Essential tuberculosis medicines and health outcomes in countries with a national essential medicines list

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ARTICLE INFO

ABSTRACT

Background: Tuberculosis (TB) remains a major cause of morbidity and mortality globally despite effective treatments. Along with high-quality health services, essential medicines are a key tool in curbing TB related mortality. Examining relationships between listing TB medicines on national essential medicines lists (NEMLs) and population health outcomes related to amenable mortality is one way to assess TB care.
Methods: In this cross-sectional study of 137 countries, we used linear regression to examine the relationship between the number of TB medicines listed on NEMLs and TB related mortality while controlling for country income, region and TB burden.
Results: Most countries listed essential TB medicines to treat latent, drug-sensitive and disseminated TB but few listed enough for multi-drug resistant TB (MDR-TB) therapy. The total number of TB medicines listed ranged from 1 to 29 (median: 19, interquartile range: 15 to 22). Over 75% of the variation in health outcomes were explained by the number of TB medicines listed, gross domestic product (GDP) per capita, region and high-burden MDR-TB status. The number of TB medicines listed was not associated with TB mortality.
Conclusion: Most countries list essential TB treatments and the variation in TB outcomes is explained by other factors such as GDP.

1. Introduction

Although tuberculosis (TB) can be prevented, treated and cured, it remains a major cause of morbidity and premature death [1–3]. TB is found world-wide and across 137 countries it was the third highest contributor to amenable deaths [4]. Global economic loss from TB related mortality between 2015 and 2030 is estimated at US$984 billion [5]. In 2018 about 10 million persons developed TB disease, 1.5 million died from TB and over half a million were infected with drug-resistant TB (DR-TB) bacteria. TB disproportionately affects low- and middle-income countries (LMICs), particularly in Africa, South-East Asia and the Western Pacific [1].

Medicines are a key tool for quality TB care in the high-quality health system framework [6]. Globally, access to high-quality TB care varies, particularly in LMICs where access to medicines remains elusive [2,6]. Compounding this is the emergence of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) which incur higher treatment costs compared to drug-sensitive TB (DS-TB) [1,2]. Providing access to appropriate and essential TB medicines – medicines selected

for their quality, safety, efficacy and cost-effectiveness [7–9] – should improve TB population health outcomes [1,10].

Many governments and national programs which espouse universal healthcare coverage (UHC) use national essential medicines lists (NEMLs), tailored to their priority healthcare needs, to guide medicine selection, appropriate use, reimbursement and procurement [8,11,12]. Excluding a medicine from an NEML can mean it is less likely to be available when needed. NEML content is an important determinant of healthcare equity [8,11]. The selection of these essential medicines on NEMLs varies considerably between countries [8,9,12] and evaluating medicines listed on NEMLs is one way to assess TB care. This approach has been used to assess non-communicable diseases and other respiratory conditions [12–14]. We aimed to examine the listings of essential TB medicines on NEMLs and to quantify the association between TB health outcomes related to mortality and the number of essential TB medicines listed on NEMLs globally. These analyses can be used to identify potential changes to NEMLs that may reduce the burden of TB, especially in LMICs. This study is also aimed at determining the relative importance of NEMLs given the known importance of TB screening,

diagnosis and follow-up care.

2. Methods

Study design: We conducted a cross-sectional study between April and August 2019, examining the associations between listing essential TB medicines on NEMLs and country characteristics (including health outcomes) via correlational analyses. Ethical approval was not required for this study as all underlying data used were publicly available at a country level.

Data collection: Countries were included from the Global Essential Medicines (GEM) database [15]; the method of data extraction for countries' NEMLs (including medicine listings and the year of publication) are detailed elsewhere [8]. We identified a list of 40 essential TB medicines by extracting medicines from Section 6.2.4 (Antituberculosis medicines) of the 20th WHO Model List of Essential Medicines (WHO Model List) published in 2017 [16] and selected WHO TB treatment guidelines for: children (2014), DS-TB (2017), DR-TB (2016 and 2019) and latent TB infection – LTBI (2018), available on the WHO's TB guidelines webpage [17] in May 2019 (Fig. S1). We then searched the NEMLs in the GEM database to determine the total number of essential TB medicines listed and grouped them by: first-line (for LTBI and DS-TB), second-line oral and injectable medicines (for DR-TB) and glucocorticoids for disseminated TB (DI-TB) to determine whether countries listed medicines to manage TB cases using a treatment matrix [18] based on these guidelines (Table S1).

