the pandemic compared with before the pandemic (ie, greatest negative impact of the COVID-19 pandemic on the national tuberculosis programme), whereas a small all-cause mortality ratio (ie, closer to 0) indicates fewer deaths during the pandemic compared with before the pandemic (ie, the smallest negative impact of the COVID-19 pandemic on the national tuberculosis programme).

proportion of affected districts in south Sumatra province (483 [94%]; figure 2A). The decline in the case notification rate was highly heterogeneous across districts (figure 3A). The top three districts with the largest decline in the case notification rate were Kepulauan Mentawai in west Sumatra (case notification

rate ratio 0·20, 95% CI 0·10–0·38), Kota Banjar Baru in south Kalimantan (0·22, 0·17–0·28), and Sorong Selatan in Papua (0·23, 0·13–0·40; appendix 2 p 4).

The quarterly treatment coverage was consistently high during Q1 of 2016 to Q4 of 2019 (median 100%, IQR 100–100), then sharply decreased from Q1 of 2020 to Q4 of 2021 (figure 1B). The overall treatment coverage ratio was 0·89 (95% CI 0·88–0·90), suggesting an 11% decline in treatment coverage during the pandemic. 98 (19·1%) districts had a significant decline in tuberculosis treatment coverage, with the highest proportion of affected districts seen in DKI Jakarta province (five [83%]; figure 2B). The decline in treatment coverage was highly heterogeneous across districts (figure 3B). The top three districts with the largest decrease in treatment coverage were Kepulauan Yapen in Papua (treatment coverage ratio 0·43, 95% CI 0·29–0·64), Padang Pariaman in west Sumatra (0·45, 0·37–0·54), and Bombana in southeast Sulawesi (0·50, 0·36–0·70; appendix 2 p 25).

The all-cause mortality rate per quarter steadily increased from Q1 of 2016 to Q4 of 2019, with a notable spike in Q1 of 2020, then decreased from Q2 of 2020 to Q4 of 2021 (figure 1C). The overall all-cause mortality rate ratio was 0·97 (95% CI 0·91–1·04), suggesting no significant changes in the all-cause mortality rate before and during the pandemic. Only 11 (2·1%) districts had a significant increase in all-cause mortality rate, with the highest proportion of affected districts seen in Banten (one [13%]; figure 2C). The heterogeneity of the all-cause mortality rate ratio is shown in figure 3C. The top three districts with the largest increase in all-cause mortality rate were Langkat in north Sumatra (all-cause mortality rate ratio 7·98, 95% CI 1·39–45·80), Lampung Selatan in Lampung (6·74, 1·10–41·11), and Gowa in south Sulawesi (4·90, 1·60–14·99; appendix 2 p 46).

The multivariable analysis showed that the significant decline in the tuberculosis case notification rate was associated with a higher COVID-19 incidence rate (adjusted OR 3·1, 95% CI 1·1–8·6, for highest *vs* lowest group), a lower number of facilities with a GeneXpert machine per 100 000 population (2·6, 1·1–6·0, for low-middle and 3·1, 1·0–9·4, for the lowest compared with highest group; table 2).

The significant decrease in tuberculosis treatment coverage was associated with a higher COVID-19 incidence rate (adjusted OR 11·7, 95% CI 1·5–93·4, for the highest *vs* lowest group), a lower number of primary health centres per 100 000 population (10·6, 4·1–28·0, for the lowest *vs* highest), and a very low number of doctors per 100 000 population (0·3, 0·1–0·9, for the low-middle *vs* lowest group; table 3).

