EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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

C. Finn McQuaid, Ted Cohen, Anna S. Dean, Rein M.G.J. Houben, Gwenan M. Knight, Matteo Zignol, Richard G. White

Please cite this article as: McQuaid CF, Cohen T, Dean AS, *et al*. Ongoing challenges to understanding multidrug and rifampicin-resistant tuberculosis in children *versus* adults. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02504-2020).

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

Authors: C Finn McQuaid[1](PhD), Ted Cohen[2](DPH), Anna S Dean[3](PhD), Rein M G J Houben[1](PhD), Gwenan M Knight[1](PhD), Matteo Zignol[3](MD), Richard G White[1](PhD)

Affiliations:

[1]TB Modelling Group, TB Centre and Centre for Mathematical Modelling of Infectious Diseases, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Yale School of Public Health, Laboratory of Epidemiology and Public Health, New Haven, CT, USA

[3] Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland

Corresponding author: C. Finn McQuaid

Address: London School of Hygiene and Tropical Medicine, Keppel Street, WC1E 7HT, London, United Kingdom. finn.mcquaid@lshtm.ac.uk. +44 (0)20 7636 8636

Previous analyses suggest children with tuberculosis (TB) are no more or no less likely to have multidrug- or rifampicin-resistant TB (MDR/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 (OR) of MDR/RR-TB among children (<15 years) with TB, compared to the odds of MDR/RR-TB among adults (≥15 years) with TB.

In most settings (45/55 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. Meanwhile, in Western Europe in general, and the UK, Poland, Finland and Luxembourg in particular, MDR/RR-TB is positively associated with age <15. Sixteen countries had sufficient data to compare over time between 2000-2011 and 2012-2018, with evidence for decreases in the OR in children compared to adults in Germany, Kazakhstan and the USA.

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. Further, the OR 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.

Keywords

MDR, TB, odds ratio, paediatric, child, adult, burden

Take-home message: 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.

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* [*M.tb*] 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.tb* strains. Disease in adults, however, 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.tb* 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-naive 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 characterize the burden and transmission risks of MDR/RR-TB in children.

Here, we reexamine 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 is 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 five 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 <15 years or adults ≥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.tb* diagnosis and DST. Age-disaggregated data is 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 (OR) for MDR/RR-TB for children (<15 years old) compared to adults (≥15 years old) by country, where the OR is given by:

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

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

We calculated 95% confidence intervals (95% CI) 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 OR for the periods 2000-2011 and 2012-2018. This represents recent data compared to when the OR for MDR/RR-TB in children compared to adults in surveillance data was last evaluated by Zignol and Colleagues,[4] since which time Xpert MTB/RIF testing has also 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 OR (99% confidence), evidence (95%), weak evidence (90%) and very weak evidence (85%).

A changing OR can be interpreted in different ways, implying different combinations of increasing or decreasing drug-susceptible and MDR/RR-*M.tb* transmission, which we outline in Table 1 – building

on previously established concepts.[9] We show in the appendix that the link between changes in the OR 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 2000-2018. 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 sizes 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, 39/55 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. Nineteen 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, Netherlands, Poland, Republic of Moldova, Spain, Sweden, Switzerland, the United Kingdom, the United States of America and Uzbekistan. In all except Namibia and Uzbekistan, where surveys were conducted, these data were derived from continuous surveillance.

Odds ratio

Aggregated ORs by country are shown in Table 2, where there were a total of 9 922 DST results for children and 605 089 for adults. Of the 55 included countries, there is strong evidence of ORs less than 1 (MDR/RR-TB is positively associated with age ≥15 years) in Georgia, Kazakhstan, Lithuania, Peru, Tajikistan, and Uzbekistan, and of ORs greater than 1 (MDR/RR-TB is positively associated with

age <15 years) in the United Kingdom and Poland. There is also weak evidence of ORs greater than 1 in Finland and Luxembourg.

