Ongoing challenges to understanding multidrug- and rifampicin-resistant tuberculosis in children *versus* adults

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Globally, the odds of drug resistance among those with TB are the same for children as for adults. However, setting-specific heterogeneity requires further investigation. Where temporal comparison is possible, the odds are stable or decreasing. https://bit.ly/2DSvzt3

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ABSTRACT Previous analyses suggest that children with tuberculosis (TB) are no more or no less likely to have multidrug (MDR)- or rifampicin-resistant (RR)-TB than adults. However, the availability of new data, particularly for high MDR/RR-TB burden countries, suggest updates of country-specific estimates are warranted.

We used data from population-representative surveys and surveillance collected between 2000 and 2018 to compare the odds ratio of MDR/RR-TB among children (aged <15 years) with TB, compared to the odds of MDR/RR-TB among adults (aged ⩾15 years) with TB.

In most settings (45 out of 55 countries), and globally as a whole, there is no evidence that age is associated with odds of MDR/RR-TB. However, in some settings, such as former Soviet Union countries in general, and Georgia, Kazakhstan, Lithuania, Tajikistan and Uzbekistan in particular, as well as Peru, MDR/RR-TB is positively associated with age ⩾15 years. Meanwhile, in Western Europe in general, and the United Kingdom, Poland, Finland and Luxembourg in particular, MDR/RR-TB is positively associated with age <15 years. 16 countries had sufficient data to compare over time between 2000–2011 and 2012–2018, with evidence for decreases in the odds ratio in children compared to adults in Germany, Kazakhstan and the United States of America.

Our results support findings that in most settings a child with TB is as likely as an adult with TB to have MDR/RR-TB. However, setting-specific heterogeneity requires further investigation. Furthermore, the odds ratio for MDR/RR-TB in children compared to adults is generally either stable or decreasing. There are important gaps in detection, recording and reporting of drug resistance among paediatric TB cases, limiting our understanding of transmission risks and measures needed to combat the global TB epidemic.

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Introduction

The World Health Organization (WHO) estimated that as many as 484 000 of an estimated 10 million incident tuberculosis (TB) cases had multidrug-resistant (MDR; *i.e. Mycobacterium tuberculosis* resistant to both rifampicin and isoniazid) or rifampicin-resistant (RR) TB in 2018. Because mortality and treatment failure rates of those with MDR/RR-TB are significantly higher than in drug-susceptible TB [1], and treatment of MDR/RR-TB requires the use of expensive, toxic drugs over extended periods of time, there is a need to better understand potential risk factors for MDR/RR-TB and trends in these over time.

TB disease may occur as a result of rapid progression after infection (within weeks to months), or many years or even decades after initial infection. Disease in young children must be the result of infection with more recently circulating *M. tuberculosis* strains. However, disease in adults can be the result of either recent or much older infections. In the case of drug resistance, it is also important to consider the possibility that the apparent burden of MDR/RR-TB among previously treated individuals (who are predominantly adults) may reflect either primary transmission of resistant strains or the emergence of acquired resistance during inadequate treatment. Thus, we would expect that the risk of MDR/RR-TB among children would be more sensitive than among adults to changing patterns of drug resistance in the circulating population of *M. tuberculosis* strains [2]. A systematic review of available data in 2014 [3] showed that the prevalence of MDR/RR-TB among TB cases in children is the same as the prevalence among treatment-naïve adults. We would expect the prevalence in both of these groups to be a result of transmission of drug-resistant strains as opposed to emergence of acquired drug-resistance during treatment. Meanwhile, a previous evaluation (2013) of global surveillance data reached similar conclusions [4]. One area of concern was the potential for an association between age and MDR-TB in southern African countries with a high HIV prevalence, although evidence to support this was somewhat limited at the time [4]. Since that time, with the introduction and roll-out of the rapid molecular cartridge-based assay, Xpert MTB/RIF, more comprehensive data from a greater number of countries have become available. However, diagnosing and ensuring access to appropriate treatment for MDR/RR-TB still remains a challenge, particularly for children [5], with the vast majority of cases unlikely to be detected [2, 6]. There is a critical need to better characterise the burden and transmission risks of MDR/RR-TB in children.

Here, we re-examine country-level data to assess the burden of MDR/RR-TB in children compared to adults, including evaluating (where possible) how this has changed over time and what the implications of this could be.

Methods

Data selection

WHO reports annually on aggregated drug resistance surveillance data collected at a national or a representative subnational level, ensuring data quality and representativeness. The data are collected through continuous surveillance of drug resistance by routinely conducting drug susceptibility testing (DST) on the majority of TB patients, or if the coverage of DST is not sufficient (<80% of bacteriologically confirmed pulmonary TB cases are tested for at least rifampicin resistance), *via* periodic drug resistance surveys of a nationally representative sample of patients, ideally repeated at least every 5 years [7]. Data for all TB patients (both new and previously treated patients combined) are captured, identifying the numbers of individuals in each age group (children aged <15 years or adults aged ⩾15 years) that are either resistant or susceptible to isoniazid and rifampicin. From 2016 onwards, only rifampicin is captured, a change which reflects an increased use of the Xpert MTB/RIF assay for *M. tuberculosis* diagnosis and DST. Age-disaggregated data are not further disaggregated by previous treatment history.