We did not identify any factors that were independently associated with the all-cause mortality rate during the pandemic. The PHDI, human development, and

	Adjusted odds ratio (95% CI)	p value
COVID-19 incidence rate per 100 000 population		
Lowest (0·0–27·4)	1 (ref)	..
Low to middle (27·5–139·0)	1·9 (0·9–3·9)	0·11
Middle to high (139·1–552·0)	1·9 (0·9–4·3)	0·10
Highest (552·1–2327·0)	3·1 (1·1–8·6)	0·029
Tuberculosis GeneXpert service per 100 000 population		
Lowest (0·0–0·2)	3·1 (1·0–9·4)	0·043
Low to middle (0·3–0·5)	2·6 (1·1–6·0)	0·028
Middle to high (0·6–1·4)	1·4 (0·6–3·1)	0·38
Highest (1·5–22·2)	1 (ref)	..
Nurses per 100 000 population		
Lowest (0·5–6·7)	1 (ref)	..
Low to middle (6·8–17·5)	1·0 (0·5–2·1)	0·95
Middle to high (17·6–43·5)	1·1 (0·5–2·4)	0·90
Highest (43·6–231·1)	0·5 (0·2–1·5)	0·24

COVID-19 mortality rate, proportion of population aged 60 years and older, Public Health Development Index,[35] and number of doctors, midwives, and primary health centres per 100 000 population were assessed in the multivariable analysis but not included in the final model. Province was included as the random-effect variable.

Table 2: **Multivariable analysis of factors associated with decrease in tuberculosis case notification rate during the COVID-19 pandemic in Indonesia**

	Adjusted odds ratio (95% CI)	p value
COVID-19 incidence rate per 100 000 population		
Lowest (0·0–27·4)	1 (ref)	..
Low to middle (27·5–139·0)	3·0 (0·6–14·6)	0·26
Middle to high (139·1–552·0)	5·2 (0·9–30·7)	0·078
Highest (552·1–2327·0)	11·7 (1·5–93·4)	0·020
COVID-19 mortality rate		
Lowest (0–1)	1 (ref)	..
Low to middle (2–4)	0·4 (0·1–1·5)	0·18
Middle to high (5–17)	0·7 (0·2–2·7)	0·57
Highest (18–61)	1·3 (0·2–7·6)	0·74
Primary health centres per 100 000 population		
Lowest (1–2)	10·6 (4·1–28·0)	<0·0001
Low to middle (3–5)	1·6 (0·8–3·3)	0·20
Middle to high (6–13)	1 (ref)	..
Highest (14–46)	NA*	
Doctors per 100 000 population		
Lowest (0·2–3·5)	1 (ref)	..
Low to middle (3·6–7·7)	0·3 (0·1–0·9)	0·036
Middle to high (7·8–18·4)	0·7 (0·3–1·9)	0·50
Highest (18·5–152·3)	1·4 (0·4–4·9)	0·64

Public Health Development Index,[35] number of midwives and number of nurses per 100 000 population, and number of facilities with tuberculosis microscopy per 100 000 population were assessed in the multivariable analysis but not included in the final model. Province was included as the random-effect variable. NA=not available. *Observations were omitted because of zero negative outcomes (ie, no districts experienced a significant decrease in treatment coverage during the COVID-19 pandemic).

Table 3: **Multivariable analysis of factors associated with decrease in tuberculosis treatment coverage during the COVID-19 pandemic in Indonesia**

sociodemographic variables were not associated with declines in case notification rate and treatment coverage.

The case notification rate ratio and treatment coverage did not vary between seasons, but there was a small seasonal effect on the all-cause mortality rate ratio (0·97 [95% CI 0·91–1·04] in the main analysis *vs* 1·08 [1·01–1·16] in the additional analysis; appendix 2 pp 67–68).

Discussion

Our analysis identified a gradual increase in nationwide tuberculosis case notifications before the start of the pandemic from 2016 to early 2020, corroborating a recently published analysis covering 2017 to 2019.[12] Our study revealed that after the onset of the pandemic in early March, 2020, the tuberculosis quarterly case notification rate decreased by 26% and treatment coverage decreased by 11% in Indonesia, signifying one of the most noticeable declines within high-burden tuberculosis countries reported by WHO.[5] The observed dynamics over time in case notification rates and treatment coverage within and between districts in Indonesia, as reported in this study, probably represent a complex, heterogeneous interplay of multiple factors: reduced diagnosis and treatment of tuberculosis cases due to interrupted or scaled-down tuberculosis services, and changes in patient health-seeking behaviours because of fear among the public, among other reasons;[22] a possible reduction in tuberculosis transmission due to physical distancing and government-mandated mobility restrictions;[23] and a possible reduction in reporting of new tuberculosis cases and treatment given the stress on the public health system during successive COVID-19 epidemic waves.

