Global and Regional Burden of Isoniazid-Resistant Tuberculosis

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abstract

BACKGROUND: Isoniazid has been the backbone of tuberculosis chemotherapy for 6 decades. Resistance to isoniazid threatens the efficacy of treatment of tuberculosis disease and infection. To inform policies around treatment of tuberculosis disease and infection in children, we sought to estimate both the proportion of child tuberculosis cases with isoniazid resistance and the number of incident isoniazid-resistant tuberculosis cases in children, by region.

METHODS: We determined the relationship between rates of isoniazid resistance among child cases and among treatment-naive adult cases through a systematic literature review. We applied this relationship to regional isoniazid resistance estimates to estimate proportions of childhood tuberculosis cases with isoniazid resistance. We applied these proportions to childhood tuberculosis incidence estimates to estimate numbers of children with isoniazid-resistant tuberculosis.

RESULTS: We estimated 12.1% (95% confidence interval [CI] 9.8% to 14.8%) of all children with tuberculosis had isoniazid-resistant disease, representing 120 872 (95% CI 96 628 to 149 059) incident cases of isoniazid-resistant tuberculosis in children in 2010. The majority of these occurred in the Western Pacific and Southeast Asia regions; the European region had the highest proportion of child tuberculosis cases with isoniazid resistance, 26.1% (95% CI: 20.0% to 33.6%).

CONCLUSIONS: The burden of isoniazid-resistant tuberculosis in children is substantial, and risk varies considerably by setting. The large number of child cases signals extensive ongoing transmission from adults with isoniazid-resistant tuberculosis. The risk of isoniazid resistance must be considered when evaluating treatment options for children with disease or latent infection to avoid inadequate treatment and consequent poor outcomes.

WHAT'S KNOWN ON THIS SUBJECT: Fifteen percent of tuberculosis cases globally are resistant to the drug isoniazid. Isoniazid resistance puts patients with tuberculosis at risk for poor treatment outcomes and threatens the effectiveness of isoniazid preventive therapy in people with latent tuberculosis infection.

WHAT THIS STUDY ADDS: We present the first global and regional estimates of the proportion of children with tuberculosis who have isoniazid-resistant disease, showing large geographic variations in risk of resistance. We estimate the number of annual incident cases of isoniazid-resistant tuberculosis in children.

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The World Health Organization (WHO) estimated that 9 million incident cases of tuberculosis (TB) and 1.5 million deaths due to TB occurred globally in 2013.[1] The drug isoniazid is an essential element of all first-line treatment regimens for TB, with demonstrated high bactericidal activity and low risk of adverse events.[2,3] Isoniazid is also highly effective in preventing disease in individuals infected quiescently with *Mycobacterium tuberculosis*.[4] Isoniazid resistance thus undermines the effectiveness of treatment of both TB disease and infection. *M tuberculosis* strains resistant to isoniazid have been observed in nearly 15% of TB cases globally.[1,5]

The burden of drug-resistant TB in children is poorly understood.[6] Drug-resistant TB is challenging to diagnose in a sick child because of the difficulty of obtaining a sample containing enough bacteria to enable drug susceptibility testing.[7] Even when a sample is obtained, drug susceptibility testing is often not performed. Undiagnosed drug resistance can lead to the inadvertent use of ineffective treatment regimens for children, increasing their risk for treatment failure and death. Children who have TB resistant to isoniazid alone and who are treated with a standard regimen[8] would only be receiving 2 or 3 effective drugs in the intensive phase and 1 in the continuation phase. Furthermore, children with TB resistant to both isoniazid and rifampin (ie, multidrug-resistant TB, or MDR TB) would be receiving no effective first-line therapy at all.

Although cases of isoniazid-resistant TB in children have been reported from a variety of geographic settings,[9] the number of children with isoniazid-resistant disease and the proportion of children sick with TB who have isoniazid-resistant disease are unknown. Both the proportion and the number are crucial measures that should guide programmatic decisions about using standardized empirical first-line regimens to treat children with TB disease and latent infection. We sought to produce global and regional estimates of the proportion of childhood TB cases that are isoniazid-resistant and the annual number of incident cases of isoniazid-resistant TB in children.