We excluded data where the coverage of DST among new bacteriologically confirmed cases was <80%, where drug resistance was not reported separately for children and adults, or where age-disaggregated drug-resistance data were available, but no paediatric cases of MDR/RR-TB had been detected.

Analysis

We calculated the odds ratio for MDR/RR-TB for children (aged <15 years) compared to adults (aged ⩾15 years) by country, where the odds ratio is given by:

$$\mathrm{OR} = \frac{\text{odds of MDR / RR} - \text{TB in children with TB}}{\text{odds of MDR / RR} - \text{TB in adults with TB}},$$

$$= \frac{(\text{notified children with MDR/RR-TB}) * (\text{notified adults with TB and a DST result but not MDR/RR-TB})}{(\text{notified children with TB and a DST result but not MDR/RR-TB}) * (\text{notified adults with MDR/RR-TB})}$$

We calculated 95% confidence intervals using the standard error of the log odds ratio. We used a random-effects meta-analysis in the meta package in R [8] to analyse available data across WHO regions,

dividing the European Region into the former Soviet Union and Western Europe, given that the percentage of new and previously treated TB cases with MDR/RR-TB in these two regions is markedly different [1] due to historic treatment and health system approaches.

Temporal change

We calculated the odds ratio for the periods 2000–2011 and 2012–2018. This represents recent data compared to when the odds ratio for MDR/RR-TB in children compared to adults in surveillance data was last evaluated by Zignol *et al.* [4], since which time, Xpert MTB/RIF testing has been introduced. To establish evidence for a trend, we used a likelihood ratio test to assess for an interaction between age group and year at various levels of confidence, noting strong evidence for a change in odds ratio (99% confidence), evidence (95%), weak evidence (90%) and very weak evidence (85%).

A changing odds ratio can be interpreted in different ways, implying different combinations of increasing or decreasing drug-susceptible and MDR/RR-*M. tuberculosis* transmission, which we outline in table 1, building on previously established concepts [9]. We show in the supplementary material that the link between changes in the odds ratio and recent transmission of MDR/RR-TB are not necessarily intuitive.

Results

Selection of countries

Of the 212 countries and territories reporting TB data to WHO, 71 did not have any high-quality MDR/RR-TB data from 2000 to 2018. Of the remaining 141 countries with good-quality data, 86 had age-disaggregated data, but reported no paediatric MDR/RR-TB cases, suggesting potential sample-size limitations in some of the 31 of these that relied on survey data. This left 55 countries with good-quality age-disaggregated data for MDR/RR-TB (figure 1).

When comparing data over the two different time periods, 39 out of 55 countries had either age-disaggregated data available for one period and not the other, and/or paediatric MDR/RR-TB cases reported in one period and not the other. 19 of these countries relied on periodic surveys.

In total, 16 countries recorded paediatric MDR/RR-TB cases in both 2000–2011 and 2012–2018; Austria, Belarus, Belgium, Germany, Kazakhstan, Latvia, Namibia, the Netherlands, Poland, Republic of Moldova, Spain, Sweden, Switzerland, the United Kingdom (UK), the United States of America (USA) and Uzbekistan. In all except Namibia and Uzbekistan, where surveys were conducted, these data were derived from continuous surveillance.

Odds ratios

Aggregated odds ratios by country are shown in table 2, where there were a total of 9922 DST results for children and 605 089 for adults. Of the 55 included countries, there is strong evidence of odds ratios <1 (MDR/RR-TB is positively associated with age ⩾15 years) in Georgia, Kazakhstan, Lithuania, Peru, Tajikistan and Uzbekistan, and of odds ratios >1 (MDR/RR-TB is positively associated with age <15 years) in the UK and Poland. In addition, there is weak evidence of odds ratios >1 in Finland and Luxembourg.

TABLE 1 Potential scenarios indicated by changes in the odds ratio (OR) in children *versus* adults

	DS-TB transmission	MDR/RR-TB transmission
OR decrease (↓)		
Scenario 1	↑	↓
Scenario 2	↑↑	↑
Scenario 3	↓	↓↓
OR increase (↑)		
Scenario 4	↓	↑
Scenario 5	↑	↑↑
Scenario 6	↓↓	↓

These include whether transmission is increasing or decreasing for drug-susceptible (DS)-tuberculosis (TB) and multidrug-resistant (MDR) or rifampicin-resistant (RR)-TB, and how the magnitude in this change compares for DS-TB *versus* MDR/RR-TB. Arrows indicate whether transmission is increasing (↑) or decreasing (↓), where multiple arrows indicate that a greater change in transmission is likely (but not guaranteed) to have taken place. See supplementary material for further details.

