COVID-19 and Tuberculosis: Findings from an ecological study

Journal:	*ERJ Open Research*
Manuscript ID	ERJOR-00247-2020
Manuscript Type:	Original Article
Date Submitted by the Author:	06-May-2020

Complete List of Authors:	Moran, Alexander; University Research Co LLC, Center for Innovation and Technology Jassim AlMossawi, Hala; University Research Co LLC, Center for Innovation and Technology Kak, Neeraj; University Research Co LLC, Center for Innovation and Technology

Key Words:	Tuberculosis (TB), COVID-19, ecological study

Target Journal: ERJ Open Research

Article Type: Original Article

COVID-19 and Tuberculosis: Findings from an ecological analysis

Alexander Moran, MSPH[1*], Hala Jassim AlMossawi, MSHCA[1] and Neeraj Kak[1]

1: University Research Co., LLC (URC), Center for Innovation and Technology, Chevy Chase, MD, USA

*Correspondence to:

Alexander Moran
5404 Wisconsin Ave. Suite 800,
Chevy Chase, MD, 20815, USA
+1 (301) 941-9625
amoran@urc-chs.com

Figures: 3

Tables: 1

References: 22

Word Count: 2101

Abstract:

Coronavirus disease 2019 (COVID-19) represents an unprecedented challenge in modern public health practice. As this pandemic grows in size and scope, understanding the associations between COVID-19 and other respiratory illnesses like tuberculosis (TB), the largest infectious disease killer globally, becomes essential. In this ecological analysis, we demonstrate an association between COVID-19 case positivity and increasing gross domestic product (GDP) per capita, in which case positivity increases by 45.10 per 100,000 people tested for a 10% increase in GDP per capita ($p=0.001$). We further examine this relationship among countries designated as high-TB burden countries by the World Health Organization (WHO) and observe a stronger association between COVID-19 case positivity and increasing GDP per capita (79.41 per 100,000 people tested). Even after controlling for TB incidence, this association holds at the ecological level (77.66 per 100,000 people tested) among high-TB burden countries. That these findings are of a higher magnitude among high-TB burden countries suggests that these countries may require additional support in responding to the COVID-19 pandemic. In a pandemic setting, we must prioritize existing health system functions to avoid resurgence or exacerbation of infectious disease threats like TB.

Introduction

Coronavirus disease 2019 (COVID-19) represents an unprecedented challenge in modern public health practice. Having spread to over 180 countries and having affected over 2.7 million individuals, the COVID-19 pandemic requires a coordinated, effective response without sacrifice to quality or availability of other essential medical services.[1] This rapidly-moving pandemic has laid bare the importance of effective surveillance, quarantine, testing and diagnosis, contact tracing and hospital infection prevention and control measures. Certain countries, including Singapore, have effectively contained community spread of the virus through early and broad quarantine, testing and contact tracing measures.[2–4] In countries like Italy and the United States – where responses were slower, narrower in focus and less consistently implemented – COVID-19 transmission has spread widely in the community, and responses have shifted from containment to mitigation.[4–6] In these countries where containment measures have failed, health systems must plan to ration life-saving medical equipment like mechanical ventilators.[7–9]

Tuberculosis (TB), from which more people die than any other single infectious agent, represents a similar public health challenge in that it is transmitted through respiratory droplet spread, causes great economic harm (either directly through treatment costs or indirectly through lost wages and family support) and requires frequent testing and contact tracing to reduce spread in the community.[10,11] TB disproportionately affects people with lower income, which is explained through structural factors like housing insecurity and more frequent exposure to congregate settings, economic factors which prevent access to high-quality preventive or curative health services except in dire emergencies, and social factors like delaying reporting or care to prevent loss of wages or social capital.[12–16]

As noted by the WHO, the Stop TB partnership and other organizations, we must ensure the provision of essential TB services while responding to the COVID-19 pandemic. As the Stop TB partnership noted in April through a rapid assessment of the impact of the COVID-19 pandemic on the TB response in high-burden countries, there are significant disruptions to TB services in high-burden countries.[17] Based on these results, we must understand the relationships between COVID-19 incidence, TB burden and gross domestic product (GDP) per capita and generate hypotheses for creating interventions which maintain TB services in the context of increasing COVID-19 caseloads.