METHODS

We estimated the proportion and number of children (0–14 years old) with all forms of isoniazid-resistant TB disease, which includes resistance only to isoniazid as well as concurrent resistance to both isoniazid and other drug(s). Our data sources included surveillance-based estimates of isoniazid resistance among all patients with TB, published reports of TB drug resistance in children and adults, and recent estimates of the number of children with TB disease (Fig 1). Analyses were performed by using R for Mac version 3.0.2 and SAS version 9.2.

Proportion of Adult TB Cases With Isoniazid Resistance

The most recent and comprehensive estimates of isoniazid resistance available were WHO regional estimates of the proportion of TB cases with resistance to isoniazid but not rifampin, and the proportion of TB cases that are multidrug-resistant.[1] Estimates of the proportion of treatment-naive adult TB cases with all forms of isoniazid resistance were unavailable. Therefore, we added together WHO regional and global estimates of the proportion of treatment-naive TB cases that have resistance to isoniazid but not rifampin (unpublished data, WHO) and the proportion of treatment-naive TB cases that are MDR TB[1] to produce regional and global estimates of the proportion of treatment-naive adult TB cases that have any form of isoniazid resistance. We assumed both percentages had been estimated from the same population and used simulation methods (similar to those used in a previous report[6]) to estimate the 95% confidence intervals (CIs) around these total estimates.

Proportion of Child TB Cases With Isoniazid Resistance

We then determined the relationship between the proportion of isoniazid-resistant cases among children and

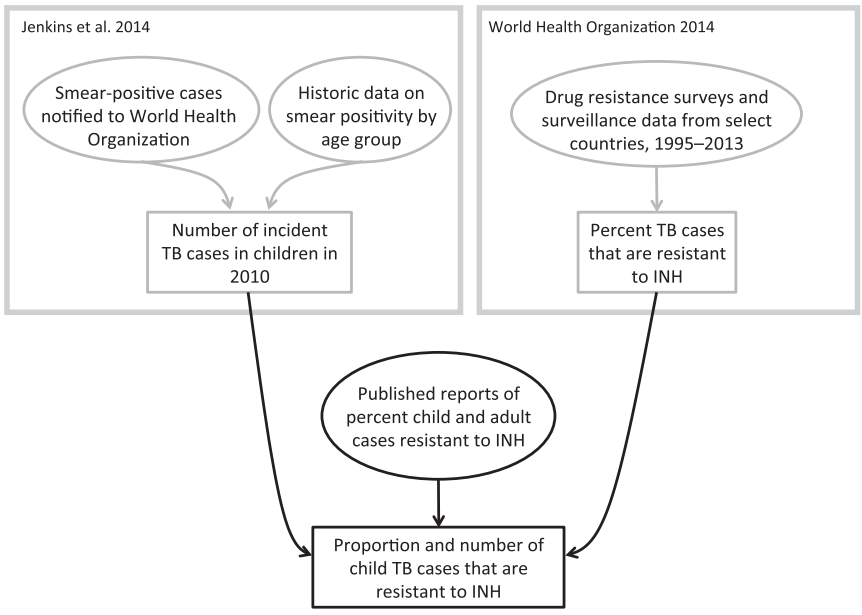

FIGURE 1
Data sources used for estimating proportion and number of incident isoniazid-resistant TB cases in children. The methods applied to produce 2 previous sets of estimates used in the current study are summarized in gray boxes. INH, isoniazid.

the proportion of isoniazid-resistant cases among treatment-naive adults. We used data from published studies that reported the proportions of isoniazid resistance among children and among adults without previous treatment in a given setting. We obtained these data from our previously published systematic review of reports on isoniazid resistance in children published through December 2011,[9] and we systematically searched the literature for additional reports published during January 2012–March 2014. We used the same search strategy, inclusion and exclusion criteria, and data extraction protocol as reported previously[9] but excluded publications that reported only on children.