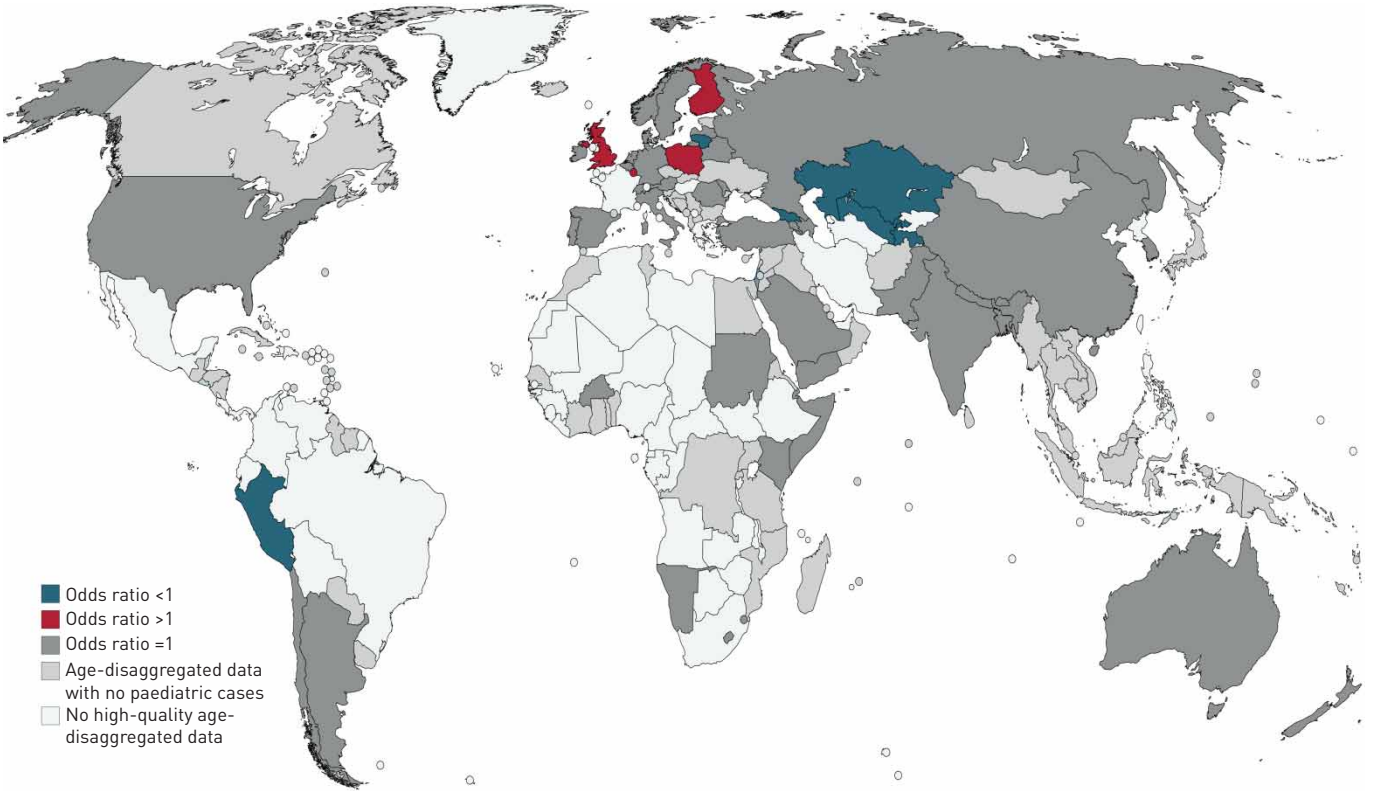

FIGURE 1 Countries with World Health Organization-reported drug resistance survey/surveillance data for 2000–2018 disaggregated by age (children aged <15 years or adults aged ⩾15 years), showing evidence for the odds ratio for multidrug-resistant (MDR) or rifampicin-resistant (RR)-tuberculosis (TB) in children *versus* adults being different to 1, *i.e.* an association between age and MDR/RR-TB.

A forest plot of the odds ratio by WHO region is shown in figure 2, where we split the WHO European Region into a former Soviet Union region (which included Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Russia, Tajikistan, Turkmenistan, Ukraine and Uzbekistan) and a Western Europe region (all other countries from the WHO European Region). There was strong evidence for an odds ratio <1 in the former Soviet Union at 0.50 (95% CI 0.41–0.60), and evidence for an odds ratio >1 in the Western Europe region at 1.34 (95% CI 1.06–1.70). There was weak evidence for an odds ratio >1 in the WHO Western Pacific Region at 1.76 (95% CI 1.00–3.09), and very weak evidence in the African Region at 1.37 (95% CI 0.89–2.11). Globally, there was no evidence for an odds ratio significantly different to 1, at 1.11 (95% CI 0.92–1.33).