TB population health outcomes related to mortality were assessed by the 2016 healthcare access and quality score for TB (TB health outcome score); a standardized estimate of amenable mortality which is used as a proxy measure for national TB care [19]. Briefly, a list of causes of death amenable to healthcare (including TB) was modelled across location (195 countries and territories), year (1990–2016), age (0–79 years) and sex (both sexes) using the Global Burden of Disease (GBD) study data [19]. TB deaths were risk-standardized, to mitigate variations in deaths not easily addressed through healthcare (*e.g.,* location-specific behavioural and environmental risk exposure), by applying a global level of joint risk exposure. The risk-standardized deaths were aggregated by sex and using the GBD population age standard, complied age-standardize risk-standardized death rates by location and year. To finalize amenable TB mortality scores across location-year, the standardized death rates were transformed to a 0 to100 index, with 0 as the first percentile (highest deaths; poorest care) and 100 as the 99th percentile (lowest deaths; best care) [19]. We extracted these scores from the Global Health Data Exchange website [19,20]. We also collected country data on metrics that may help to explain the differences between countries' listings of TB medicines and TB health outcome scores: 1) 2016 income level and 2) gross domestic product (GDP) per capita based on purchasing power parity in current international dollars (I$) both obtained from the World Bank [21], 3) geographic region and 4) high-burden MDR-TB status (Table S2) both obtained from the WHO [22,23].

Data Analysis: For descriptive data we calculated medians with interquartile ranges (IQRs) or proportions. We selected approaches to explore associations of interests based on previous studies of NEMLs [8,12–14]. Kruskal-Wallis test was used to examine associations between listing essential TB medicines and country characteristics. The association between TB health outcome scores (dependent variable) and the total number of essential TB medicines listed on NEMLs (main independent variable) was examined by linear regression. We also controlled for region and GDP (a known health systems influencer) and added high-burden MDR-TB status as an effect modifier to our model as these countries may behave differently (*e.g.,* greater health system demands and atypical patients). We categorized the total numbers of medicines (low, medium and high) and log transformed GDP to meet assumptions of linearity. STATA version 14.2 (Stata Corp. College Station, TX, USA) was used for statistical analyses; probability values (*p*-values) less than 0.05 were considered significant for associations and we report: adjusted coefficient of determination (R^2), regression coefficients and 95% confidence intervals (95% CI) for relevant covariates.

Data sharing statement: The study data is available online at Figshare database (https://doi.org/10.6084/m9.figshare.12939557.v1).

Table 1
Tuberculosis health outcomes and medicine groupings by country characteristics.

Country groupings	TB health outcome score* *Median (IQR)*	Total TB medicines listed on NEMLs (n = 40) *Median (IQR)*	Total TB medicines listed on NEMLs with equivalents & alternatives considered (n = 20) *Median (IQR)*
Overall (n = 137)	54 (30–74)	19 (15–22)	12 (10–14)
WHO region (n = 137)			
Africa (n = 36)	24 (17–29.5)	17.5 (14.5–22.5)	12 (10–14)
Eastern Mediterranean (n = 16)	64 (32.5–80.5)	20.5 (15.5–22.5)	12.5 (10–14.5)
Europe (n = 26)	76.5 (60–91)	19.5 (12–22)	11.5 (6–14)
South-East Asia (n = 11)	44 (33–66)	19 (14–21)	13 (11–14)
The Americas (n = 30)	68 (62–78)	19 (17–22)	12 (10–13)
Western Pacific (n = 18)	45 (38–58)	14 (13–19)	10 (9–13)
p-value	*0.0001*	*0.1763*	*0.1135*
World Bank income level (n = 135)[†]			
Low-income (n = 28)	23 (15–36.5)	18.5 (15.5–22)	12.5 (10.5–14)
Lower-middle income (n = 40)	40 (30–51.5)	19 (14–22)	11.5 (10–14)
Upper-middle income (n = 45)	67 (59–79)	19 (15–22)	12 (10–14)
High-income (n = 22)	81.5 (75.5–94)	19 (15–22)	10.5 (8–12)
p-value	*0.0001*	*0.9166*	*0.1474*
WHO MDR-TB burden status (n = 137)			
High-burden (n = 27)	33 (25–54)	21 (15–25)	14 (11–15)
Other (n = 110)	61.5 (35–77.5)	18 (14–22)	11 (10–13)
p-value	*0.001*	*0.0525*	*0.0046*

Table notes: MDR-TB: multi-drug resistant tuberculosis; n: the number of countries or identified medicines for each grouping respectively; NEMLs: national essential medicines lists; TB: tuberculosis; WHO: World Health Organization. TB health outcome score refers to the healthcare access and quality score for TB; a risk-age-standardized measure of amenable TB deaths by location and year that is used as a proxy measure for national TB care. *Cook Islands, Nauru, Niue, Palau, Saint Kitts and Nevis and Tuvalu had missing health outcome data; †Cook Islands and Niue had missing income level data. The median and interquartile ranges (IQR) are reported for each grouping and the *p*-values between groups are based on the Kruskal-Wallis test (with Dunn's test and Bonferroni adjustment if initially significant; that is, *p* < 0.05).