Briefly, we included articles that reported drug susceptibility test results for at least isoniazid among both children and adults from a sample of patients who could be considered representative of some underlying population (eg, patients in a hospital, patients in a geographic area); we contacted authors for additional information if we could not determine results specifically for children or treatment-naive adults. Although we included reports that defined children as 0 to 14 years old or 0 to 15 years old, we defined children as 0 to 14 years old in our requests for additional data. If multiple studies analyzed the same or overlapping populations of patients, only the definitive report was included. For each included study, we extracted data about the number of children and treatment-naive adults with TB disease who had isolates tested for susceptibility to at least isoniazid and the number of those who had strains resistant to isoniazid (regardless of resistance to other drugs).

We constructed a linear regression model using the proportion of child TB cases with isoniazid-resistant TB as the dependent variable and the proportion of treatment-naive adult TB cases with isoniazid-resistant TB as the explanatory variable. We weighted the regression by the number of child cases in each study with drug susceptibility test results and calculated robust standard errors to allow for the potential impact of multiple studies from 1 country. We applied this linear relationship to the estimated proportions of treatment-naive adult TB cases with isoniazid resistance to produce estimates of the proportion of childhood TB cases with isoniazid resistance, by region and globally. We used simulation methods to estimate these proportions and their 95% CIs.

Number of Child TB Cases With Isoniazid Resistance

We generated 1000 estimates of the number of children who fell sick with TB in 2010, by region and globally, using the method we developed for a previous study.[6] For each region (and globally), we multiplied each of these 1000 estimates by 1000 estimates of the proportion of childhood TB cases with isoniazid resistance for that region (or globally). This produced 1 million estimates of the annual number of incident cases of childhood isoniazid-resistant TB that occurred in each region (and globally) in 2010. We reported the median and the 2.5th and the 97.5th percentiles of each of these 1 million estimates.

Secondary Analysis

To examine the robustness of our method, we conducted a second exercise to estimate the proportion and number of children with isoniazid-resistant TB. We assumed that the relationship between the proportion of cases that are multidrug-resistant and the proportion of cases that are resistant to isoniazid but not rifampin is the same among treatment-naive adult TB cases and child cases. We calculated these relationships from WHO regional estimates of both types of resistance (WHO[1] and unpublished data, WHO). We applied these relationships, by region, to regional estimates of the numbers of incident child MDR TB cases in 2010.[6]

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RESULTS

We identified 43 publications reporting proportions of both child and treatment-naive adult TB cases with isoniazid resistance in nonoverlapping populations (Fig 2 and Table 1). Of these, 29 publications[10–38] were identified from our earlier systematic review,[9] and 14 publications[39–52] through our updated systematic review. In total, 32 countries and territories were represented, with a median of 14 children per report (interquartile range: 7–55).

The regression model based on data from these publications yielded the following relationship between the proportion of isoniazid-resistant cases among child TB cases (Y) and the proportion of isoniazid-resistant cases among treatment-naive adult TB cases (X): $Y = -0.003 + 1.05X$ (95% CI for the intercept = −0.021 to 0.015, 95% CI for the slope = 0.94 to 1.17). When the largest study (from the United States[51]) was removed, the relationship was $Y = 0.010 + 1.02X$; when the 2 largest studies (from the United States and Kazakhstan[44]) were removed, the relationship was: $Y = 0.011 + 1.00X$ (Fig 3).

Applying this relationship to the global WHO estimate of the proportion of treatment-naive cases with isoniazid resistance yielded a global estimate of 12.1% (95% CI: 9.8% to 14.8%) of all incident TB cases among children that were isoniazid-resistant. This proportion