Of the 16 countries with data for both 2000–2011 (when there were 3564 DST results for children and 166 726 for adults in the 16 countries considered here) and 2012–2018 (2460 DST results for children and 159 150 for adults) in the majority (n=9), confidence intervals were too wide to show evidence of a changing odds ratio over time (figure 3; further details in the supplementary material). We found strong evidence for decreases in the odds ratio of MDR/RR-TB in children compared with adults between 2000–2011 and 2012–2018 in three countries: Germany (1.64 (95% CI 1.12–2.39) in 2000–2011, decreasing to 0.26 (95% CI 0.07–1.07) in 2012–2018); Kazakhstan (from 1.03 (95% CI 0.71–1.5) to 0.38 (95% CI 0.31–0.45)); and the USA (from 2.35 (95% CI 1.45–3.80) to 0.63 (95% CI 0.28–1.42)). We found weak evidence for an increasing odds ratio in Belgium (significant at a 90% level of confidence), and very weak evidence for a declining odds ratio in Belarus, Namibia and Uzbekistan (significant at an 85% level of confidence), with no evidence for a changing odds ratio in the remaining nine countries. In a random-effects meta-analysis with all included countries, the mean odds ratio decreased from 1.39 (95% CI 1.05–1.84) in the 2000–2011 period to 0.72 (95% CI 0.49–1.06) in the 2012–2018 period.

In an analysis of the WHO European Region, as described earlier we divided it into Western Europe (comprised here of Austria, Belgium, Germany, the Netherlands, Poland, Spain, Sweden, Switzerland and the UK) and the former Soviet Union (comprised of Belarus, Kazakhstan, Latvia, Republic of Moldova and Uzbekistan). We found no evidence for a changing odds ratio in Western Europe (1.63 (95% CI 1.27–2.10) compared to 1.18 (95% CI 0.68–2.07)). However, there was evidence for a decreasing odds ratio in the former Soviet Union (from 0.95 (95% CI 0.72–1.26) to 0.43 (95% CI 0.31–0.60)), although this was no

TABLE 2 Countries with at least one paediatric multidrug-resistant (MDR)- (pre-2016) or MDR/rifampicin-resistant (RR)-tuberculosis (TB) (post-2016) case, identifying years with age disaggregation with and without paediatric cases