The reported data showed a steep initial rise in all-cause mortality in Q1 of 2020, which is likely to be explained by excess mortality due to COVID-19, starting as early as January 2020, based on burial data.[24] The district-level data available through the national tuberculosis programme did not permit ascertainment of the cause of death, and it is therefore likely that, besides tuberculosis-associated mortality, a fraction of the mortality was attributable to COVID-19 as well as to other health conditions such as cardiovascular events and cancer, which are likely to have been exacerbated by interrupted or scaled-down general health services. The absence of association between all-cause mortality and any of the explanatory variables might be due to the very low proportion of districts with a significant increase in all-cause mortality (11 [2·1%]), thus lacking the statistical power to detect any existing associations. In contrast with existing evidence of higher tuberculosis transmission and notification during the winter months in temperate climates,[21] we did not discern any marked seasonal differences in the tuberculosis case notification rate in Indonesia's tropical climate.

These findings suggest early signs of partial recovery in the health system from Q1 to Q4 of 2021 with regard to the case notification rate and from Q2 of 2020 to Q4 of 2021 with regard to the all-cause mortality rate. However, it should be noted that the estimated 170 000 people in Indonesia who were undiagnosed in the preceding year, as well as the extended reductions in treatment coverage, could lead to a considerable escalation in tuberculosis transmission in the coming years.[5]

Even without pandemic-related disruptions to tuberculosis case finding and diagnostic and treatment services, the clinical pathways to reach a tuberculosis diagnosis and access effective treatment are already complex for patients, often involving long delays and visits to multiple health-care providers.[4] The social and economic shocks associated with the COVID-19 pandemic have deeply exacerbated the fraught path to recovery, especially when combined with challenges in the delivery of vital health services. Indeed, we observed substantial heterogeneity in the impact of the COVID-19 pandemic between districts with regard to all three study outcomes, and several local health-system factors were identified that could offer at least partial explanations for the substantial differences observed between districts.

Our findings indicate that districts with a higher COVID-19 incidence and an under-resourced health system experienced the most detrimental impacts on tuberculosis notification and treatment coverage. Specifically, this was true for districts with fewer health facilities with tuberculosis GeneXpert diagnostic services, fewer primary health centres per 100 000 population, and a very low number of doctors per 100 000 population. In Indonesia's decentralised health system, resource allocations are mostly the responsibility of district-level governments, and as such are highly dependent on local government resources, policy strategies, and priorities. The pandemic forced local governments to reallocate already scarce health resources to the COVID-19 response,[22] which, nationally, included an approximately 30% decrease in total tuberculosis financing in 2020 compared with 2019. Moreover, a recent review of Indonesia's health-care system suggested that the existing medical workforce was largely insufficient and not evenly distributed to deal with the COVID-19 pandemic.[25]

In the years before the pandemic, the Indonesian Government invested in strengthening its molecular tuberculosis diagnostic capacity, which increased nationwide utilisation from 32 583 tests on 139 GeneXpert machines in 2016 to 930 206 tests on 909 machines in 2019.[26] The first pandemic year (2020) recorded a 24% decrease in the recorded number of tuberculosis tests to 703 878 on 1053 machines, rising again to 1 038 902 on 1684 machines in 2021.[26] These changes in diagnostic capacity also involved the temporary re-allocation of existing GeneXpert machines and the instalment of

additional machines to support SARS-CoV-2 molecular diagnosis, which have now become available to support the national tuberculosis programme. Thus, our data call for further structural investments in health-system preparedness, and more targeted and efficient use of available resources through better integration and coordination, especially in districts that are most vulnerable to health emergencies such as COVID-19.[27,28]