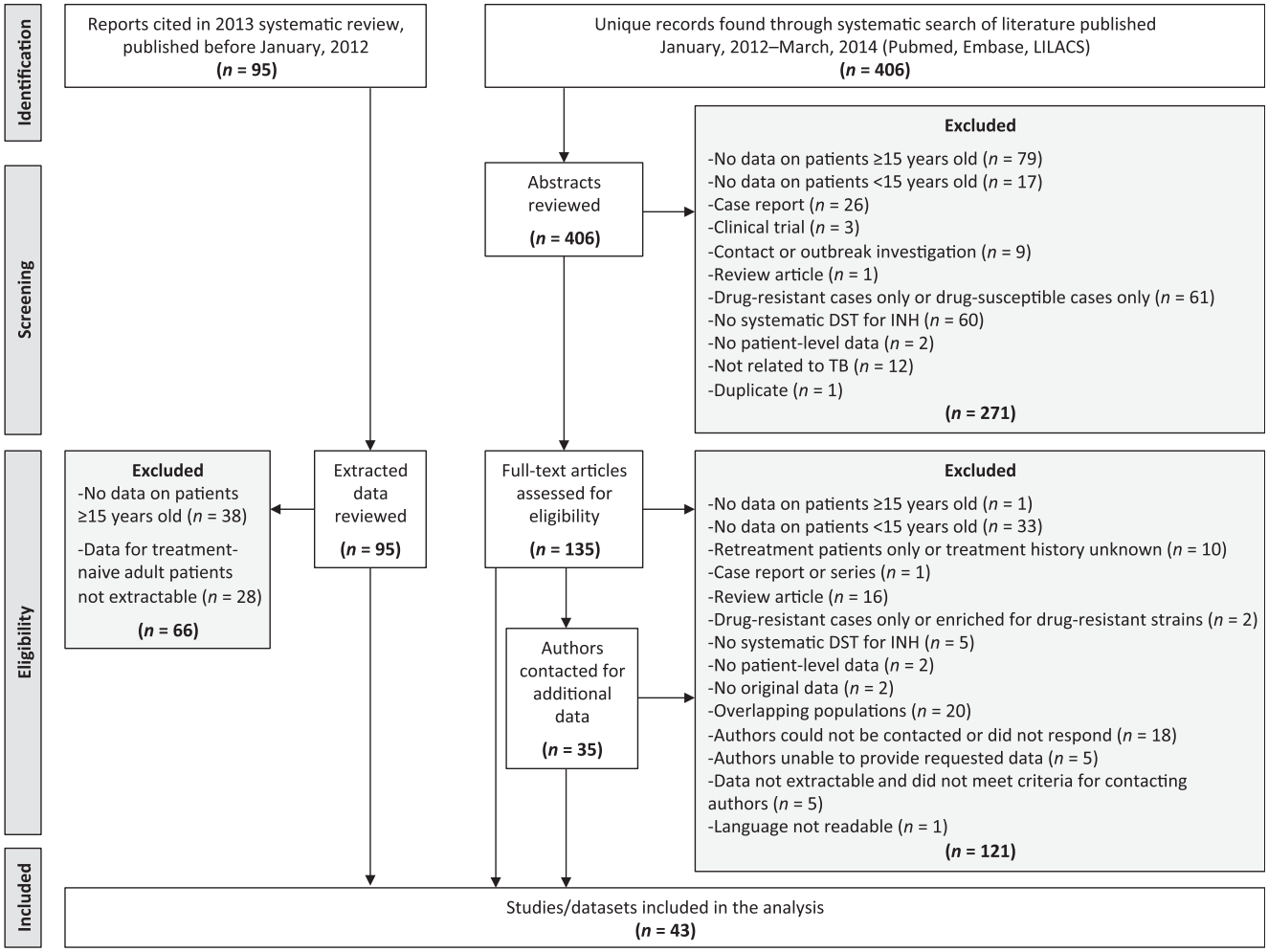

FIGURE 2

Identification of publications reporting the proportion of isoniazid-resistant TB cases among children and among adults with no history of previous TB treatment. DST, drug susceptibility testing; INH, isoniazid.

varied greatly by region, ranging from 5.7% (95% CI: 2.2% to 9.2%) in the American region to 26.1% (95% CI: 20.0% to 33.6%) in the European region (Fig 4). Applying these proportions to estimates of incident TB cases in children yielded an estimated 120 872 (95% CI: 96 628 to 149 059) incident cases of isoniazid-resistant TB disease in children in 2010. Estimates of regional numbers of incident cases are shown in Table 2.