	Year/s with paediatric case/s	Year/s without paediatric case/s	Cases tested (and identified) for isoniazid and rifampicin[#] resistance n		Pooled OR (95% CI)
			Age <15 years	Age ⩾15 years	
Argentina	2005		17 (1)	793 (35)	1.35 (0.17–10.5)
Armenia	2016	2007, 2017	9 (2)	1772 (424)	0.91 (0.19–4.39)
Australia	2005, 2008, 2011	2002–2004, 2012–2015, 2017	172 (4)	7227 (170)	0.99 (0.36–2.70)
Austria	2006, 2012	2000–2005, 2007, 2008, 2011, 2013–2015	227 (5)	7151 (177)	0.89 (0.36–2.18)
Azerbaijan	2007		11 (3)	1090 (428)	0.58 (0.15–2.20)
Bangladesh	2011		13 (1)	1331 (98)	1.05 (0.13–8.15)
Belarus	2011, 2014–2017	2010	72 (27)	12037 (5581)	0.69 (0.43–1.12)
Belgium	2002, 2003, 2005, 2012–2014	2001, 2004, 2006–2008, 2011, 2015	353 (7)	9068 (185)	0.97 (0.45–2.08)
Bhutan	2017		3 (1)	382 (52)	3.17 (0.28–35.62)
Burkina Faso	2017		9 (1)	1131 (40)	3.41 (0.42–27.92)
Chile	2015	2014, 2017	66 (1)	4410 (77)	0.87 (0.12–6.32)
China	2013	2002, 2004, 2005	47 (2)	12509 (951)	0.54 (0.13–2.23)
Denmark	2006	2002, 2003, 2004, 2005, 2007, 2008, 2011–2015, 2017	145 (1)	3332 (23)	1.00 (0.13–7.45)
Djibouti	2015		11 (1)	355 (32)	1.01 (0.13–8.14)
Eswatini	2017	2018	127 (6)	3305 (286)	0.52 (0.23–1.20)
Finland	2012, 2014	2000–2003, 2004, 2005, 2006, 2007, 2008, 2011, 2013, 2015–2017	45 (2)	4176 (52)	3.69 (0.87–15.63)
Georgia[¶]	2013–2017	2006, 2011, 2012	99 (8)	16922 (2805)	0.44 (0.21–0.91)
Germany	2001–2008, 2011, 2015	2012–2014	1042 (31)	43419 (1066)	1.22 (0.85–1.75)
Hong Kong	2017	2005, 2007, 2008, 2011	93 (1)	14614 (124)	1.27 (0.18–9.19)
India	2006	2004	36 (1)	2799 (220)	0.33 (0.05–2.46)
Ireland	2007	2000, 2001, 2002, 2003–2006, 2011–2013, 2014, 2015	51 (1)	2892 (35)	1.63 (0.22–12.15)
Israel	2013	2008, 2011, 2012, 2014–2017	31 (1)	1568 (86)	0.57 (0.08–4.26)
Italy	2012	2015	65 (2)	3104 (101)	0.94 (0.23–3.91)
Kazakhstan[¶]	2011–2013, 2015		663 (201)	43401 (20735)	0.48 (0.40–0.56)
Kenya	2014		37 (1)	1780 (13)	3.78 (0.48–29.64)
Latvia	2002–2006, 2008, 2012	2007, 2011, 2013–2016, 2017	151 (19)	11347 (1618)	0.87 (0.53–1.40)
Lesotho	2014		18 (2)	1843 (68)	3.26 (0.74–14.48)
Lithuania[¶]	2006, 2008, 2011	2003–2005, 2007, 2012–2015, 2017	64 (5)	17371 (3474)	0.34 (0.14–0.85)
Luxembourg	2011	2000–2006, 2012, 2014	9 (1)	310 (4)	9.56 (0.96–95.48)
Namibia	2008, 2015		92 (7)	4340 (227)	1.49 (0.68–3.26)
Nepal	2011	2007	29 (1)	1681 (82)	0.70 (0.09–5.18)
The Netherlands	2002, 2011, 2016	2000, 2001, 2003–2008, 2012–2015, 2017	228 (3)	9727 (133)	0.96 (0.30–3.04)
New Zealand	2005	2004, 2006, 2007, 2008, 2009, 2011, 2012	64 (1)	1931 (22)	1.38 (0.18–10.38)
Norway	2000, 2007, 2008	2001–2006, 2011–2015, 2017	121 (3)	3198 (65)	1.23 (0.38–3.96)
Pakistan	2013		37 (1)	1513 (91)	0.43 (0.06–3.20)
Peru[¶]	2014–2016	2006	1203 (58)	51418 (4060)	0.59 (0.45–0.77)
Poland[¶]	2011, 2012, 2016	2013–2015, 2017	97 (3)	30207 (280)	3.41 (1.07–10.83)
Portugal	2005, 2011	2000–2004, 2006–2008, 2012	159 (2)	15932 (312)	0.64 (0.16–2.58)
Republic of Korea	2016	2017	56 (2)	33526 (1539)	0.77 (0.19–3.16)
Republic of Moldova	2006, 2011, 2012, 2015–2017		47 (14)	13408 (5350)	0.64 (0.34–1.20)
Romania	2015–2017		131 (5)	24688 (1499)	0.61 (0.25–1.50)
Russian Federation	2004	2003, 2005, 2006	5 (1)	2733 (532)	1.03 (0.12–9.27)
Saudi Arabia	2010		82 (2)	1822 (74)	0.59 (0.14–2.45)
Somalia	2011		12 (1)	918 (86)	0.88 (0.11–6.89)
Spain	2002, 2015	2003–2005	101 (2)	3515 (85)	0.82 (0.20–3.36)
Sudan	2017		14 (2)	1210 (67)	2.84 (0.62–12.96)

Continued

TABLE 2 Continued

	Year/s with paediatric case/s	Year/s without paediatric case/s	Cases tested (and identified) for isoniazid and rifampicin[#] resistance n		Pooled OR (95% CI)
			Age <15 years	Age ⩾15 years	
Sweden	2002, 2007, 2011, 2014	2000, 2001, 2003–2006, 2008, 2012, 2013, 2015, 2017	197 (8)	5565 (127)	1.81 (0.87–3.76)
Switzerland	2005, 2012	2000–2004, 2006, 2008, 2011, 2013–2015	126 (2)	5285 (99)	0.84 (0.21–3.46)
Tajikistan[¶]	2014, 2017	2009	422 (40)	5291 (1074)	0.41 (0.29–0.57)
Turkey	2012, 2013, 2015–2017	2011, 2014	363 (14)	27121 (1217)	0.85 (0.50–1.46)
United Kingdom[¶]	2001–2008, 2011, 2012	2000, 2013–2015, 2017	1193 (27)	56905 (664)	1.96 (1.33–2.89)
United States of America	2005, 2007, 2011–2014	2015–2017	1231 (24)	62858 (892)	1.38 (0.92–2.08)
Uzbekistan[¶]	2011, 2017	2005	204 (23)	7643 (2287)	0.30 (0.19–0.46)
Vanuatu	2017		1 (1)	45 (0)	
Yemen	2011		22 (1)	1215 (31)	1.82 (0.24–13.95)

[#]: rifampicin only for 2016–2018; [¶]: 95% confidence interval for the odds ratio for MDR/RR-TB for children (age <15 years) compared to adults (⩾15 years) not overlapping 1.

longer the case if data from Kazakhstan were removed (from 0.85 (95% CI 0.54–1.35) to 0.48 (95% CI 0.27–0.84)).