3. Results

Country characteristics: Across 137 countries, most (84%) were classified as LMICs and 27 (20%) were high-burden MDR-TB; of these none were high-income. NEMLs were published between 2001 and 2017 (median: 2011, IQR: 2009 to 2013). We collected TB health outcome scores for 131 countries, which ranged from 0 to 100 (median: 54, IQR: 30 to 74; missing: 5 from the Western Pacific and 1 from the Americas; detailed in Table S3); scores differed significantly across WHO regions, income group and high-burden status ($p = 0.0001$, 0.0001 and 0.001, respectively; Table 1).

Medicine listings on NEMLs and management of TB: Countries' listings of the 40 essential TB medicines identified are summarized in Fig. 1 and detailed in Fig. S2. Commonly listed (by about 90% of countries) were first-line TB medicines and some glucocorticoids while uncommonly listed (by about 10% of countries) included second-line oral medicines

like bedaquiline, delamanid, gatifloxacin, rifabutin and thioacetazone. Six countries: Guinea, Lesotho, Lithuania, Pakistan (high-burden MDR-TB), Poland and Venezuela did not list vitamin B6 (pyridoxine) but included isoniazid on their NEMLs. Fig. 2 illustrates the percent of countries listing regimens to manage TB cases; most countries (about 90%) listed medicines to treat LTBI, DS-TB and DI-TB, about 40% (over half being high-burden states) listed enough medicines for at least one MDR-TB treatment regimen and 6% listed enough to manage XDR-TB.

