Published in final edited form as:
Pediatr Infect Dis J. 2013 May ; 32(5): e217–e226. doi:10.1097/INF.0b013e3182865409.

Isoniazid-Resistant Tuberculosis in Children: A Systematic Review

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Abstract

Background—Isoniazid resistance is an obstacle to the treatment of tuberculosis disease and latent tuberculosis infection in children. We aim to summarize the literature describing the risk of isoniazid-resistant tuberculosis among children with tuberculosis disease.

Methods—We did a systematic review of published reports of children with tuberculosis disease who had isolates tested for susceptibility to isoniazid. We searched PubMed, Embase and LILACS online databasesuptoJanuary 12, 2012.

Results—Our search identified 3,403 citations, of which 95 studies met inclusion criteria. These studies evaluated 8,351 children with tuberculosis disease for resistance to isoniazid. The median proportion of children found to have isoniazid-resistant strains was 8%; the distribution was right-skewed (25th percentile: 0% and 75th percentile: 18%).

Conclusions—High proportions of isoniazid resistance among pediatric tuberculosis patients have been reported in many settings suggesting that diagnostics detecting only rifampin resistance are insufficient to guide appropriate treatment in this population. Many children are likely receiving sub-standard tuberculosis treatment with empirical isoniazid-based regimens, and treating latent tuberculosis infection with isoniazid may not be effective in large numbers of children. Work is needed urgently to identify effective regimens for the treatment of children sick with or exposed to isoniazid-resistant tuberculosis and to better understand the scope of this problem.

Keywords

drug resistance; mono-resistance; pediatric; INH; LTBI

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Conflict Of Interest Statement and Source of Funding: The authors have no conflicts of interest or funding to disclose.

Contributors: CMY, AWT, and MCB designed the study. CMY, AWT, and JBP participated in data extraction. CMY analyzed the data. TC and SK guided data interpretation. CMY and MCB wrote the manuscript draft and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in manuscript revisions and approved the final manuscript.

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INTRODUCTION

Isoniazid-resistant tuberculosisin adults and children is an obstacle to effective treatment of both tuberculosis disease and latent tuberculosisinfection (LTBI). According to recent global estimates,13.9% of new tuberculosis cases outside of the Eastern European region and 44.9% of new cases within the Eastern European regionhad isoniazid-resistant tuberculosis.[1]To date, no attempt has been made to quantify the risk of isoniazidresistance among children with tuberculosis.Understanding this risk is important because children are a sentinel population for transmission,[2,3] and because isoniazid resistance may impact the choice of regimen used to treat children with both active tuberculosis disease and LTBI.

Studies of adults have demonstrated thatpatients with isoniazid-resistant tuberculosis have higher rates of treatment failure compared to patients with susceptible strains when treated with standard chemotherapy regimens.[4,5]This increased risk of failure is present for both new and retreatment patients,[5,6]for patients with concurrent rifampin resistance and for those with other resistance patterns.[6] Although data on the treatment outcomes ofchildren with isoniazid-resistant tuberculosis are quite limited, isoniazidresistance may also erode the efficacy of combination regimens among young patients, and may contribute tothe amplification of resistance.

Although a number of regimens for treating latent tuberculosis infection have been developed,[7]the regimens most commonly recommended for the treatment of children are based on isoniazidalone.[8,9] However, children with isoniazid-resistant tuberculosis may not benefit from this prophylaxis. Case reports highlight the potential inefficacy of prophylaxis in child contacts of drug-resistant tuberculosis cases when the source case has a strain resistant to one or more of the drugs on which the prophylaxis regimen is based.[10,11]

Here we review the literature on isoniazidresistance in pediatric tuberculosis patients in order to better understand its potential impact on the treatment of children with tuberculosis disease and latent tuberculosis infection.

METHODS

Search strategy

Our search strategy (Figure 1)aimed to identify studies that could provide an estimate ofthe proportion of children with isoniazid-resistant tuberculosisdisease based on drug-susceptibility testing (DST). We reviewed all published studies that reported this measure among a patient population that we expected would be representative of risk of isoniazid resistance among pediatric patients in the study base. Accordingly, we excluded reports where the inclusion of subjects may have been related to drugresistance (e.g., clinical trials, case-control studies). We also excluded reportsfrom outbreak or contact investigations, where resistance among the included subset of patients is expected to be highly correlated and less likely to represent resistance in the study base of all children with tuberculosis disease.We did not restrict the language of the publications reviewed.