We obtained similar results with the secondary analysis, which yielded a global estimate of 108 037 (95% CI: 67 276 to 183 812) incident cases of isoniazid-resistant TB in children in 2010, representing 11.0% (95% CI: 6.9% to 18.5%) of all incident childhood TB cases. Regional variation in the proportion of cases with isoniazid resistance was also similar (Supplemental Information).

DISCUSSION

Our results suggest that ~120 000 children worldwide fall sick with isoniazid-resistant forms of TB each year, representing ~12% of all TB cases in children. The majority of cases occur in the Western Pacific and Southeast Asia regions. However, the European region has the highest proportion of childhood cases that are isoniazid-resistant.

The finding that 1 in 8 children with TB globally have isoniazid-resistant disease has enormous implications for the effectiveness of treatment. All forms of TB are substantially underdiagnosed in children,[6,53,54] and diagnosis of drug resistance presents a particular challenge in children because of lack of bacteriologic confirmation.[7] Hence, it is likely that the majority of these 120 000 children receive either no TB treatment or a standardized empirical first-line regimen, with the latter group receiving at most 3 effective drugs in the intensive phase of treatment and only 1 effective drug in the continuation phase. In cases in which resistance to other first-line drugs is also present or a 3-drug regimen is used, a child may be receiving even fewer effective drugs. Both of these

TABLE 1 Publications Identified Through Systematic Review, Which Contributed Data to the Regression Between the Proportions of Incident TB Cases That Are Isoniazid-Resistant in Children and in Treatment-Naive Adults

Setting	Years Patients Enrolled	Children With DST Results	Children With INH-Resistant TB (%)	Treatment-Naive Adults With DST Results	Treatment-Naive Adults With INH-Resistant TB (%)
Algeria (Algiers)[10]	1963–1966	152	10 (7)	233	26 (11)
Australia[39]	2010	21	8 (38)	1028	139 (14)
Austria[11]	1995–1998	108	2 (2)	2653	70 (3)
Bangladesh (Greater Mymensingh District)[12]	2001	11	0 (0)	933	60 (6)
Brazil (Rio de Janeiro)[13]	2004–2006	1	0 (0)	432	38 (9)
Brazil (Sao Paolo)[14]	1995–1887	4	0 (0)	222	13 (6)
Brazil (Sao Paolo)[15]	2000–2002	5	2 (40)	293	14 (5)
Burundi (Bujumbura)[16]	2002–2003	13	2 (15)	483	29 (6)
China (25 provinces)[40]	Not stated	90	29 (32)	130	42 (32)
Colombia (Cali and Buenaventura)[41]	2007–2008	7	4 (57)	176	55 (31)
Djibouti[42]	2010–2011	10	5 (50)	15	6 (40)
Ethiopia (Addis Ababa)[17]	2005	11	3 (27)	179	14 (8)
Finland[18]	1959–1961	26	7 (27)	118	4 (3)
Haiti (Central)[19]	1988	12	1 (8)	210	41 (20)
Hong Kong[20]	1986–1999	429	21 (5)	48 496	2133 (4)
India (Andhra Pradesh State)[21]	2004–2005	22	2 (9)	476	63 (13)
India (Ernakulum District)[22]	2004	1	0 (0)	304	27 (9)
India (New Delhi)[43]	2007–2011	27	9 (33)	79	12 (15)
Japan[23]	2002	7	0 (0)	2698	77 (3)
Kazakhstan[44]	2007–2011	712	286 (40)	28 550	10 914 (38)
Kenya (11 districts)[24]	1964	96	5 (5)	536	60 (11)
Kenya (11 districts)[25]	1984	55	9 (16)	693	58 (8)
Mexico (Monterrey)[26]	Not stated	1	1 (100)	136	15 (11)
Mexico (Sinaloa)[27]	1997–2004	7	1 (14)	458	72 (16)
Mexico (9 states)[45]	2008–2009	14	4 (29)	2107	193 (9)
Mongolia[28]	2007	11	3 (27)	640	80 (13)
New Zealand[29]	2001–2010	105	6 (6)	2433	188 (8)
Pakistan (Karachi)[46]	2006–2009	32	4 (13)	818	72 (9)
Poland[47]	2011–2013	55	5 (9)	12 452	405 (3)
Republic of Korea (Seoul)[48]	2009–2011	1	0 (0)	323	42 (13)
Saudi Arabia (Riyadh)[30]	1995–2000	10	2 (20)	297	21 (7)
Spain (Barcelona)[31]	1995–1997	72	1 (1)	1467	57 (4)
Spain (Barcelona)[32]	2003–2004	15	0 (0)	469	22 (5)
Spain (Santiago de Compostela)[33]	1996–2006	2	0 (0)	135	12 (9)
Taiwan (Changhua County)[34]	2001–2002	2	0 (0)	454	68 (15)
Taiwan (Eastern)[49]	2004–2010	16	2 (13)	992	135 (14)
Thailand (Bangkok and 4 districts)[50]	2004–2008	77	5 (6)	8900	798 (9)
Thailand (Chiang Rai Province)[35]	1996–1998	19	5 (26)	1077	142 (13)
Turkmenistan (Dashoguz) and Uzbekistan (Karakalpakstan)[36]	2001–2002	3	0 (0)	208	78 (38)
United Republic of Tanzania (15 districts)[37]	1969–1970	42	2 (5)	594	38 (6)
United States of America[51]	1993–2012	4543	341 (8)	224 592	17 401 (8)
Uzbekistan[52]	2010–2011	5	2 (40)	700	296 (42)
Yemen[38]	2004	14	1 (7)	493	19 (4)