The total number of TB medicines listed on NEMLs ranged from 1 to 29 (median: 19, IQR: 15 to 22) and was not associated with WHO region, World Bank income level and high-burden MDR-TB status ($p = 0.1763$, 0.9166 and 0.0525, respectively; Table 1); however when medicine equivalents (any of the aminoglycosides, carbapenems, fluoroquinolones and/or glucocorticoids identified) or alternatives (ethionamide or protionamide and cycloserine or terizidone) were considered, high-burden MDR-TB states listed more TB medicines
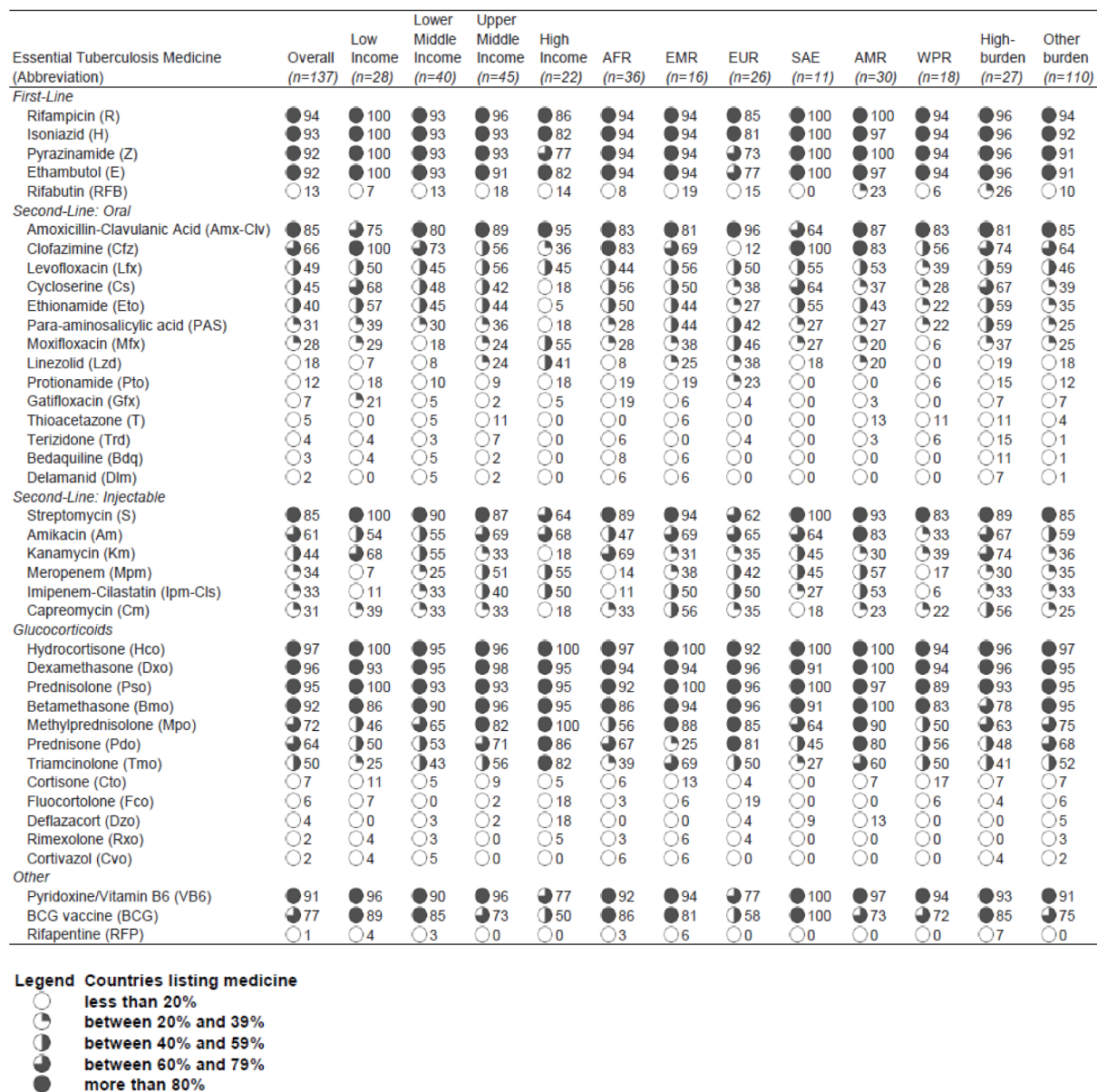
Essential Tuberculosis Medicine (Abbreviation)	Overall (n=137)	Low Income (n=28)	Lower Middle Income (n=40)	Upper Middle Income (n=45)	High Income (n=22)	AFR (n=36)	EMR (n=16)	EUR (n=26)	SAE (n=11)	AMR (n=30)	WPR (n=18)	High-burden (n=27)	Other burden (n=110)
First-Line													
Rifampicin (R)	94	100	93	96	86	94	94	85	100	100	94	96	94
Isoniazid (H)	93	100	93	93	82	94	94	81	100	97	94	96	92
Pyrazinamide (Z)	92	100	93	93	77	94	94	73	100	100	94	96	91
Ethambutol (E)	92	100	93	91	82	94	94	77	100	97	94	96	91
Rifabutin (RFB)	13	7	13	18	14	8	19	15	0	23	6	26	10
Second-Line: Oral													
Amoxicillin-Clavulanic Acid (Amx-Clv)	85	75	80	89	95	83	81	96	64	87	83	81	85
Clofazimine (Cfz)	66	100	73	56	36	83	69	12	100	83	56	74	64
Levofloxacin (Lfx)	49	50	45	56	45	44	56	50	55	53	39	59	46
Cycloserine (Cs)	45	68	48	42	18	56	50	38	64	37	28	67	39
Ethionamide (Eto)	40	57	45	44	5	50	44	27	55	43	22	59	35
Para-aminosalicylic acid (PAS)	31	39	30	36	18	28	44	42	27	27	22	59	25
Moxifloxacin (Mfx)	28	29	18	24	55	28	38	46	27	20	6	37	25
Linezolid (Lzd)	18	7	8	24	41	8	25	38	18	20	0	19	18
Protionamide (Pto)	12	18	10	9	18	19	19	23	0	0	6	15	12
Gatifloxacin (Gfx)	7	21	5	2	5	19	6	4	0	3	0	7	7
Thioacetazone (T)	5	0	5	11	0	0	6	0	0	13	11	11	4
Terizidone (Trd)	4	4	3	7	0	6	0	4	0	3	6	15	1
Bedaquiline (Bdq)	3	4	5	2	0	8	6	0	0	0	0	11	1
Delamanid (Dlm)	2	0	5	2	0	6	6	0	0	0	0	7	1
Second-Line: Injectable													
Streptomycin (S)	85	100	90	87	64	89	94	62	100	93	83	89	85
Amikacin (Am)	61	54	55	69	68	47	69	65	64	83	33	67	59
Kanamycin (Km)	44	68	55	33	18	69	31	35	45	30	39	74	36
Meropenem (Mpm)	34	7	25	51	55	14	38	42	45	57	17	30	35
Imipenem-Cilastatin (Ipm-Cls)	33	11	33	40	50	11	50	50	27	53	6	33	33
Capreomycin (Cm)	31	39	33	33	18	33	56	35	18	23	22	56	25
Glucocorticoids													
Hydrocortisone (Hco)	97	100	95	96	100	97	100	92	100	100	94	96	97
Dexamethasone (Dxo)	96	93	95	98	95	94	94	96	91	100	94	96	95
Prednisolone (Pso)	95	100	93	93	95	92	100	96	100	97	89	93	95
Betamethasone (Bmo)	92	86	90	96	95	86	94	96	91	100	83	78	95
Methylprednisolone (Mpo)	72	46	65	82	100	56	88	85	64	90	50	63	75
Prednisone (Pdo)	64	50	53	71	86	67	25	81	45	80	56	48	68
Triamcinolone (Tmo)	50	25	43	56	82	39	69	50	27	60	41	41	52
Cortisone (Cto)	7	11	5	9	5	6	13	4	0	7	17	7	7
Fluocortolone (Fco)	6	7	0	2	18	3	6	19	0	0	6	4	6
Deflazacort (Dzo)	4	0	3	2	18	0	0	4	9	13	0	0	5
Rimexolone (Rxo)	2	4	3	0	5	3	6	4	0	0	0	0	3
Cortivazol (Cvo)	2	4	5	0	0	6	6	0	0	0	0	4	2
Other													
Pyridoxine/Vitamin B6 (VB6)	91	96	90	96	77	92	94	77	100	97	94	93	91
BCG vaccine (BCG)	77	89	85	73	50	86	81	58	100	73	72	85	75
Rifapentine (RFP)	1	4	3	0	0	3	6	0	0	0	0	7	0