Discussion

In most settings (45 out of 55 countries with high-quality data and reporting paediatric cases of MDR/RR-TB), and globally as a whole, there is no evidence that age is associated with odds of MDR/RR-TB. However, in some settings such as the former Soviet Union countries in general, and Georgia, Kazakhstan, Lithuania, Tajikistan and Uzbekistan in particular, as well as Peru, MDR/RR-TB is positively associated

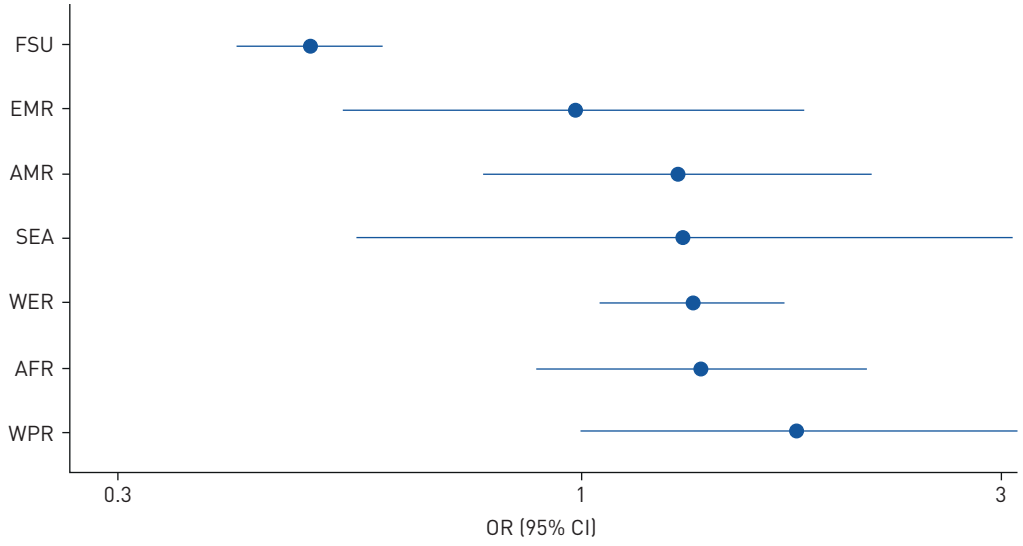

FIGURE 2 Forest plot showing odds ratios and 95% confidence intervals for multidrug-resistant or rifampicin-resistant tuberculosis in children (age <15 years) *versus* adults (age ⩾15 years) by World Health Organization region, with the European Region separated into the former Soviet Union (FSU) and Western Europe (WER). EMR: Eastern Mediterranean Region; AMR: Region of the Americas; SEA: South-East Asia Region; AFR: African Region; WPR: Western Pacific Region. Data among all (new and re-treated) cases are presented.