DST, drug susceptibility test; INH, isoniazid.

situations considerably increase the likelihood of poor outcomes including treatment failure and death.[55] Moreover, the use of inadequate regimens increases the risk of further amplifying drug resistance,[56] especially if resistance to other first-line drugs results in treatment with only 1 or 2 effective drugs.

WHO guidelines recommend children sick with TB be treated with a 3-drug regimen only in settings of low HIV prevalence and low prevalence of isoniazid resistance.[57] Our results suggest that the risk of isoniazid resistance among children with TB varies widely among geographic settings. Thus, when the risk of isoniazid resistance is unknown and when a bacteriologic sample cannot be obtained, a minimum 4-drug regimen should be used for the initiation phase of treatment. Moreover, if isoniazid mono-resistance is known or suspected based on the child's exposure to a mono-resistant source case, prudence would call for the child to be given at least three effective drugs (rifampicin, pyrazinamide, and ethambutol) for the full 6 months of treatment.[58]

Child contacts of TB patients are one of the most highly prioritized groups for receiving preventive therapy to avert development of TB disease,[59]

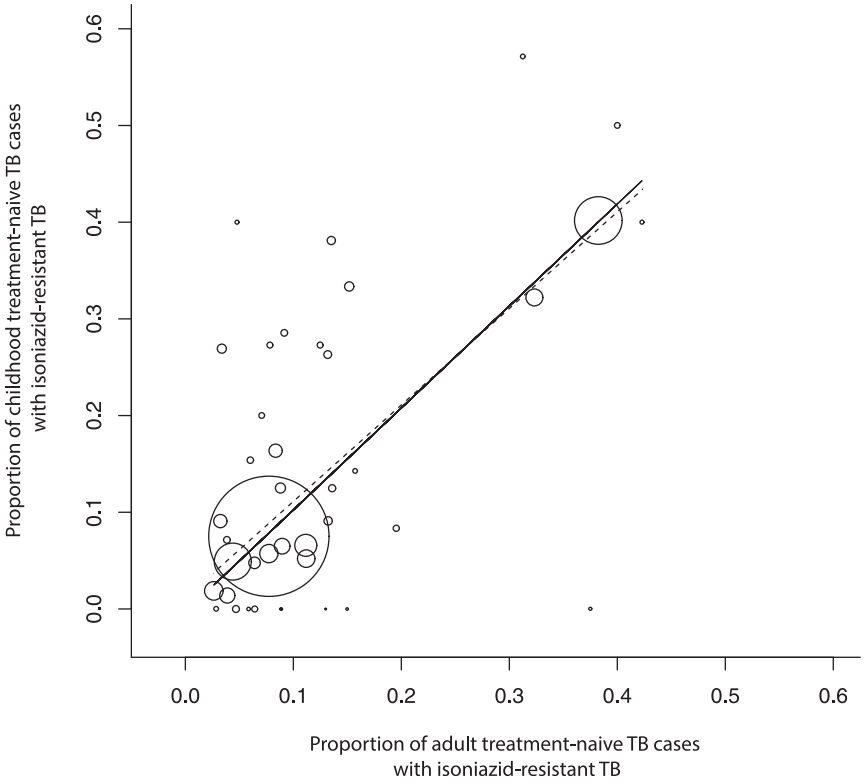

FIGURE 3
Linear regression between the proportions of incident TB cases that are isoniazid-resistant in children and in treatment-naive adults. Each circle represents 1 study with circle size proportional to the number of children in the study. Solid line = all studies included; dashed line = 2 largest studies excluded (sensitivity analysis).

with isoniazid the most commonly used regimen for preventive therapy in children. However, the sizeable number of children sick with isoniazid-resistant TB implies a much larger number who are latently infected with isoniazid-resistant strains, for whom isoniazid preventive therapy is unlikely to be