We systematically searched the PubMed, Embase and LILACS electronic databases for primary studies and review articles published through January 12, 2012. The search terms used controlled vocabulary and free text and included combinations intended to capture reports of drug-resistant tuberculosis (e.g. “resist*” and “tuberculosis,” “drug-resistant tuberculosis”) in children (e.g. “infan*,” “adolescen*,” “child*”).The complete search strategy is detailed in Addendum 1.

To identify relevant articles not found in these primary electronic databases, we also reviewed the reference lists of primary studies and reviews for additional references and searched the Western Pacific, Africa, South East Asia, and Eastern Mediterranean regional databases of the World Health Organization.

Initial review of studies

We compiled an initial database from the electronic searches and removed duplicate citations. Two reviewers (AWT and MCB or CMY) screened these citations by reviewing the title and abstract to capture relevant studies. Studies were eligible for inclusion if they reported the proportion of children with culture-confirmed tuberculosisdisease who had isolates tested for susceptibility toisoniazid. We resolved disagreements among the reviewers by consensus. For the group of citations that met the screening criteria, we obtained the full text to assess for eligibility. With the aid of translators, studies in multiple languageswere assessed for inclusion.

We contacted authors for additional information if the report met all of the following criteria: (a) the drug-susceptibility test results in the report were not disaggregated by age group (0-14 and ≥15 years), (b) published after 2000, and (c) published in English or Spanish. All correspondence was conducted through email.

Studies were excluded if they met any of the following criteria: no pediatric (0-14 years old) patients, the study population was limited to patients with resistant tuberculosisorthese patients were preferentially enrolled, patients were identified through contact investigations of drug-resistant source cases, the study contained no original data or no patient-level data, or we could not determine the total number of pediatric patients with any isoniazidresistance (e.g. studies that explicitly omitted one or more subcategories of isoniazidresistance such as monoresistance).Additionally, studies for which data on the pediatric age group (defined as 0-14 years or 0-15 years) could not be extracted were excluded if authors were unable to provide additional data or did not respond to requests for data. If multiple studies analyzed the same or overlapping populations of patients, only the definitive report was included. Literature reviews and meta-analyses were excluded from data extraction, and their references were hand-searched for additional records.

Data extraction

Two reviewers (CMY, AWT) extracted all study data. A third reviewer (JBP) arbitrated any discrepancies between the first two reviewers. All final data was double-entered into a relational database designed for this purpose in Microsoft Access.

For each study, we extracted data about the number of children with tuberculosisdisease who had isolates tested forsusceptibility to isoniazid, and the proportion of those who had strains resistant to isoniazid. Where possible, we also extracted data about the number of children who had tuberculosis resistant to any drug and the number of children who had multidrug-resistant tuberculosis (MDR-TB), defined as those resistant to both isoniazid and rifampin(the backbone of the first-line anti-tuberculosis therapy).

The data extracted included the following information: location and enrollment year(s) of study, data source (e.g. national/regional surveillance, institution-based, randomized sample), patient population restrictions (e.g. failed treatment, HIV co-infected, extra-pulmonary tuberculosis), type of laboratory in which DST was performed, and DST data on children with culture-confirmed tuberculosis.

For each study that met inclusion criteria, we reportthe number of children with tuberculosisdisease who had strains tested for susceptibility to isoniazid, and the proportion of those children found to have strains resistant toisoniazid.

RESULTS

Of the 3,403 abstracts, we identified 95 studies that were eligible for inclusion (Figure 1).[12-106]The most common reason for exclusion was that resistance data on a pediatric age group were not extractable and the report did not meet our criteria for contacting the authors(n=211). We attempted to contact 214 authors and received 70 responses, of which 33 contained unpublished datathat we included in this review.

The 95 studies evaluated 8,351 children with tuberculosis disease who had isolates tested for susceptibility to isoniazid;69 studies (73%) reported at least one child with isoniazid-resistant tuberculosis. The proportion of isoniazid-resistant strains detected among children tested in each study isshown in Table 1.The median proportion of children found to have isoniazid-resistant strains was 8%. The distribution of this proportion was right-skewed: the25th percentile for thisproportion was 0%, and the 75thpercentile was 18%. Figure 2 shows the frequency of studies reporting each proportion of isoniazid resistance.

Studies were classified according to their setting, data source, and restriction(s) on study population (when applicable) (Table 2).Studies reporting results from 57 countries and territories were included.