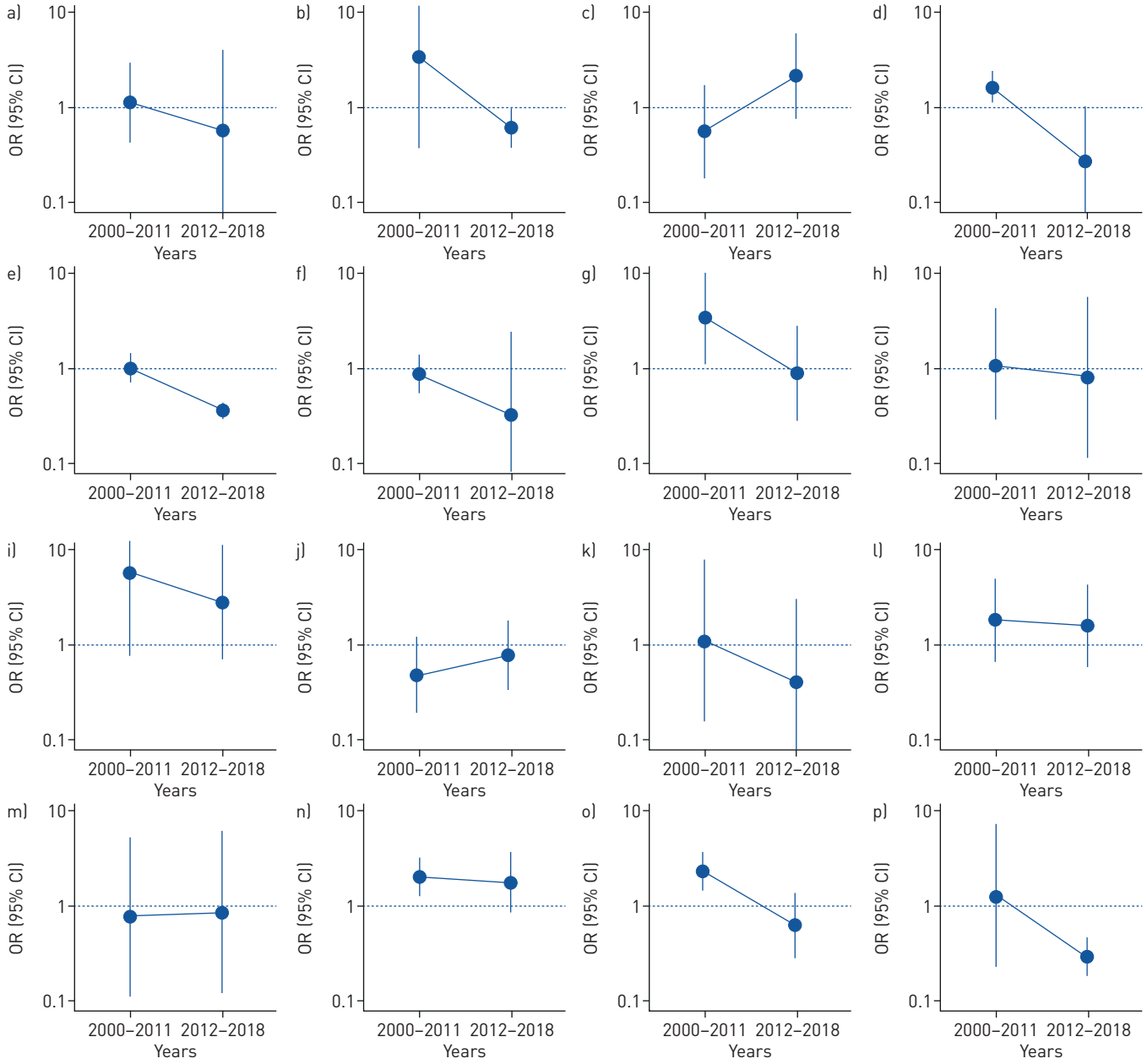

FIGURE 3 Trends over time in odds ratios for multidrug-resistant or rifampicin-resistant tuberculosis in children (age <15 years) *versus* adults (age ⩾15 years) using 95% confidence intervals. a) Austria; b) Belarus; c) Belgium; d) Germany; e) Kazakhstan; f) Latvia; g) Namibia; h) the Netherlands; i) Poland; j) Republic of Moldova; k) Spain; l) Sweden; m) Switzerland; n) United Kingdom; o) United States of America; and p) Uzbekistan.

with age ⩾15 years. Meanwhile, in the rest of Europe in general, and the UK, Poland, Finland and Luxembourg in particular, MDR/RR-TB is positively associated with age <15 years. In addition, there is weak evidence that MDR/RR-TB is positively associated with age <15 years in the Western Pacific and African regions, which warrants further investigation.

16 countries, primarily located in the WHO European Region, had sufficient data to compare the change over time between 2000–2011 and 2012–2018. We found strong evidence for decreases in the odds ratio of MDR/RR-TB in children compared to adults in Germany, Kazakhstan and the USA, and very weak evidence for a decline in Belarus, Namibia and Uzbekistan. At the same time, total TB incidence was decreasing, suggesting that transmission of drug-susceptible TB was decreasing (scenario 3 in table 1; supplementary material). This may mean that MDR/RR-TB transmission may have been decreasing over time in those settings (further details in the supplementary material), although we note that the low number of children with MDR/RR-TB in particular means that it is difficult to draw broad conclusions

about changes in transmission. Unfortunately, weak evidence for an increasing odds ratio in Belgium is difficult to interpret and could reflect either an increase or decrease in MDR/RR-TB transmission (scenarios 4 or 6 in table 1). As a caveat, we note that in countries where a large fraction (often the majority) of TB occurs among foreign-born individuals, the interpretation of the odds ratio as a measure of the relative risk of local transmission of MDR/RR-*M. tuberculosis versus* drug-susceptible *M. tuberculosis* is probably not valid. In Germany, the USA and Belgium in particular, low rates of local transmission [10] mean that changes in the odds ratio reflect changes that are happening outside those countries.

In general agreement with previous research [3, 4], we find that in the majority of settings, there is no evidence that the odds of MDR/RR-TB for children are likely to be different to adults. The inclusion of data from an additional 20 countries, including seven high MDR/RR-TB burden countries not previously considered, totalling an additional 3852 (63%) children and 288 113 (91%) adults, strengthens these findings. In addition, we find some very weak evidence to support previous concerns over the odds for children in southern African countries with a high HIV burden, such as Namibia, Lesotho and Eswatini, although data for these countries remain limited and it is difficult to draw broad conclusions. Indeed, only in Western Europe, a setting with very low numbers of MDR/RR-TB cases [1], is there evidence of worse odds for children than adults, in line with previous findings from >5 years ago [4]. We do find that the odds for children compared to adults may be setting-specific, with evidence that children have much lower odds of MDR/RR-TB in countries of the former Soviet Union (where higher-quality data are more widely available), an aspect that had not previously been identified. As such, previous calculations [3, 6, 11] of the number of children with MDR/RR-TB in these high MDR/RR-TB burden settings may have been overestimated. In addition, several settings, particularly Western Europe, but also the Western Pacific and Africa Regions, require further investigation to identify whether children do indeed have higher odds of MDR/RR-TB in these settings, and if so, why.