A forest plot of the OR 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, 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 OR less than 1 in the Former Soviet Union at 0.50 [95% CI 0·41-0·60], and evidence in for an OR greater than 1 in the Western Europe region at 1.34 [95% CI 1.06-1.70]. There was weak evidence for an OR greater than 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 OR 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 OR over time (Figure 3, see appendix for further details). We found strong evidence for decreases in the OR 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 (1·03[95% CI 0·71-1·5] to 0·38[95% CI 0·31-0·45]) and the USA (2·35[95% CI 1·45-3·80] to 0·63[95% CI 0·28-1·42]). We found weak evidence for an increasing OR in Belgium (significant at a 90% level of confidence), and very weak evidence for a declining OR in Belarus, Namibia and Uzbekistan (significant at an 85% level of confidence), with no evidence for a changing OR in the remaining nine countries. In a random-effects meta-analysis with all included countries, the mean OR 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, we divided this as described above into Western Europe (comprised here of Austria, Belgium, Germany, Netherlands, Poland, Spain, Sweden, Switzerland and the United Kingdom) and the Former Soviet Union (comprised of Belarus, Kazakhstan, Latvia, Republic of Moldova and Uzbekistan). We found no evidence for a changing OR 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 OR in the Former Soviet Union (0·95 [95% CI 0·72-1·26] to 0·43 [95% CI 0·31-0·60]), although this was no longer the case if data from Kazakhstan was removed (0·85 [95% CI 0·54-1·35] to 0·48 [95% CI 0·27-0·84]).

DISCUSSION

In most settings (45/55 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 with age ≥15 years. Meanwhile, in the rest of Europe in general, and the United Kingdom, Poland, Finland and Luxembourg in particular, MDR/RR-TB is positively associated with age <15 years. There is also weak evidence that MDR/RR-TB is positively associated with age <15 years in the Western Pacific and African regions, which warrants further investigation.

Sixteen 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 OR 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 (see appendix and scenario 3 in table 1). This may mean that MDR/RR-TB transmission may have been decreasing over time in those settings (see appendix for further details), 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. Weak evidence for an increasing OR in Belgium is unfortunately 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 OR as a measure of the relative risk of local transmission of MDR/RR-*M.tb* versus drug-susceptible *M.tb* is likely not valid. In Germany, the USA and Belgium in particular, low rates of local transmission[10] mean that changes in the OR reflect changes that are happening outside the country.

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 7 high MDR/RR-TB burden countries not previously considered, totaling an additional 3 852 (63%) children and 288 113 (91%) adults, strengthens these findings. We also 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 remains 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 if 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 in fact 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 the biases mentioned above, 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 is 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 above, 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 naive 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 Russian Federation, yet only limited high quality data were available; indeed, in each country there was only one 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 OR 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.

AVAILABILITY OF DATA

All data generated or analysed during this study are included in this published article and its supplementary information files.

CONTRIBUTORS

CFM, TC, MZ and RGW conceived and designed the study. CFM did all the data analysis and wrote a first draft of the article. CFM, TC, ASD, RMGJH, GMK, MZ and RGW designed the methodology and critiqued the results. All authors contributed to editing the final draft.

ACKNOWLEDGEMENTS

We thank Daniel Grint (LSHTM) and Marek Lalli (LSHTM) for valuable advice on data analysis.

FUNDING

The study was not funded separately. CFM was funded by the Bill and Melinda Gates Foundation [grant number TB MAC OPP1135288]. GMK was supported by a fellowship from the UK MRC [grant number MR/P014658/1]. RMGJH received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme [grant agreement no 757699]. RGW is funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement that is also part of the EDCTP2 programme supported by the European Union [grant number MR/P002404/1], the Bill and Melinda Gates Foundation [grant numbers TB MAC: OPP1084276/OPP1135288, CORTIS: OPP1137034/OPP1151915, Vaccines: OPP1160830], UNITAID [grant number 4214-LSHTM-Sept15; PO 8477-0-600], and ESRC [grant number ES/P008011/1].

CONFLICT OF INTEREST

None declared.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland; 2019.
2. Becerra MC, Swaminathan S. Commentary: a targets framework: dismantling the invisibility trap for children with drug-resistant tuberculosis. *J Public Health Policy* 2014: 35(4): 425-454.
3. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Perez-Velez CM, Pagano M, Becerra MC, Cohen T. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014: 383(9928): 1572-1579.
4. Zignol M, Sismanidis C, Falzon D, Glaziou P, Dara M, Floyd K. Multidrug-resistant tuberculosis in children: evidence from global surveillance. *European Respiratory Journal* 2013: 42(3): 701-707.
5. Reuter A, Hughes J, Furin J. Challenges and controversies in childhood tuberculosis. *Lancet* 2019: 394(10202): 967-978.
6. Jenkins HE, Yuen CM. The burden of multidrug-resistant tuberculosis in children. *Int J Tuberc Lung Dis* 2018: 22(5): 3-6.

7. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. 5th ed. World Health Organization, Switzerland, 2015.
8. Schwarzer G. meta: an R package for meta-analysis. *R News* 2007: 7: 40-45.
9. Dye C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. *Nat Rev Microbiol* 2009: 7(1): 81-87.
10. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. *BMC Medecine* 2016: 14: 48.
11. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet Infect Dis* 2016: 16(10): 1193-1201.
12. Biadglegne F, Rodloff AC, Sack U. Review of the prevalence and drug resistance of tuberculosis in prisons: a hidden epidemic. *Epidemiol Infect* 2015: 143(5): 887-900.
13. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, Falzon D, Floyd K, Gargioni G, Getahun H, Gilpin C, Glaziou P, Grzemska M, Mirzayev F, Nakatani H, Raviglione M, for WsGTBP. WHO's new end TB strategy. *Lancet* 2015: 385(9979): 1799-1801.

FIGURES AND TABLES

Figure 1: Countries with WHO-reported drug resistance survey/surveillance data for 2000–2018 disaggregated by age (children <15 years or adults ≥15 years), showing evidence for the odds ratio for MDR/RR-TB in children versus adults being different to 1; i.e. an association between age and MDR/RR-TB.

Figure 2: Forest plot showing odds ratios and 95% confidence interval for MDR/RR-TB in children (<15 years) versus adults (≥15 years) by WHO region (Region of the Americas AMR, African Region AFR, Eastern Mediterranean Region EMR, South-East Asia Region SEA, Western Pacific Region WPR, with the European Region separated into the Former Soviet Union FSU and Western Europe WER). Data among all (new and retreated) cases are presented.

Figure 3: Trends over time in odds ratios for MDR/RR-TB in children (<15 years) versus adults (≥15 years) using 95% confidence intervals. Countries (indicated by iso3 code) are (a) Austria, (b) Belarus, (c) Belgium, (d) Germany, (e) Kazakhstan, (f) Latvia, (g) Namibia, (h) Netherlands, (i) Poland, (j) Republic of Moldova, (k) Spain, (l) Sweden, (m) Switzerland, (n) United Kingdom, (o) United States of America and (p) Uzbekistan.

Table 1: Potential scenarios indicated by changes in the odds ratio (OR) in children vs. adults. These include whether transmission is increasing or decreasing for DS-TB and MDR/RR-TB, and how the magnitude in this change compares for DS-TB vs. MDR/RR-TB. Arrows indicate whether transmission is increasing (↑) or decreasing (↓), where multiple arrows indicate a greater change in transmission is likely (but not guaranteed) to have taken place. See appendix for further details.

	DS-TB transmission	MDR/RR-TB transmission

OR decrease (↓)	Scenario 1	↑	↓
	Scenario 2	↑↑	↑
	Scenario 3	↓	↓↓
OR increase (↑)	Scenario 4	↓	↑
	Scenario 5	↑	↑↑
	Scenario 6	↓↓	↓

Table 2: Countries with at least 1 paediatric MDR- (pre-2016) or MDR/RR-TB (post-2016) case, identifying years with age disaggregation with and without paediatric cases. Countries in bold have a 95% confidence interval (CI) for the odds ratio for MDR/RR-TB for children (<15 years old) compared to adults (≥15 years old) not overlapping 1.

Country	**Year/s with paediatric case/s**	**Year/s without paediatric case/s**	**Number of cases tested (and identified in [ ]) for isoniazid and rifampicin* resistance**		**Pooled odds ratio (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]	1 772 [424]	0·91 (0·19-4·39)
Australia	2005, 2008, 2011	2002-2004, 2012- 2015, 2017	172 [4]	7 227 [170]	0·99 (0·36-2·70)
Austria	2006, 2012	2000- 2005, 2007, 2008, 2011, 2013-2015	227 [5]	7 151 [177]	0·89 (0·36-2·18)
Azerbaijan	2007		11[3]	1 090[428]	0·58 (0·15-2·20)
Bangladesh	2011		13[1]	1 331[98]	1·05 (0·13-8·15)
Belarus	2011, 2014-2017	2010	72 [27]	1 2037 [5581]	0·69 (0·43-1·12)
Belgium	2002, 2003, 2005, 2012-2014	2001, 2004, 2006-2008, 2011, 2015	353 [7]	9 068 [185]	0·97 (0·45-2·08)
Bhutan	2017		3 [1]	382 [52]	3·17 (0·28-35·62)
Burkina Faso	2017		9 [1]	1 131 [40]	3·41 (0·42-27·92)