In 52 of the 71 studies that also reported DST results for drugs other than isoniazid, the majority of children with strains resistant to any drug had isolates resistant to isoniazid.In 35 of the 55 studies that reportedrifampinsusceptibilityresults for children with isoniazid-resistant tuberculosis, the majority of the children with strains resistant to isoniaziddid not have MDR-TB (Figure 3).

DISCUSSION

This is the first systematic review of isoniazid-resistant tuberculosis in children. Longitudinal drug-resistance surveillance data, which are based almost exclusively on isolates obtained in adults,suggesta rising risk of isoniazidresistance for incident tuberculosis casesin many parts of the world.In 51 locations that reported data on isoniazidresistance for at least three time points between 1994 and 2009, 14showedan increasing risk of isoniazidresistance among new tuberculosis cases, while only two showed a decrease.[1]Among the studies that were included in the present analysis, we found a substantial risk of isoniazid resistance among children with tuberculosis disease(Figure 3).This finding has bearing on the treatment of both tuberculosis disease and latent tuberculosisinfection in children.

It is notable that we found only 95 studies (out of over 3000 abstracts screened) from which we could extract a prevalence of isoniazidresistance in a population of children with tuberculosis disease, and that two thirds of these studies included fewer than 50 children (Table 2). The paucity of reporting on anti-tuberculosis drugresistance in children reflects the challenges in diagnosing tuberculosis in children.[107]Bacteriologicconfirmation of tuberculosis in pediatric patients is more difficult than in adults, and the usefulness of sputum-based tests in particular is limitedbecausechildrenfrequently havepaucibacillarydisease and very young children cannotexpectorate.[108]Rapid DNA-based diagnostic approaches have shown some promise for identifying tuberculosis in sputum-smear negative pediatric populations.[108,109] Since the most dominant of these testing modalities relies on identification of mutationsassociated with rifampinresistance, our finding that alarge proportion of children whosetuberculosisstrains haveisoniazidresistance without concurrent rifampin resistance raises concerns about using this approach alone for ensuring that children with tuberculosis disease receive appropriate therapy.

There are two principalconclusions that can be taken from this review of the literature.First are the implications on treatment of active disease and latent infection. We found reports of isoniazid resistance in pediatric tuberculosis patients from around the world, suggesting that clinicians and programs should be aware that this may be an emerging problem for their practice, even if no data have yet been reported from their locale. Adults with isoniazid-resistant tuberculosistreated with four-drug short-course chemotherapy are at higher risk for both treatment failureand amplification of resistance, compared to those with drug-susceptible disease.[6,110,111]Few reports describe treatment outcomes in children with isoniazid mono-resistant disease.[112,113]Indeed, in areas with low prevalence of isoniazid resistance, young children with uncomplicated disease can be treated with three drugs (isoniazid, rifampin, and pyrazinamide) during the intensive phase followed by isoniazid and rifampin only during the continuation phase.[114] However, in areas where the prevalence of isoniazid resistance is high, ifa program uses a three-drug regimen to treat children, a substantial proportion of themmay receive only two effective drugs during the intensive phase of treatment and only one effective drug during the continuous phase.It is therefore important to determine the prevalence of isoniazid resistance in a population and, if this prevalence is high,to use a four-drug regimen for the treatment of children as recommended in the 2010 update of the international treatment guidelines for pediatric tuberculosis.[114]Although clear definitions of the threshold at which isoniazid resistance is considered high have not been established, our finding that a median of 8% of children with tuberculosis disease have isoniazid resistance is cause for a concern.

The widespread presence of isoniazid resistance in children also points to the need for alternative regimens to treat isoniazid-resistant tuberculosis in children. The implications of unrecognized isoniazid resistance for treatment outcomes are best illustrated in tuberculous meningitis. Tuberculous meningitis is a severe manifestation of tuberculosis with disease onset occurringwithin weeks of infection; it is more frequent in young children than in older children and adults, and,if untreated, it is uniformly fatal.[115]Untreated patients diein a median of 20 days.[116]A large cohort study of all tuberculousmeningitis cases reported in the U.S.over 13 years showed that isoniazidresistance was significantly associated with a higher risk of death despite treatmentamong patients who had positive cerebrospinal fluid cultures.[117] However, a study from South Africa,has demonstrated thatalternative regimens that include a number of effective drugs with good cerebrospinal fluid penetration can eliminate the excess risk of child deaths that would be expected when isoniazid-based regimens are used to treat tuberculous meningitis.[113]More work to identify alternative regimens is urgently needed.