In this ecological analysis, we seek to understand possible associations between COVID-19 cases and GDP per capita and TB and GDP per capita. We also aim to elucidate whether these relationships differ when restricted to high-burden TB countries alone. Finally, we seek to compare these individual disease analyses to understand any similarities in the trends observed between the individual diseases and GDP per capita.

Methods

COVID-19 case data were retrieved from the Johns Hopkins Center for Systems Science and Engineering (JHU CSSE) Coronavirus Resource Center and include confirmed COVID-19 cases through 4-April 2020.[18] We retrieved all confirmed COVID-19 cases at the national level for all available countries. We also retrieved COVID-19 testing data from Worldometer, in which we collected number of tests reported at the national level. Testing data were available for 148 countries.[19] Tuberculosis incidence data were retrieved from available WHO data as of 4-April 2020, in which we included data from 2018 for all countries with available data.[20] A total of 142 countries had data for COVID-19 cases, COVID-19 testing and TB incidence. GDP per capita and population data were retrieved from World Bank data sources, for which we retained 2018 values from each available country.[21] A total of 133 countries had available data for COVID-19 cases, TB incidence and GDP per capita.

We collated and examined data using Stata/SE 15.1 (StataCorp, College Station, TX). We computed crude incidence of TB per 100,000 people using WHO estimated incident TB cases in 2018 and World Bank population estimates for 2018. We then considered creating a COVID-19 incidence measure based on confirmed COVID-19 cases and World Bank population statistics, but found this to be insufficient in describing incidence due to wide variation in testing coverage globally. We decided to use COVID-19 positivity, in which we calculated the number of confirmed COVID-19 cases per 100,000 people tested for SARS-CoV-2 (the viral agent that causes COVID-19) using JHU CSSE confirmed case data to date and Worldometer testing data as a proxy for COVID-19 incidence. Given that testing rates vary in many countries, that many COVID-19 cases are mild, and that many cases are treated based on clinical suspicion versus a confirmed test, we decided to use case positivity as the most robust comparative measure given the available data.

We began by examining the distribution of incident TB cases per 100,000 people, COVID-19 case positivity per 100,000 people tested and GDP per capita. We reviewed box plots for each distribution and noted potential outliers. We noted that high values of GDP per capita (above $50,000 USD) were potential outliers and that these values skewed the distribution, so we transformed GDP per capita to the natural logarithm of GDP to normalize the distribution. We chose this transformation in favor of a square-root transformation. We did not transform COVID-19 case positivity per 100,000 people tested nor TB incidence per 100,000 people.

We plotted both COVID-19 case positivity per 100,000 people tested and TB incidence per 100,000 people against the natural logarithm of GDP using Tableau Desktop Professional Edition 10.5 (Tableau Software, Inc., Seattle, WA). We also plotted these values among the 30 highest TB burden countries (of which 20 had fully available data) according to the latest WHO Global TB Report (2019) to understand any differences in these plots compared to the general country plots. We performed a simple linear regression (SLR) of COVID-19 case positivity per 100,000 people tested on the natural logarithm of GDP per capita and an SLR of TB incidence per 100,000 people on the natural logarithm of GDP to understand possible crude associations at the ecological level. Finally, we performed a multiple linear regression of COVID-19 case positivity per 100,000 people tested and TB incidence per 100,000 people on the natural logarithm of GDP to understand possible remaining associations between COVID-19 and GDP per capita after controlling for TB incidence per 100,000 people. All statistical analyses were performed using Stata/SE 15.1 (College Station, TX).

Results

TB incidence varied from 0 to 549.2 per 100,000 with an interquartile range (IQR) of 8.7 to 143.6 per 100,000. COVID-19 case positivity per 100,000 people tested varied from 57.7 to 30,614.7 per 100,000 with an IQR of 1,184.2 to 5,281.2 per 100,000. GDP per capita ranged from $389.40 USD to $87,208.54 with an IQR of $2,028.90 to $17,277.97. The natural logarithm of GDP per capita ranged from 5.751 to 11.667 with an IQR of 7.667 to 9.867. Figure 1 describes the change in distribution observed after transforming GDP per capita to the natural logarithm of GDP per capita.