Legend Countries listing medicine
- less than 20%
- between 20% and 39%
- between 40% and 59%
- between 60% and 79%
- more than 80%

Fig. 1. Percent of countries listing identified essential tuberculosis medicines across listings. *Figure Notes:* Overall refers to all countries listing a medicine; total number of countries (n) are provided for each country characteristic grouping. Income grouping for countries used were assigned by the World Bank; 2 countries (Cook Islands and Niue) did not have assigned levels. World Health Organization (WHO) regions were abbreviated as AFR: Africa, EMR: Eastern Mediterranean, EUR: Europe, SEA: South-East Asia, AMR: The Americas, WPR: Western Pacific. High-burden refers to WHO designated high-burden multi-drug resistant tuberculosis countries; all other countries were categorized as Other burden. Medicines were first grouped by tuberculosis case use and then by highest to lowest overall listings.
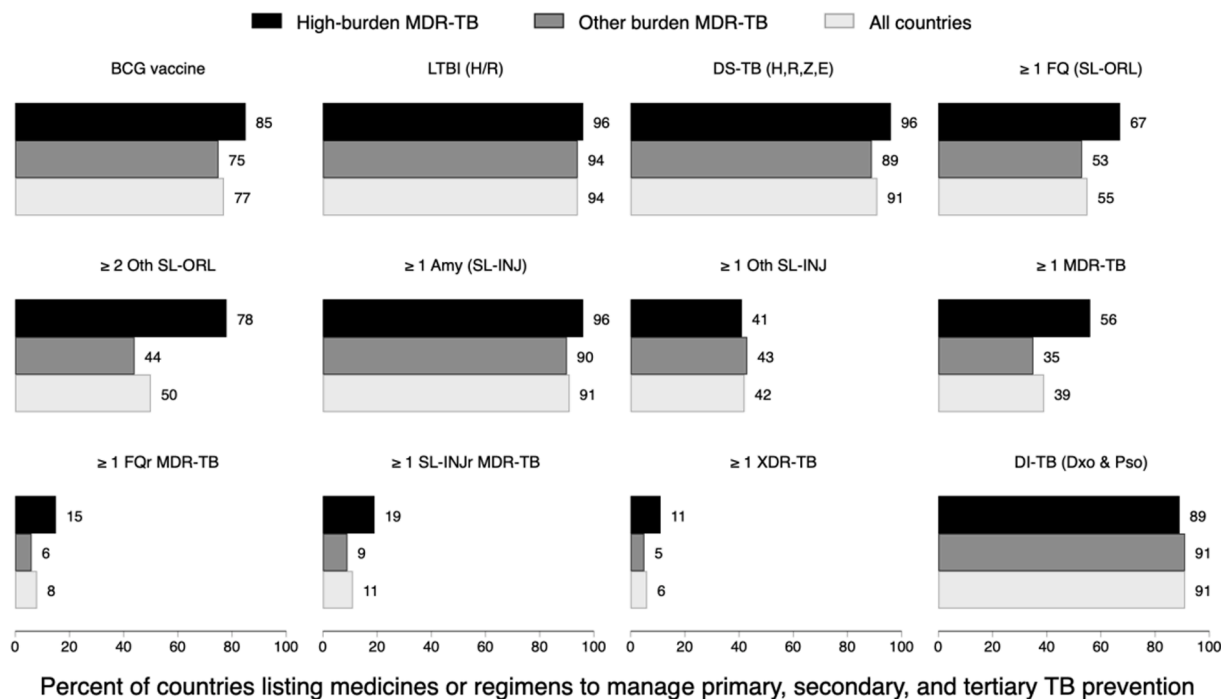
Percent of countries listing medicines or regimens to manage primary, secondary, and tertiary TB prevention