In terms of preventive treatment, our reviewsuggeststhat a significant proportion of children with LTBI may require alternativeprophylactic regimens.Most national policies currently indicateisoniazidprophylaxis to treat children with LTBI and child contacts of infectious tuberculosis cases.However, studies in adults have shown isoniazidprophylaxis to be ineffective at preventing tuberculosis disease caused by isoniazid-resistant strains.During an outbreak of isoniazid-resistant tuberculosis in the homeless population of Boston, patients found to be tuberculin skin-test positive and treated prophylactically withrifampin had a significantly reduced occurrence of tuberculosis disease in the follow-up period compared to those who declined prophylaxis, but no reduction was observed among those given a prophylactic regimen consisting ofisoniazidalone.[118]In a study of Southeast Asian refugees who had received isoniazidprophylaxis, almost half of the cases of tuberculosis disease that developed despite prophylaxis had strains resistant to isoniazid.[102]Some evidence exists to support the efficacy of alternative prophylactic regimens for preventing tuberculosis diseasein adolescent contacts of isoniazid-resistant TB cases[119] and child contacts of MDR-TB cases.[120]However, no controlled trials and very few cohort studies have evaluated alternativestrategies in children.[121,122]Our findings suggest that such research is critical.

The second principal conclusion to be taken from this review followsfrom the vast heterogeneity that we observed in the proportion of children with isoniazid-resistant diseaseacross studies. This is a strong reminder thata better understanding of local variability of the burden of pediatric drug-resistant tuberculosis will be critical to guide the decisions of clinicians and programs, such as the choice ofrapid diagnostics,alternative regimens,andthe procurement of specific drugs and pediatric formulations.While there are substantialchallengesin estimating the burden of drug-resistant tuberculosis among adults,[123]the challenges will be even greater for estimating the pediatric burden, given the difficulty of obtaining suitable sputum specimens from children. Thus, our reviewsuggests a need forinnovative efforts toestimate the burden of drug-resistant tuberculosis in pediatric tuberculosis patients specifically.

Our reportis subject to a number of limitations. First, almost 30% of the studies included in the finalstep (data extraction)reported 10 or fewer children who had strains tested for isoniazid resistance. In addition, very few of the reports were true population-based surveys with attempts to do representative sampling. For both these reasons, it is difficult to draw conclusions about the true prevalence of isoniazid resistance in childrenwith tuberculosis in the study locales.Second,because this is the first systematic review of this topic, wedeliberately employed broad inclusion criteria, which resulted indifferences among the populations of children in the included reports. Third, the vast majority of studies did not assess or provide information about the underlying isoniazid-resistance-conferring mutations.

In sum, this systematic review of the available literature shows that isoniazid-resistant tuberculosis in children is a widespread, geographically variable, but poorly quantified phenomenon. A better understanding of this problem is necessary to inform improvements to the management of tuberculosis in children, including optimizing approaches to the treatment of tuberculosis disease and latent infection, and to thedetection of drug resistance. Furthermore, improving access to timely susceptibility testing for at least both isoniazid and rifampin is critical, so that children can receive effective therapy. A one-size-fits-all approach may have deleterious consequences for large numbers of children with tuberculosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the following authors who provided us with additional information not included in their published reports: Ibrahim Abubakar, Dissou Affolabi, VikasAgashe, SohailAkhtar, Abdulrahman A. Alrajhi, Gerardo Amaya Tapia, Jaffar A. Tawfiq, Delphine Antoine, Aparna B. Srikantam, George F. Araj, Adnan Bajraktarevic, Michael Baker, SayeraBanu, D. Bendayan, RutgerBennet, Sonia Borrell, Adrian Canizalez-Roman, M. Donald Cave, A. Chaiprasert, ImaneChaoui, Anne-Sophie Christensen, Helen Cox, Mohammed El Mzibri, LucilaineFerrazoli, Beatriz E. Ferro, Ines Suarez-Garcia, Zoe Gitti, Judith Glynn, Julian González-Martín, Helen Heffernan, Rein Houben, Y.-C. Huang, Kai Man Kam, Michael Kimerling, OzgülKisa, Khin Mar Kyi Win, Rafael Laniado-Laborin, Ana LuísaLeite, Theophile C.E.Liu, AthanasiosMakristhathis, Beatriz Mejuto, Julie Millet, P.R. Narayanan, OhkadoAkihiro , Françoise Portaels, T.Prammananan, NalinRastogi, Leen Rigouts, Camilla Rodrigues, ShubhadaShenai, GirumShiferaw, ArchanaSingal, Rupak Singla, SoumyaSwaminathan, Maria Alice Telles, Aleyamma Thomas, Griselda Tudó, Viral Vadwai, Armand Van Deun, Karin Weyer, Peter C.W. Yip, Takashi

Yoshiyama, and theServizo de Control de Enfermidades Transmisibles, Dirección Xeral de Innovación e Xestión da Saúde Pública, Consellería de Sanidade.