The distributions of incident TB cases per 100,000 people and natural logarithm of GDP per capita and of COVID-19 case positivity per 100,000 people tested and natural logarithm of GDP per capita are presented in Figures 2a and 2b, respectively. Figure 2a describes a slightly positive association between proxy COVID-19 incidence per 100,000 people tested and the natural logarithm of GDP, whereas figure 2b describes a negative association between TB incidence per 100,000 people and the natural logarithm of GDP. Figures

3a and 3b present these same findings, respectively, after having restricted to the 30 highest TB burden countries (among which 20 had complete data).

The results of our simple linear regression analyses are presented in Table 1. Considering our use of a log-transformed predictor on a linear regression, we present some methodological details to guide interpretation along with our results.[22]

In the first SLR (GDP on natural logarithm of COVID-19 case positivity), we use the following model:

$$COVID19\ Case\ Positivity = \beta_0 + \beta_1 \times \text{Ln}\ (GDP)$$

Using a 10 percent change in GDP, we arrive at the following:

$$COVID19(GDP_2) - COVID19(GDP_1) = \beta_1 \times \left[\ln\left(\frac{GDP_2}{GDP_1}\right)\right] = \beta_1 \times \ln\ (1.1)$$

To interpret these results, we understand that a unit increase in GDP will be the same, regardless of baseline. In linear terms, we take the log of the percentage increase (10%, for the purposes of this analysis) and multiply by the predictor (GDP) coefficient. We then interpret the result as the change in COVID-19 case positivity per 100,000 people tested after a 10% increase in GDP per capita. We present original coefficients, change in COVID-19 case positivity per 100,000 tested per 10% increase in GDP, p-values and 95% confidence intervals for the original coefficient. The same interpretation can be applied to the SLR results for TB incidence, where we used the following model:

$$TB\ Incidence = \beta_0 + \beta_1 \times \text{Ln}\ (GDP)$$

Table 1. Results of three simple linear regressions examining change in COVID-19 case positivity with change in GDP per capita in $USD. Outcome variable is COVID-19 case positivity and change in GDP is 10%.

	Log(GDP) all countries	Log(GDP), high-burden countries	TB incidence per 100,000 people
Coefficient	1,089.68	1,918.45	-51.05
Change in COVID-19 case positivity per 100,000 per 10% increase in GDP per capita	45.10	79.41	-2.11
p-value	0.001	0.065	<0.001
95% Confidence Interval	(426.64 - 1752.71)	(-130.46 - 3,967.37)	(-62.88 - -39.22)

In the multiple linear regression model, we noted similar results as in the individual SLRs in Table 1. Using the following model, we sought to understand the change in COVID-19 case positivity per 100,000 people tested with a 10% increase in GDP after controlling for TB incidence per 100,000 people:

$$COVID19\ Case\ Positivity = \beta_0 + \beta_1 \times TB\ Incidence + \beta_2 \times Ln(GDP)$$

After controlling for TB incidence per 100,000 people, we found a significant relationship between COVID-19 case positivity per 100,000 people tested and GDP. With 10% increase in GDP, we observed a 35.97 per 100,000 people tested (95% CI: 67.62 – 1,760.57; p=0.034) increase in COVID-19 case positivity per

100,000 people tested after controlling for TB incidence. Among high-TB burden countries, we observe an increase in case positivity of 77.66 per 100,000 people tested (95% CI: -294.86 – 4,047.15; p=0.086).

Discussion

These findings confirm the negative association between TB and GDP per capita, and further elucidate associations between COVID-19 and GDP per capita, even after controlling for TB incidence. We also note that among high-burden TB countries specifically, the increase in COVID-19 case positivity per 100,000 people tested is of a larger magnitude (79.41, 95%CI: -130.46 – 3,967.37, p=0.065) than the general relationship when including all countries. This finding raises important concerns for COVID-19 control in high-burden TB countries.