Fig. 2. Percent of countries listing medicines and therapeutic regimens to prevent and manage tuberculosis cases across 137 national essential medicines lists. *Figure Notes:* All 137 countries' national essential medicines lists were examined; 27 were high-burden multi-drug resistant (MDR) tuberculosis (TB) states. For primary prevention, BCG: bacillus Calmette–Guérin vaccine and secondary prevention, LTBI: latent tuberculosis infection treatment with H: isoniazid or R: rifampicin (rifapentine excluded as uncommonly listed). Tertiary prevention: DS-TB: drug sensitive TB treatment (with 4 first-line medicines, H, R, Z: pyrazinamide and E: ethambutol) and cases of MDR-TB treatment requiring several medicines to constitute a therapeutic regimen; we highlight selected listings that may constitute these regimens ≥ 1 FQ (SL-ORL): at least 1 fluoroquinolone (second-line oral medicine, either levofloxacin/moxifloxacin listed; gatifloxacin excluded as uncommonly listed), ≥ 2 Oth SL-ORL: at least 2 other (second-line oral medicines listed, includes clofazimine, cycloserine/terizidone, ethionamide/protionamide, linezolid, para-aminosalicylic acid, ethambutol or pyrazinamide, bedaquiline, delaminid and thioacetazone excluded as uncommonly listed); ≥ 1 Amy (SL-INJ): at least 1 aminoglycoside (second-line injectable listed, either amikacin/capreomycin/ kanamycin/streptomycin); ≥ 1 Oth SL-INJ: at least 1 other (second-line injectable listed, carbapenems either meropenem/imipenem-cilastatin plus amoxicillin with clavulanic acid); ≥ 1 MDR-TB: at least 1 multidrug-resistant TB regimen listed; ≥ 1 FQr MDR-TB: at least 1 fluoroquinolone resistant MDR-TB regimen listed; ≥ 1 SL-INJr MDR-TB: at least 1 second-line injectable resistant MDR-TB regimen listed; ≥ 1 XDR-TB: at least 1 extensively-drug resistant TB regimen listed; DI-TB: disseminated TB (includes both dexamethasone and prednisolone).
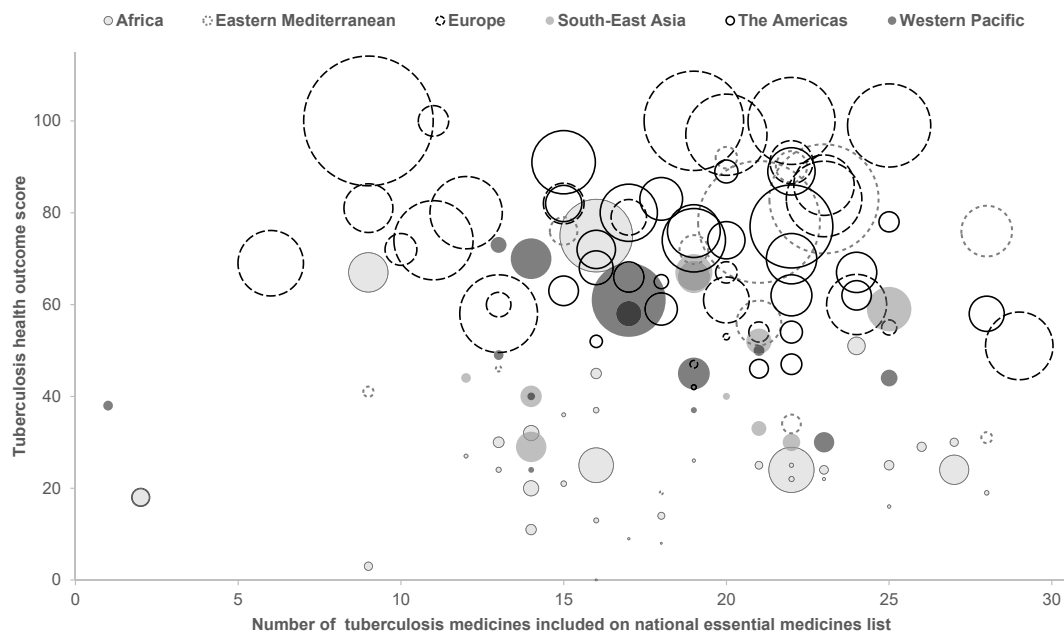
Fig. 3. The unadjusted relationship between tuberculosis health outcomes related to mortality and listing essential tuberculosis medicines on national essential medicines lists, country income and geographic region. *Notes:* The bubble width represents country's 2016 gross domestic product per capita based on purchasing power parity in current international dollars.

compared to other countries (median: 14 and 11, respectively; $p =$ 0.0046; Table 1).

TB health outcomes and listing essential TB medicines: We included 124 countries in the regression analyses; 13 countries were excluded due to missing covariates: TB health outcome score (Nauru, Palau, Saint Kitts and Nevis and Tuvalu), GDP (Cuba, DPRK/North Korea, Djibouti, Eritrea, Somalia, Syrian and Venezuela) or missing both health outcome score and GDP (Cook Islands and Niue).

We categorized the total number of TB medicines into three groups: low (1–14 medicines), moderate (15–22 medicines) and high (23–29 medicines). The regression indicated that the total number of TB medicines listed on NEMLs, WHO region, high-burden MDR-TB status and GDP per capita explained approximately 76.5% of the differences between countries' TB health outcome scores but the number of TB medicines listed was not associated with TB health outcome scores before and after adjusting for the covariates (Fig. 3 shows this unadjusted relationship). However, region, high-burden status and GDP were associated with health outcome scores (Fig. 4).