We would also like to thank the following individuals who read articles in foreign languages and helped us to extract data from them:Tara Banani, Vera Bakman, Sophie Becker, YevgenyBrudno, Sun Chung, Anna Drachuk, Nadza Durakovic, Lisa Freinkman, Michinao Hashimoto, JitkaHiscox, Chuan-Chin Huang, CristianJitianu, Maria Joachim, RafalKorytkowski, ViktoriyaLivchits, Karolina Maciag, Aaron Shakow, MatyldaTomaszczyk, Angelique Wils, and Stephanie Wu.

And finally, we would like to thank reference and education librarian Paul Bain for his assistance with developing our search strategy, and Jonathan Eisenberg, Lowell Nicholson, Casey Traylor, and Vanessa Van Doren for research assistance.

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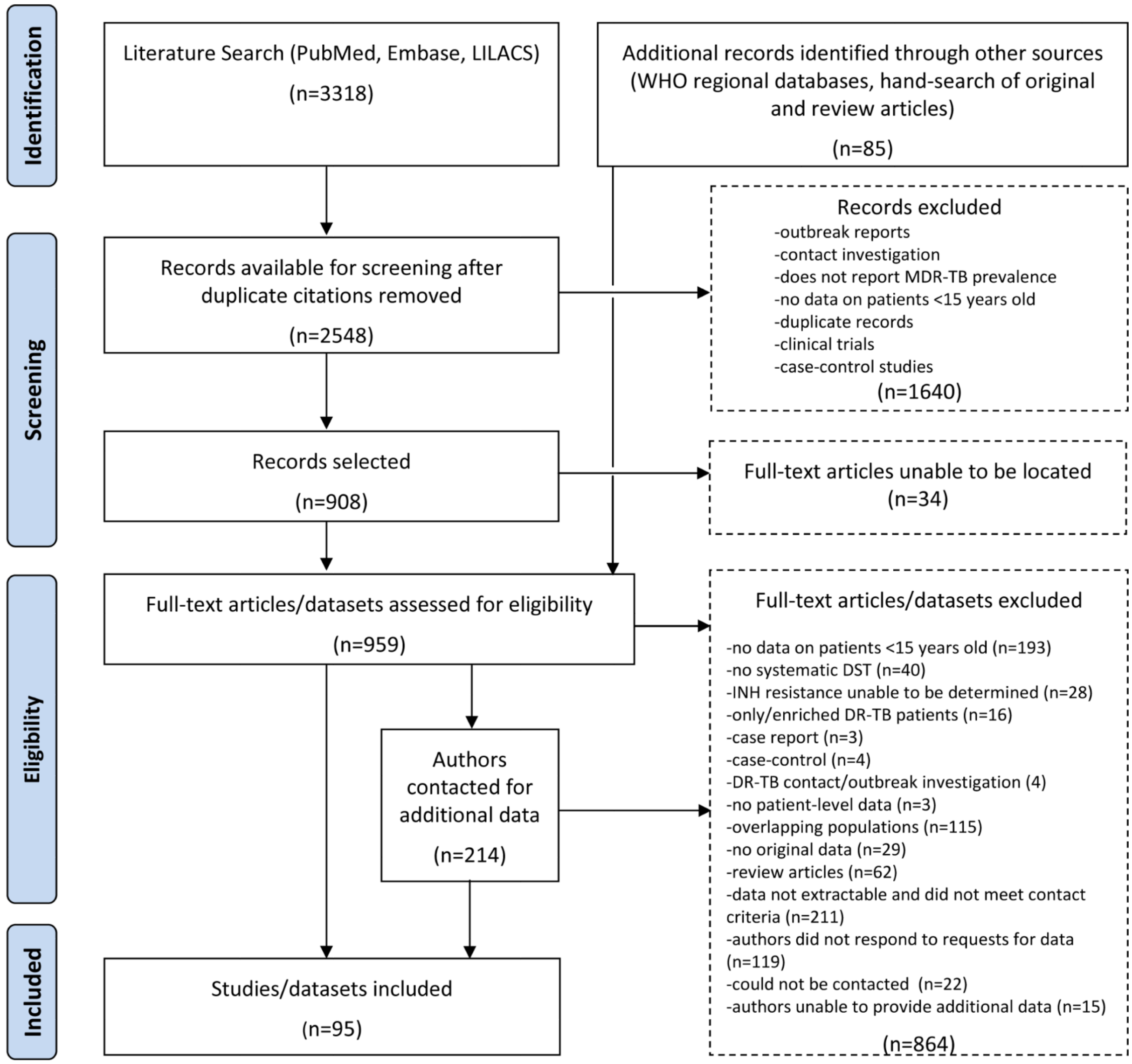