This study suffers from certain limitations, chief among these is the ecological design. The authors have taken care in ensuring standardized data sources and calculations while remaining focused in the findings and analysis from this study. We recognize that these results are only applicable at the population level and do not represent individual level data or findings. This analysis remains useful in that it helps identify possible associations between COVID-19 and GDP per capita among all countries affected by COVID-19 and specifically among the highest-burden TB countries.

Despite these limitations, this study remains as one of the first to examine the relationship between COVID-19 and GDP per capita in the context of TB incidence and GDP per capita, and one of the first to discuss these results in the context of high-burden TB countries. These countries are at especially high risk for COVID-19 transmission due to the extant population with lung disease and the possibly enabling environments which drive TB transmission, including congregate settings, migrant workers, smokers and other people at especially high risk for TB. We must leverage existing TB control programs in these countries to effectively respond to COVID-19 and to prevent an increase in incident TB cases during a demand surge for emergency services, when regular TB services may be disrupted or unavailable.

Areas for collaboration are numerous and include prevention, diagnosis, treatment and care, digital health technology, procurement, supply chain, risk management, human resources and capacity building efforts. We present some examples for a collaborative, TB-aware COVID-19 response below:

Prevention: While modes of transmission differ between these diseases, similar measures can be taken to prevent infection in congregate settings and in health care facilities. These include application of administrative controls, environmental controls and personal protective equipment, which are hallmarks of successful TB control programs. These existing efforts should be intensified in light of COVID-19 and leveraged to ensure a seamless response.

Testing and diagnosis: Accurate diagnostic tests remain essential for TB and for COVID-19. While testing methods differ, there are extensive TB sample transport and testing mechanisms in place in high-TB burden countries which should be leveraged for COVID-19 testing and diagnosis.

Human resources and capacity building: Physicians, nurses, pulmonologists and TB specialists, along with nurses and health care workers at the primary care level should be trained on COVID-19 diagnosis and treatment protocols including updated case definitions and care protocols. TB specialists serve as an entry point for buy-in and training as this cadre has similar training in infection prevention and control and in decentralized patient management. COVID-19 responses can benefit from the extensive capacity building network in high-TB burden countries, in which infection prevention and control, contact tracing, household and community-based care and surveillance and monitoring systems are robust and functional.

National TB control programs, especially in high-burden TB countries, are well-suited for respiratory disease control and should be consulted and funded to aid in the COVID-19 response. In an unprecedented public health emergency, we must leverage every possible opportunity to collaborate and to build on existing systems, rather than building new and untested parallel structures.

References

1. Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/. Accessed April 20, 2020.

2. Novel Coronavirus (2019-nCoV) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed March 25, 2020.

3. Liew MF, Siow WT, MacLaren G, See KC. Preparing for COVID-19: early experience from an intensive care unit in Singapore. *Crit Care*. 2020;24(1):83. doi:10.1186/s13054-020-2814-x

4. Wong JEL, Leo YS, Tan CC. COVID-19 in Singapore—Current Experience: Critical Global Issues That Require Attention and Action. *JAMA*. February 2020. doi:10.1001/jama.2020.2467

5. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. March 2020. doi:10.1001/jama.2020.4683

6. Parodi SM, Liu VX. From Containment to Mitigation of COVID-19 in the US. *JAMA*. March 2020. doi:10.1001/jama.2020.3882

7. Emanuel EJ, Persad G, Upshur R, et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med*. 2020;0(0):null. doi:10.1056/NEJMsb2005114

8. *Rational Use of Personal Protective Equipment for Coronavirus Disease 2019 (COVID-19)*. Geneva: World Health Organization; 2020.

9. Truog RD, Mitchell C, Daley GQ. The Toughest Triage — Allocating Ventilators in a Pandemic. *N Engl J Med*. 2020;0(0):null. doi:10.1056/NEJMp2005689

10. WHO | Global tuberculosis report 2019. WHO. http://www.who.int/tb/publications/global_report/en/. Accessed March 25, 2020.

11. World Health Organization. *WHO Guidelines on Tuberculosis Infection Prevention and Control: 2019 Update.*; 2019. http://www.ncbi.nlm.nih.gov/books/NBK539297/. Accessed March 14, 2020.

12. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar M, Raviglione M. Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. *PLoS Med*. 2014;11(9):e1001693. doi:10.1371/journal.pmed.1001693

13. Davis JL. Bringing patient-centered tuberculosis diagnosis into the light of day. *BMC Med*. 2017;15(1):219. doi:10.1186/s12916-017-0992-4

14. Chen S, Zhang H, Pan Y, et al. Are free anti-tuberculosis drugs enough? An empirical study from three cities in China. *Infect Dis Poverty*. 2015;4:47. doi:10.1186/s40249-015-0080-y

15. Suthar AB, Zachariah R, Harries AD. Ending tuberculosis by 2030: can we do it? doi:info:doi/10.5588/ijtld.16.0142

16. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J*. 2014;43(6):1763-1775. doi:10.1183/09031936.00193413

17. We did a rapid assessment: the TB response is heavily impacted by the COVID-19 pandemic. http://stoptb.org/news/stories/2020/ns20_014.html. Accessed April 17, 2020.

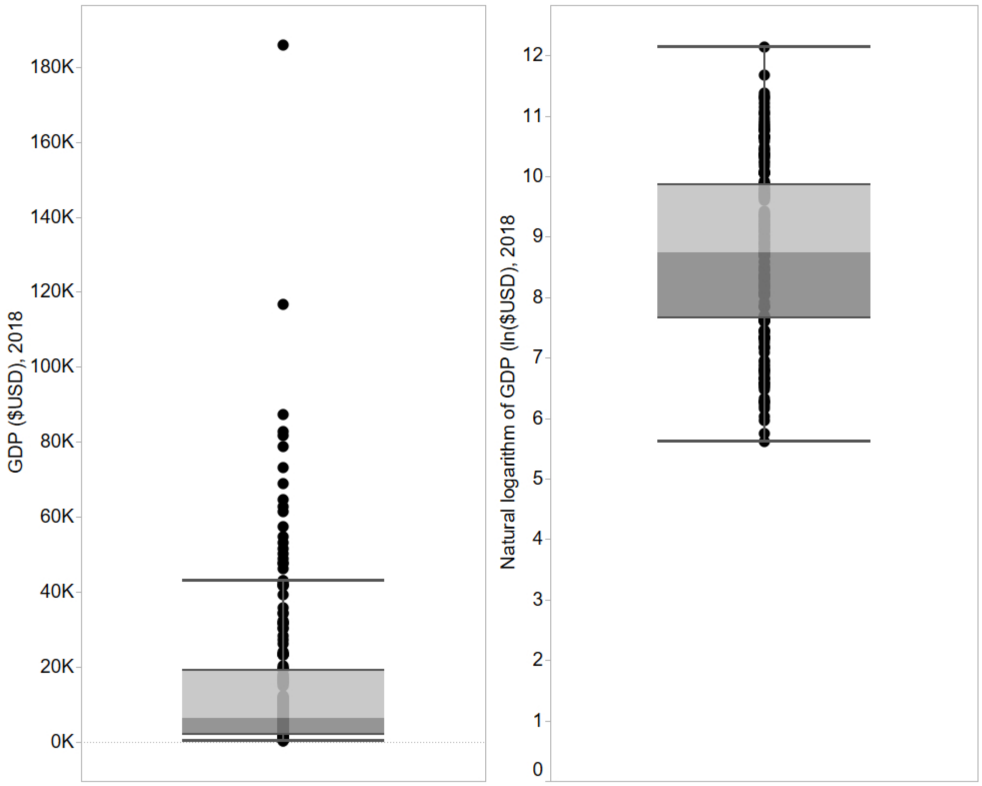
18. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Map. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/map.html. Accessed April 16, 2020.