We then considered medicine equivalents and alternatives and re-categorized the number of TB medicines: low (1–10 medicines), moderate (11–13 medicines) and high (14–18 medicines). Again, there was no association between the number of TB medicines and health outcome scores but the covariates were associated with health outcome scores (F (9, 114) = 4.47, $p < 0.0001$, $R^2 = 0.7608$; Fig. S3).

We also updated the model using high-burden MDR-TB status as an effect modifier, there was again no association between the TB health outcome score and number of TB medicines but WHO region and GDP remained associated with the TB health outcome scores: with all listed TB medicines ($R^2 = 0.7643$; Fig. 4) and when equivalent and alternative medicines were considered (F(11, 112) = 35.81, $p < 0.0001$, $R^2 = 0.7569$; Fig. S3).

4. Discussion

Most countries list medicines to treat LTBI, DS-TB and DI-TB but many did not list enough to treat DR-TB as second-line medicines

(fluoroquinolones, newer and repurposed antibiotics) were not commonly listed. Across countries, the TB health outcome score was explained by factors such as GDP while the number of TB medicines listed on NEMLs was not associated with the health outcome scores.

Factors associated with TB health outcomes: The poor TB health outcomes in African, South-East Asian, Western Pacific, LMICs and high-burden MDR-TB countries despite listing essential TB medicines may be explained by the available healthcare services [3,24,25]. Multiple studies have identified gaps in the TB care across TB cases, countries and patient characteristics [1,2,4,6]. Global capacity to engage, diagnose, link to care and prevent TB related mortality is inadequate as available services lack sufficient patient-centeredness, infrastructure and skilled personnel, and access to good-quality care is variable [2,3,25,26]. A 2017 Mongolian survey found that less than 25% of health facilities offered TB services; many lacked TB diagnostic capacity and only 6.7% had all first-line TB medicines available [2] though they were listed on its NEML. In South Africa most TB patients engaged the public health system but only half were successfully treated due to losses to follow-up care with substantially higher losses observed among DR-TB cases [2]. Despite convincing evidence of preventative therapy for LTBI saving lives, these medicines are infrequently offered [2].

Access to care typically requires people affected by TB to reach facilities that provide those services and to stay in contact with healthcare providers (HCPs) which is often costly and time-consuming [2,25,28].

Factors associated with listing essential TB medicines: Studies have found associations between number of essential medicines, classes of medicines and therapy areas (including TB) across WHO regions, income levels and disease burden, and have attributed these associations with healthcare priorities and system resources [2,8,9,11–13,27].

It is concerning that some countries included isoniazid on their NEMLs but did not list pyridoxine (vitamin B6), that is recommended by WHO guidelines because it prevents painful neuropathies caused by isoniazid [17]. Rifabutin, recommended by the WHO to replace rifampicin in patients with human immune-deficiency virus (HIV) receiving protease inhibitors, was listed by few countries although HIV is a major risk factor for TB infection and disease [17]. The exclusion of
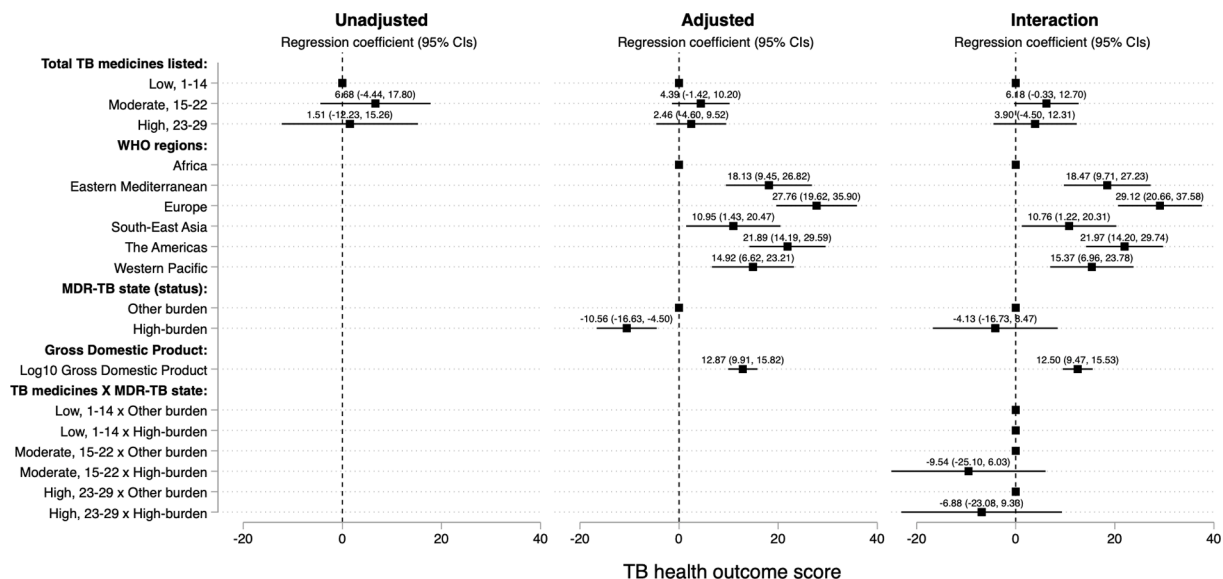
Fig. 4. Association between tuberculosis health outcomes related to mortality and listing of all identified essential tuberculosis medicines on 124 national essential medicines lists. *Figure Notes:* In the plotted regressions, the square represents the regression coefficient; the horizontal line is the 95% confidence interval (95% CI) and the numbers above the horizontal line reflect the values of the regression coefficient and the 95% CI. If the horizontal line crosses zero (the vertical dashed line), the variable is not statistically significant. The number of tuberculosis (TB) medicines listed on national essential medicines lists was not associated with TB health outcome scores before and after adjusting for the covariates. However, World Health Organization (WHO) region, high-burden multi-drug resistant (MDR) TB status and gross domestic product (GDP) per capita were associated with TB health outcome scores: Unadjusted regression: F(2, 121) = 0.87, p= 0.4234, $R^2 = 0.0141$ and Adjusted Model: F(9, 114) = 45.59, $p < 0.0001$, adjusted $R^2 = 0.7654$. Exploring high-burden MDR-TB status as an effect modifier had similar findings for number of medicines listed, WHO region and GDP, Interaction Model: F(11, 112) = 37.26, $p < 0.0001$, adjusted $R^2 = 0.7643$.