Figure 1.
Search strategy

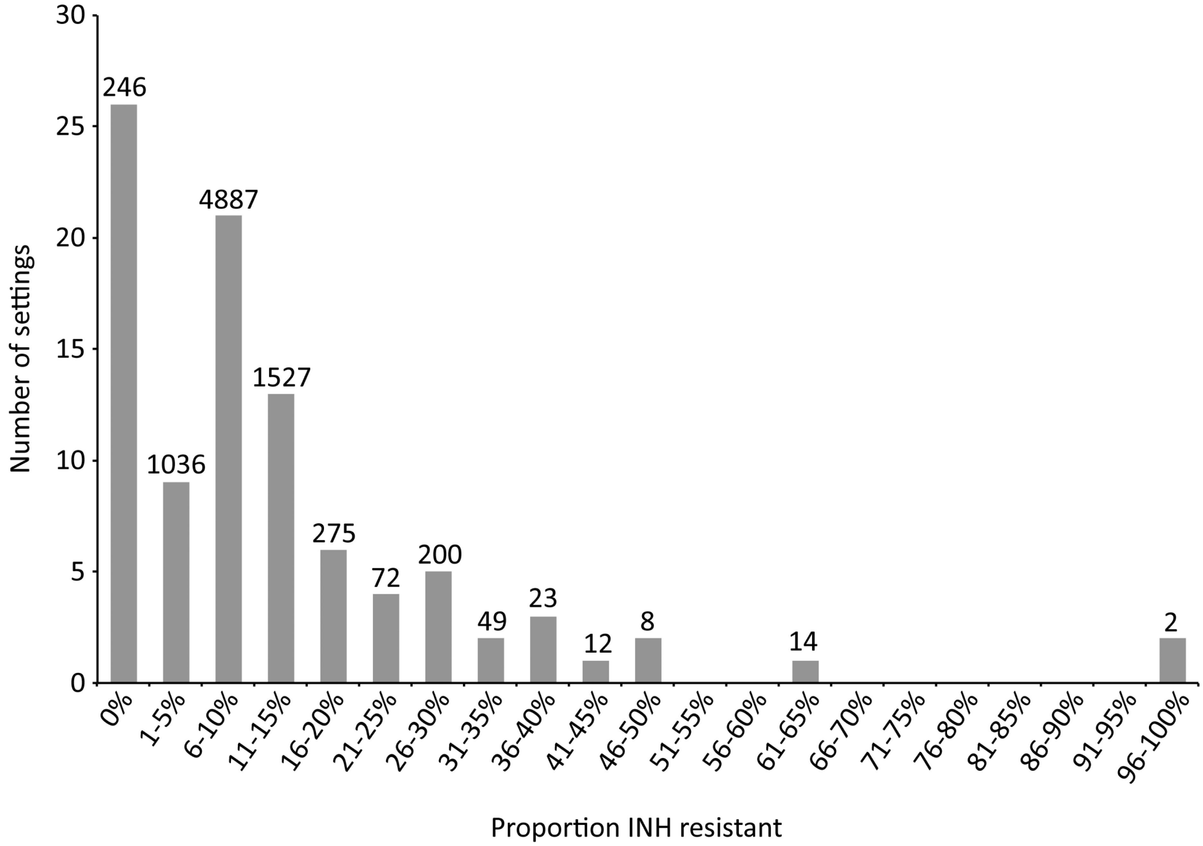

Figure 2.
Frequency distribution of the proportion of children with isoniazid-resistanttuberculosis. Numbers above bars indicate the total number of children contributing to the denominator for each proportion.