Chile	2015	2014, 2017	66 [1]	4 410[77]	0·87 (0·12-6·32)
China	2013	2002, 2004, 2005	47 [2]	12 509 [951]	0·54 (0·13-2·23)
Denmark	2006	2002, 2003, 2004, 2005, 2007, 2008, 2011-2015, 2017	145 [1]	3 332 [23]	1·00 (0·13-7·45)
Djibouti	2015		11 [1]	355 [32]	1·01 (0·13-8·14)
Eswatini	2017	2018	127 [6]	3 305 [286]	0·52 (0·23-1·20)
Finland	2012, 2014	2000-2003, 2004, 2005, 2006, 2007, 2008, 2011, 2013, 2015-2017	45 [2]	4 176 [52]	3·69 (0·87-15·63)
Georgia	2013- 2017	2006, 2011, 2012	99 [8]	16 922 [2 805]	0·44 (0·21-0·91)
Germany	2001-2008,	2012-2014	1 042 [31]	43 419 [1 066]	1·22 (0·85-1·75)

	2011, 2015				
Hong Kong	2017	2005, 2007, 2008, 2011	93 [1]	14 614 [124]	1·27 (0·18-9·19)
India	2006	2004	36[1]	2 799[220]	0·33 (0·05-2·46)
Ireland	2007	2000, 2001, 2002, 2003-2006, 2011-2013, 2014, 2015	51 [1]	2 892 [35]	1·63 (0·22-12·15)
Israel	2013	2008, 2011, 2012, 2014-2017	31 [1]	1 568 [86]	0·57 (0·08-4·26)
Italy	2012	2015	65 [2]	3 104 [101]	0·94 (0·23-3·91)
Kazakhstan	2011-2013, 2015		663 [201]	43 401 [20 735]	0·48 (0·40-0·56)
Kenya	2014		37[1]	1 780[13]	3·78 (0·48-29·64)
Latvia	2002- 2006, 2008, 2012	2007, 2011, 2013-2016,	151 [19]	11 347 [1 618]	0·87 (0·53-1·40)

		2017			
Lesotho	2014		18 [2]	1 843 [68]	3·26 (0·74-14·48)
Lithuania	2006, 2008, 2011	2003-2005, 2007, 2012-2015, 2017	64 [5]	17 371 [3 474]	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]	4 340 [227]	1·49 (0·68-3·26)
Nepal	2011	2007	29 [1]	1 681 [82]	0·70 (0·09-5·18)
Netherlands	2002, 2011, 2016	2000, 2001, 2003- 2008, 2012-2015, 2017	228 [3]	9 727 [133]	0·96 (0·30-3·04)
New Zealand	2005	2004, 2006, 2007, 2008, 2009, 2011, 2012	64 [1]	1 931[22]	1·38 (0·18-10·38)
Norway	2000, 2007,	2001-2006, 2011-2015,	121 [3]	3 198 [65]	1·23 (0·38-3·96)