gatifloxacin and thioacetazone from the WHO Model List [16], though both were listed on WHO guidelines, may be due to safety concerns and safer alternatives are already included on the WHO Model List [9]. As many countries use the WHO Model List as a template for their NEMLs, some may be heavily influenced to not include these medicines which is reflected by them being uncommonly listed [8,9].

As expected, many of the commonly listed essential TB medicines (like isoniazid, rifampicin and prednisolone) identified on NEMLs were older and established. The management of LTBI, DS-TB and DI-TB have remained relatively unchanged for decades while the advent of DR-TB has introduced newer or repurposed antibiotics for TB treatment [28]. Many NEMLs assessed were published prior to 2015; this may explain the uncommon listings of newer TB medicines like bedaquiline, delamanid, linezolid and rifapentine (added to the WHO Model List in 2015) [25,28,29]. Previous work supports this and highlights the need for countries to regularly review their NEMLs, possibly every 2 years as is done with the WHO Model List [7,8]. Other factors such as cost burden (newer medicines tend to be more expensive) [30,31] and the failure of some countries (*e.g.*, sloth of national drug policies in introducing new medicines) and manufacturers (*e.g.*, reluctance to medicine registration and economics - affordability versus profit) to ensure medicines accessibility may also explain poor medicine listings [28]. It is also possible that TB medicines may be listed elsewhere (like BCG vaccine on immunization formularies or rifabutin on HIV pharmacopeias) or accessed through other procurement mechanisms like the Global Fund [1,23] and Strategic Fund of the Pan American Health Organization [9].

Strengths and Limitations: This is the largest study assessing the association between listing TB medicines on NEMLs and population health outcomes relating to amenable mortality. This study may support existing public health and TB care policies and can complement other designs to further assess the relationships between TB population health outcomes and essential TB medicines using data on medicine availability, affordability, access and utilization over time.

As an observational study, we cannot determine causality. Although the selected covariates and number of essential TB medicines listed explained over half of variations in TB health outcome scores, there are other confounding factors including: quality of care (*e.g.*, timelines between TB infection, diagnosis and management, HCPs training and cultural influences on medicine use), essential medicine characteristics (*e.g.*, dosing, forms and combinations) and health system organization (*e.g.*, TB program medicines funding and expense), that may influence TB population health outcomes [1–3,6,18,32], which were not assessed as our exploration was limited to quantitative measures that were available for almost all countries.

Listing TB medicines on an NEML does not necessarily imply medicines are consistently available, affordable, accessible, prescribed and used appropriately [11,18,26,33]. Some countries promote access to essential medicines by eliminating charges to patients but others do not. Uptake of essential medicines are affected by a myriad of factors including disease burden, national medicines policies, health system needs and resources and socio-cultural factors [25,34]. The GEM database used NEMLs that were abstracted from the WHO's repository during 2017 [8]. Finally, limitations in calculating TB health outcome scores or covariate data are applicable to this study; for example, outcome scores utilize TB mortality data which may be underreported yielding artificially higher scores or may be overreported producing exaggerated lower scores [19,26].

5. Conclusion

Many countries listed sufficient essential TB medicines on their NEMLs but had significantly different TB health outcomes related to mortality. Factors other than listing medicines explain variation in TB outcomes. Further work should explore the extent to with TB medicines are actually available. Efforts toward universal health coverage must focus on the availability of important medicines such as those for TB.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2022.100305.

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