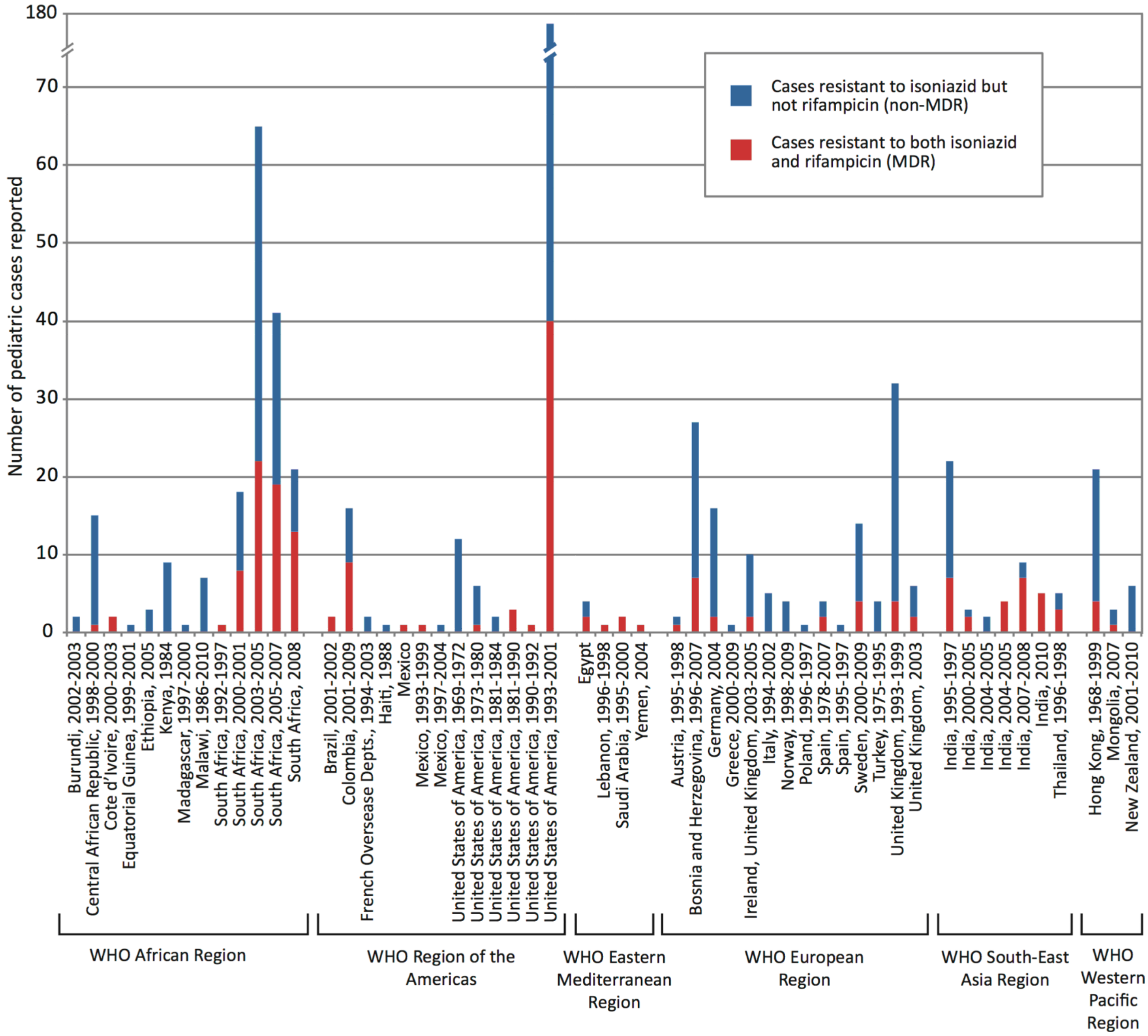

Figure 3.

Number of children with isoniazid-resistant strains with and without concomitant rifampin resistance (MDR-TB), from studies reporting rifampin susceptibility results for all isoniazid-resistant cases.