Several additional factors, which our analysis was not able to fully capture, might have further exacerbated the impact of the COVID-19 pandemic on tuberculosis case finding and diagnostic and treatment services. First, high rates of SARS-CoV-2 infection and deaths from COVID-19 among front-line health-care workers resulted in substantial absenteeism and task-shifting, especially during the early phases of the pandemic.[29] Notably, a recent report estimated that Indonesian health-care workers had a five times higher risk of dying from COVID-19 than the general population.[29] Second, the pandemic affected health-seeking behaviours of patients as well as access to essential health services, because of the fear of contracting COVID-19, extra costs of personal protective equipment, and government-mandated local lockdowns.[30] Third, emerging data suggest that biological interactions between *Mycobacterium tuberculosis* and SARS-CoV-2 can result in shared dysregulation of immune responses and a dual risk of severe COVID-19 and poor tuberculosis outcomes.[31] The interplay between these co-prevalent infections warrants further research.

This study had several limitations. First, this analysis was based on direct reports from health facilities into the SITB, which were verified at the district and provincial health offices. Since we could not conduct any further validation of the source data, potential gaps in quality control as well as underreporting could exist, which were possibly exacerbated by the COVID-19 pandemic. Notably, an inventory study in 2016 estimated that only half of incident tuberculosis cases were detected and reported to the national tuberculosis programme (31% for government facilities and 75% for private facilities).[32] Second, there was incomplete data ascertainment for several factors that can affect tuberculosis case notification and all-cause mortality, at the patient level, health-care provider level, and health-system level, which means that unmeasured confounding could have influenced the effect estimates. There were also various sources of heterogeneity in the study population, both within and between the districts, that could not be completely accounted for in the analysis, such as pandemic-related mobility restrictions, mask wearing, differences in access to and quality of health-care services, health-seeking behaviour, and background health risks, which could have influenced the observed associations. For example, we could not control for district-level HIV and diabetes prevalence, which are known risk factors for tuberculosis infection, disease progression, and poor treatment outcomes.[16] Third, the reported mortality data analysed in this study did not include patients with tuberculosis who died before receiving treatment or who were lost to follow-up during treatment, thus likely underestimating the true mortality. Fourth, because of the observational design of the study, the associations found do not necessarily demonstrate causality. Last, given that the SITB registers drug-susceptible and rifampicin-resistant tuberculosis cases only, we could not assess the impact of the COVID-19 pandemic on multidrug-resistant and extensively drug-resistant tuberculosis. Although Indonesia is one of the 30 high-burden countries for drug-resistant tuberculosis, incidence estimates at the district level are scarce and might be underreported due to inadequate diagnostic capacities in many remote, under-resourced districts.

In conclusion, Indonesia and other countries with a high tuberculosis burden will need to intensify efforts to identify missed cases of undiagnosed and untreated tuberculosis in order to prevent further deaths due to tuberculosis in excess of expected numbers. Our analysis affirms the notion that settings in which access to quality health-care services was already inadequate before the pandemic experienced the most acute and severe hardships during the pandemic. Resilient health systems will be crucial to be better prepared for the inevitable next pandemic.

Contributors

RLH and IRFE were the principal investigators. RLH, IRFE, and HS conceptualised the study. HS designed the analysis, and did the analysis with assistance from EP, with critical input from IRFE, AF, GT, RvC, AHS, JKB, and RLH. HS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HS, EP, DD, TTP, EL, SS, and SMD contributed to data collection and verification. IRFE and RLH contributed to funding acquisition. HS, IRFE, and RLH drafted the Article, with critical input from AF, GT, RvC, AHS, and JKB. All authors critically revised the manuscript for important intellectual content and all authors gave final approval for the version to be published. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. No authors were precluded from accessing data in the study, and all authors accepted responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

After publication, the datasets used for this study will be made available to others on reasonable request via email to the corresponding author and the Sub-Directorate of Tuberculosis, Ministry of Health of Indonesia, including a detailed research proposal, study objectives, and statistical analysis plan.

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