19. Worldometer. COVID-19 Pandemic. https://www.worldometers.info/coronavirus/. Accessed April 17, 2020.

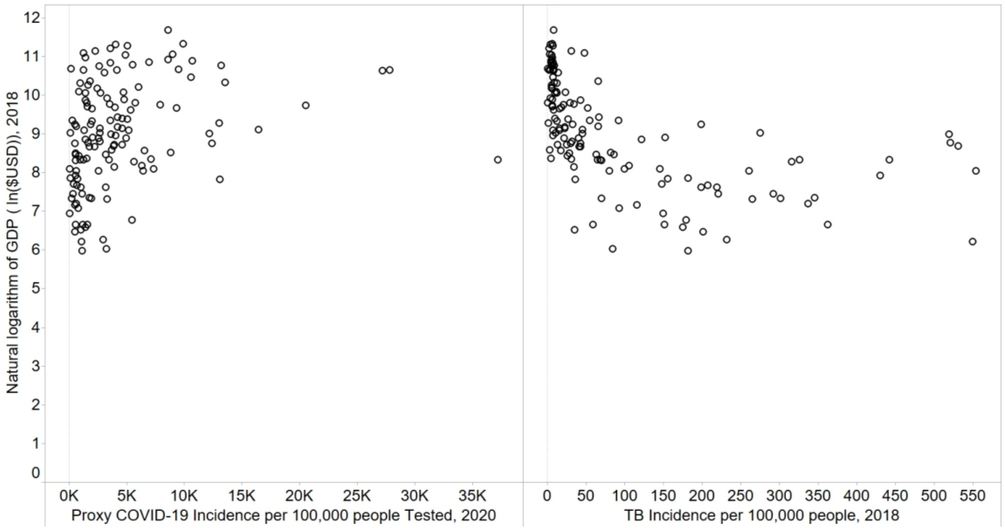
20. World Health Organization. Tuberculosis data. https://www.who.int/tb/data/en/. Accessed April 17, 2020.

21. World Bank. World Bank Open Data. https://data.worldbank.org/. Accessed April 17, 2020.

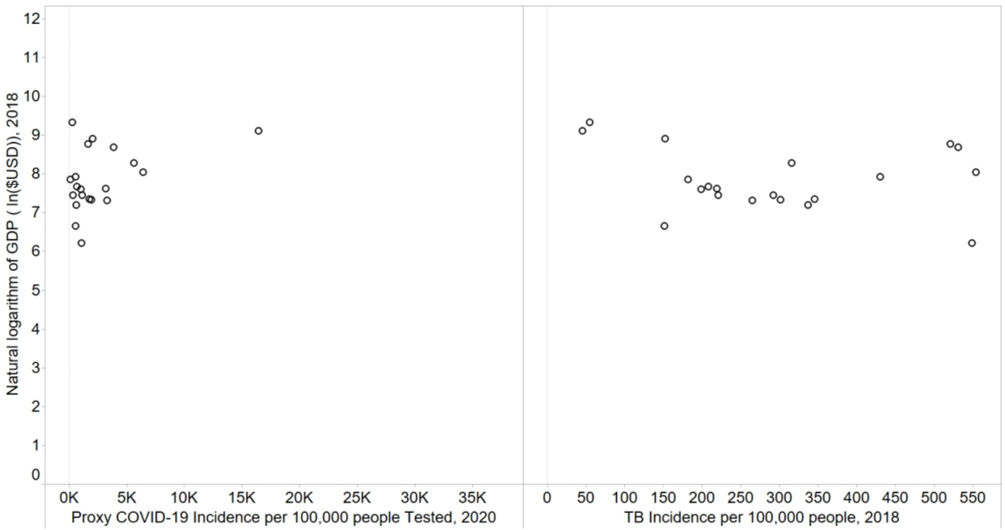
22. UCLA: Statistical Consulting Group. Interpreting Regression Models with Log-Transformed Data. https://stats.idre.ucla.edu/other/mult-pkg/faq/general/faqhow-do-i-interpret-a-regression-model-when-some-variables-are-log-transformed/. Accessed April 17, 2020.



Left: Distribution of GDP per capita, 2018. Right: Distribution of natural logarithm of GDP per capita, 2018



a (left): COVID-19 case positivity per 100,000 people tested, 2020 (to date) vs. the natural logarithm of GDP per capita, 2018. b (right): TB incidence per 100,000 people, 2018 vs. the natural logarithm of GDP per capita, 2018.



a (left): COVID-19 case positivity per 100,000 people tested, 2020 (to date) vs. the natural logarithm of GDP per capita, 2018 among high burden TB countries. b (right): TB incidence per 100,000 people, 2018 vs. the natural logarithm of GDP per capita, 2018 among high burden TB countries.