Table 1

Children with INH-resistant strains among all children with DST results in each of 95 studies

Authors	**Country**	**Years of enrollment**	**INH-resistant cases/cases with DST (%)**
Grosset et al.[12]	Algeria	1963-1966	10/152 (7)
Stauffer et al.[13][†]	Austria	1995-1998	2/108 (2)
Van Deun et al.[14][†]	Bangladesh	2001	0/11 (0)
Bajraktarevic et al.[15][†]	Bosnia and Herzegovina	1996-2007	27/444 (6)
Silveira et al.[16]	Brazil	1963-1970	35/133 (26)
Ferrazoli et al.[17][†]	Brazil	1995-1997	0/4 (0)
Telles et al.[18][†]	Brazil	2000-2002	2/5 (40)
Brito et al.[19]	Brazil	2004-2006	0/1 (0)
Sanders et al.[20][†]	Burundi	2002-2003	2/13 (15)
Farzad et al.[21]	Canada	1993-1994	0/14 (0)
Kassa-Kelembho et al.[22]	Central African Republic	1998-2000	15/165 (9)
Shen et al.[23]	China	2004-2005	0/3 (0)
Llerena et al.[24]	Colombia	2001-2009	16/128 (13)
Elenga et al.[25]	Cote d'lvoire	2000-2003	2/5 (40)
Thomsen et al.[26]	Denmark		0/18 (0)
Christensen et al.[27][†]	Denmark	2000-2008	0/7 (0)
Espinal et al.[28]	Dominican Republic	1994-1995	0/2 (0)
Morcos et al.[29]	Egypt	Unknown	4/73 (0)
Tudo et al.[30][†]	Equatorial Guinea	1999-2001	1/5 (20)
Ejigu et al.[31][†]	Ethiopia	2005	3/11 (27)
Aho et al.[32]	Finland	1959-1961	7/26 (27)
Aho et al.[33]	Finland	1964-1965	1/2 (50)
Breton et al.[34]	France	1952	3/39 (8)
Kaplan et al.[35]	France	1955-1959	9/127 (7)
Brudey et al.[36][†]	French overseas departments	1994-2003	2/16 (13)
Kessler and Bartmann[37]	Germany	1959, 1961, 1962, 1964, 1965	7/48 (15)
Forssbohm et al.[38]	Germany	1997-2000	11/198 (6)
Haas et al.[39]	Germany	2004	16/90 (18)
Gitti et al.[40][†]	Greece	2000-2009	1/12 (8)
Scalcini et al.[41]	Haiti	1988	1/12 (8)
Kam and Yip[42][†]	Hong Kong	1985-1989	21/429 (5)
Swaminathan et al.[43]	India	1995-1997	22/175 (13)
Kumar et al.[44]	India	2000-2005	3/6 (50)
Joseph et al.[45]	India	2004	0/1 (0)
Aparna et al.[46][†]	India	2004-2005	2/22 (9)
Baveja et al.[47]	India	2004-2005	4/22 (18)
Agashe et al.[48][†]	India	2007-2008	9/14 (64)
Vadwai et al.[49][†]	India	2010	5/12 (42)
Romano et al.[50]	Italy	1994-2002	5/13 (38)
Osato et al.[51]	Japan	1964-1968	3/95 (3)
Tuberculosis research committee (Ryoken)[52][†]	Japan	2002	0/7 (0)

†Unpublished data received from author(s)

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Table 2

Characteristics of the 95 studies that met inclusion criteria

Reports included	95
Countries and territories included	57
Year range during which data were collected	1952-2010
Total pediatric patients with drug-susceptibility testing (DST) results for at least isoniazid and rifampicin	8351
New (%)	2980 (36)
Previously treated (%)	226 (3)
Unknown/unspecified treatment history (%)	5145 (62)

	Number of reports (%)	Number of pediatric patients (%)
Number of pediatric patients with DST results per report		
0-10	28 (29)	114 (1)
11-50	35 (37)	749 (9)
51-100	14 (15)	1128 (14)
101-500	15 (16)	2802 (34)
>500 (max. 2,456)	3 (3)	3558 (43)
Source of data used in report		
Reported surveillance data	20 (21)	3908 (47)
Hospital records	48 (51)	2736 (33)
Laboratory records	9 (9)	802 (10)
Representative population sample	9 (9)	270 (3)
Other or not specified	4 (4)	542 (6)
Reports with restricted study populations*	32 (34)	720 (9)

*Includes study populations restricted to patients with pulmonary TB, smear positive TB, extrapulmonary TB, TB meningitis, TB pleurisy, or HIV coinfection; patients with no previous treatment, patients who failed treatment, or patients on DOTS treatment; patients with HIV-infected family member(s); refugees; and/or contacts of source cases with DST results.