However, we note that interpretation of our results is based on the implicit assumption that the odds ratio calculated reflects the ratio of actual MDR/RR-TB burden in children compared to adults. In reality, our results are only for the subset of cases for whom DST results are available, which is particularly challenging in children [2]. If the case-detection ratio for MDR/RR-TB compared to DS-TB is different for adults than children, then the odds we calculate could be biased upward or downward. Examples of such biases include rigorousness of DST testing for children (who are less likely to obtain bacteriological confirmation than adults), particularly if this increases for household contacts of MDR/RR-TB cases, and systematic screening in adult populations with a high MDR/RR-TB prevalence, such as prison populations in the former Soviet Union. The latter could explain the high odds of MDR/RR-TB in adults in the former Soviet Union. The available data do not allow us to determine the magnitude of these detection biases in our analysis.

Beyond these biases, in some settings such as the former Soviet Union clustering of MDR/RR-TB cases in certain settings composed of adults, notably prisons [12], could explain why adults have higher odds of MDR/RR-TB. Meanwhile, high odds of MDR/RR-TB for children in Western Europe, where DST rates are high [1], could represent an association that data elsewhere is not representative enough to identify. Potentially high odds of MDR/RR-TB for children in the Western Pacific and African regions are worrying, where the latter and its potential interaction with HIV has been previously identified as a concern [4]. However, the evidence from our results here is weak, and requires further investigation.

Where there are data to compare any change over time, in many cases the odds for children compared to adults are either unchanged or improving. Given the potential importance of children as sentinels for TB transmission [2], this is in line with a comparatively stable MDR/RR-TB incidence globally [1], although more evidence is required before conclusions can be drawn. Indeed, we note that this lack of statistical significance for country-specific odds is not necessarily an indication of a similar force of infection for children and adults, but may reflect limitations in available data, particularly the low number of recorded children with MDR/RR-TB.

As mentioned earlier, differences in case detection remain a further limitation of our study; namely, changes in the TB diagnostic algorithm over time may have been implemented differently among children compared to adults. In particular, the adoption of Xpert MTB/RIF as the initial diagnostic test in place of smear microscopy may have been more common in children, due to resource limitations in some settings preventing testing of all patient groups. The available data do not allow an assessment of how the proportion of bacteriologically confirmed cases for which DST was performed has changed over time for children compared to adults. At the same time, as in work by Zignol *et al.* [4], we were not able to separate treatment-naïve from previously treated cases in our data, where, as previously noted, the latter are more likely to be adults. In comparison, Jenkins *et al.* [3] compare children to treatment-naïve adults only, finding no difference. In our results, in addition to both previous instances, there is no evidence for a difference in

odds by age, suggesting that either the importance of resistance acquisition in adults due to previous treatment is limited, or, more likely, that additional evidence is required to better understand the odds.

Finally, our analysis included data from only 13 of the 30 high MDR/RR-TB burden countries defined by WHO for the period of 2016–2020, and only four had data available for both time periods examined, namely, Belarus, Kazakhstan, Republic of Moldova and Uzbekistan. Half of the world's estimated incident RR-TB cases in 2018 were found in India, China and the Russian Federation, yet only limited high-quality data were available; indeed, in each country there was only 1 year where any paediatric MDR/RR-TB cases were reported. These gaps highlight the urgent need to strengthen diagnostic capacity through expanded sample referral systems and laboratory networks. Countries should strive towards achieving universal DST for all people with TB, as called for in WHO's End TB Strategy [13]. This should be coupled with the establishment of electronic case-based surveillance systems which would allow for finer age disaggregation than the cut-off of 15 years of age that we use here, allowing for comparisons in risk between groups such as younger children, adolescents and older adults. Without these advances in diagnosis, recording and reporting of cases in children, we cannot fully understand the burden and transmission risks of MDR/RR-TB in children, or trends in these over time.

Conclusion

Our results support previous findings that, in most settings, there is no evidence for a difference in odds of MDR/RR-TB for children compared to adults; a child with TB is as likely as an adult with TB to have MDR/RR-TB. However, there is evidence of setting-specific heterogeneity in the former Soviet Union and Western Europe, as well as weak evidence in the Western Pacific and African Regions. For the small number of countries where sufficient data are available, the odds ratio for MDR/RR-TB in children compared to adults is generally either stable or decreasing, which is in line with the stable incidence of MDR/RR-TB at the global level. This analysis highlights important gaps in the detection, recording and reporting of drug resistance among paediatric TB cases, limiting our understanding of transmission risks and measures needed to combat the global TB epidemic.

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