effective. If one assumes that the risk of isoniazid resistance among children sick with TB reflects the risk of being latently infected with an isoniazid-resistant strain of *M tuberculosis*, then applying our estimated proportion of isoniazid resistance among incident child cases to the estimated 7.6 million new annual latent infections in the 22 countries with high TB burdens[53] and scaling up the number to a global estimate would suggest that >1 million children are newly infected with isoniazid-resistant strains each year. The use of rifamycin-based regimens rather than isoniazid alone for preventive therapy[59] would be especially warranted in settings such as Eastern Europe, where 33.5% of treatment-naive adult cases are estimated to be isoniazid-resistant.[5] Most high-TB-incidence countries have yet to adopt these proven, shorter preventive regimens. Our findings should spur more TB programs to consider using them to expand access to effective TB prevention.

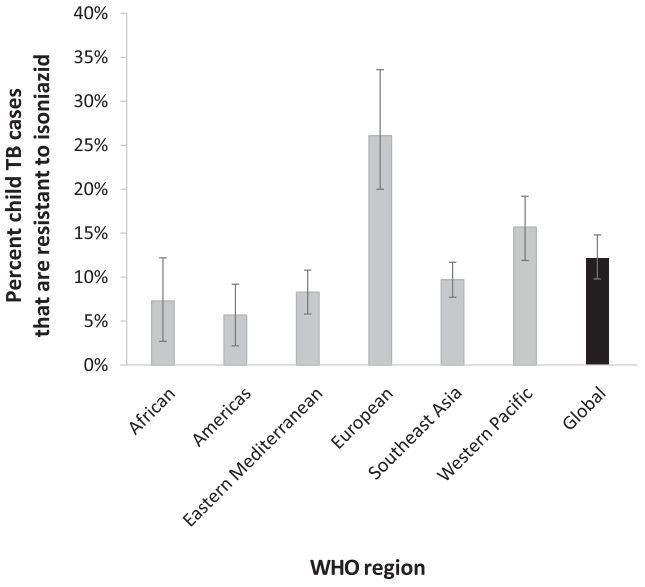

FIGURE 4
Estimated percentage of child TB cases that are resistant to isoniazid, by WHO region.

Although there are clear treatment implications in regions of high general risk of isoniazid-resistant TB, the lowest regional risk we observed was not insignificant, representing 1 in 20 children sick with TB. Our study underlines the need in all settings to ascertain the likely drug-resistance profile of children with TB disease or latent infection. Because children with TB have often been infected by someone close to them, contact tracing and drug susceptibility testing of adults with TB can provide crucial data to inform treatment of children with nonmicrobiologically confirmed TB and of apparently healthy children with latent TB infection. Our findings also underscore the importance of developing rapid point-of-care tests capable of ascertaining resistance to at least both isoniazid and rifampin in the pediatric population.

TABLE 2 Estimated Number of Incident Cases of Isoniazid-Resistant TB Disease in Children in 2010, by WHO Region

WHO Region	Children With Isoniazid-Resistant TB, *n*	95% CI
African	20 339	7141 to 34 616
Americas	1547	581 to 2519
Eastern Mediterranean	5935	3979 to 8163
European	11 262	8431 to 14 742
South-East Asia	38 507	29 709 to 47 869
Western Pacific	28 170	20 865 to 35 921
Total	120 872	96 628 to 149 059

The comparison of our results with a recent estimate of the number of incident MDR TB cases in children suggests that there are approximately twice as many children with TB resistant to isoniazid but not rifampin as there are children with MDR TB.[6] Because cases in children predominantly reflect recent transmission, this finding is indicative of the ongoing transmission of strains that are resistant to isoniazid but not rifampin. Indeed, in some settings, >5 times as many newly diagnosed TB patients have isoniazid resistance without concurrent rifampin as have MDR TB.[60,61] Notably, these patients would not be diagnosed with drug-resistant TB if the sole diagnostic used were Gene Xpert MTB/RIF assay, which only tests for rifampin resistance. Although this assay is a valuable rapid diagnostic tool, the current US$26 million initiative aimed at quickly scaling up its use[62] risks the unintended result of leading programs to neglect diagnosis of isoniazid resistance. Our results suggest the importance of coordinating rapid diagnosis of isoniazid resistance with rapid diagnosis of rifampin resistance to ensure effective treatment.

Estimating the burden of drug-resistant TB is fraught with challenges.[63] Our method of estimation required several assumptions and incorporated previously published estimates, which themselves had important limitations. First, the WHO regional drug resistance estimates were based on data from a subset of countries, with data missing from many African countries and only older data available from many countries in the Americas.[5] Second, we assumed that these estimates reflected the proportion of resistance among adults; although we do not know that children were explicitly excluded from all of the surveillance and survey data that contributed to those estimates, the number of children included, if any, was likely to be negligible. Third, our estimates relied on previously published estimates of the numbers of children with TB, which were made assuming that historical data on the proportion of childhood TB cases that were sputum smear-positive were generalizable to all settings in the present.[6] Finally, in estimating the number of incident child cases of isoniazid-resistant cases in 2010, we assumed that the WHO drug resistance estimates were applicable to 2010, even though they were based on data spanning 1995 to 2013.

Because of the limited data available on isoniazid resistance, we were unable to use country-level data or account for the variation that can be expected in levels of isoniazid resistance among countries within a geographic region and within countries as well.[5,64] For instance, rates of isoniazid resistance in Eastern Europe have been shown to be substantially higher than in Western Europe,[5] but the present analysis is unable to capture this difference. Finally, although we attempted to test the robustness of our methodology by using a secondary approach, the 2 were not fully independent because both relied on the aforementioned regional and global estimates of isoniazid resistance and numbers of children with TB. Alternative estimates of the number of incident TB cases in children were published in 2014.[53] In that report, the number of childhood TB cases in the 22 high-burden countries was estimated, and the authors noted that global numbers would be ~25% higher. This estimated 800 000 global childhood TB cases, multiplied by our proportion estimate of 12.1%, would result in ~96 800 childhood isoniazid-resistant TB cases, which falls within the confidence limits of our estimate.

CONCLUSIONS

We estimate that 1 in 8 children with TB globally has TB resistant to isoniazid. That figure reaches 1 in 4 in the European region. Our findings have critical implications for the diagnosis and treatment of both TB disease and infection. The large number of child cases signals extensive ongoing transmission from untreated TB patients with isoniazid-resistant strains (with and without rifampin resistance) and the urgency to treat all forms of TB disease effectively. The scope and regional variation of the problem underline the importance of understanding the local epidemiology of isoniazid-resistant TB and the drug resistance profiles of adult cases, which are the likely source cases for the children around them. Our results also indicate that current diagnostic approaches and empirical first-line treatment regimens may be exposing large numbers of children to inadequate TB treatment, putting them at risk for treatment failure, development of further resistance, and death.

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ABBREVIATIONS

CI: confidence interval
MDR TB: multidrug-resistant tuberculosis
TB: tuberculosis
WHO: World Health Organization

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