	2008	2017			
Pakistan	2013		37 [1]	1 513 [91]	0·43 (0·06-3·20)
Peru	2014-2016	2006	1 203 [58]	51 418 [4 060]	0·59 (0·45-0·77)
Poland	2011, 2012, 2016	2013-2015, 2017	97 [3]	30 207 [280]	3·41 (1·07-10·83)
Portugal	2005, 2011	2000-2004, 2006-2008, 2012	159 [2]	15 932 [312]	0·64 (0·16-2·58)
Republic of Korea	2016	2017	56 [2]	33 526 [1 539]	0·77 (0·19-3·16)
Republic of Moldova	2006, 2011, 2012, 2015-2017		47 [14]	13 408 [5 350]	0·64 (0·34-1·20)
Romania	2015-2017		131 [5]	24 688 [1 499]	0·61 (0·25-1·50)
Russian Federation	2004	2003, 2005, 2006	5 [1]	2 733 [532]	1·03 (0·12-9·27)
Saudi Arabia	2010		82 [2]	1 822 [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]	3 515 [85]	0·82 (0·20-3·36)
Sudan	2017		14 [2]	1 210 [67]	2·84 (0·62-12·96)
Sweden	2002, 2007, 2011, 2014	2000, 2001, 2003-2006, 2008, 2012, 2013, 2015, 2017	197[8]	5 565 [127]	1·81 (0·87-3·76)
Switzerland	2005, 2012	2000- 2004, 2006, 2008, 2011, 2013-2015	126 [2]	5 285 [99]	0·84 (0·21-3·46)
Tajikistan	2014, 2017	2009	422 [40]	5 291 [1074]	0·41 (0·29-0·57)
Turkey	2012, 2013, 2015-2017	2011, 2014	363 [14]	27 121 [1 217]	0·85 (0·50-1·46)
United Kingdom	2001- 2008, 2011, 2012	2000, 2013-2015, 2017	1 193 [27]	56 905 [664]	1·96 (1·33-2·89)
United States of America	2005, 2007, 2011- 2014	2015- 2017	1 231 [24]	62 858 [892]	1·38 (0·92-2·08)

Uzbekistan	2011, 2017	2005	204 [23]	7 643 [2 287]	0·30 (0·19-0·46)
Vanuatu	2017		1 [1]	45 [0]	-
Yemen	2011		22 [1]	1 215 [31]	1·82 (0·24-13·95)

*rifampicin only for 2016-2018.

APPENDIX

Implications of changing odds ratios

While TB burden (in terms of incidence and mortality) is estimated to be declining in the majority of settings (see, for example, the WHO 2019 Global TB Report[1]), trends in the MDR/RR-TB burden are less clear. While the WHO suggests that in the 13 high-burden countries with sufficient data there is a slight increasing trend in the proportion of TB cases that are due to MDR/RR-TB,[1] the proportion of TB cases that are MDR/RR-TB does not directly reveal changes in MDR/RR-*M.tb* transmission, as this indicator is affected by changes in both the numerator and denominator. Evidence suggests that the per-capita rate of MDR/RR-TB may be increasing in some settings and declining in others[2-8] although some sources suggest a more general decline.[9]

As drug resistance surveys are often challenging to do in resource-constrained settings,[10] limited data are available and understanding of MDR/RR-*M.tb* transmission relies heavily on strong and consistent data from global continuous surveillance. Comparing the incidence of MDR/RR-TB among children versus adults can therefore be difficult to directly estimate, due to gaps in case detection and reporting of MDR/RR-TB cases from many high TB burden countries. However, data allowing the calculation of the odds ratio (OR) for MDR/RR-TB *vs.* DS-TB (i.e. the proportion of TB cases with a drug susceptibility test that are drug resistant) in children compared to adults are available in some settings. We propose that this indicator may be useful for measuring trends in the relative transmission of MDR/RR-*M.tb* vs DS-*M.tb*. While childhood MDR/RR-TB incidence and mortality has been investigated previously and compared to that in adults,[11-13] no previous studies, to our knowledge, have investigated trends in the relative odds of MDR/RR-TB by age group over time. Identifying trends in MDR/RR-*M.tb* transmission is vital to inform progress on the WHO's End TB Strategy[14] that seeks to end the global TB epidemic by 2030, particularly as MDR/RR-TB cases contribute disproportionately to TB mortality and the catastrophic costs incurred by affected households.[1]

Infection with MDR/RR-*M.tb* is not an observable event and, because of the variable times between infection and disease onset, incident cases of TB disease occurring among adults may reflect transmission occurring both recently and in the distant past. We propose that examination of the changes in the relative risk of MDR/RR-TB among children (which reflect the relative frequency of MDR/RR-*M.tb* strains vs. DS-*M.tb* strains present in recently circulating strains) and MDR/RR-TB among adults (which reflect the relative frequency of MDR/RR-*M.tb* strains vs. DS-*M.tb* strains over a longer period of exposure, as well as acquired resistance) can serve as a useful indicator of changes in the risk of exposure to MDR/RR-*M.tb* as compared with DS-*M.tb* over time.

As a reminder to ourselves, the odds ratio (OR) is given by

$$OR = C^+/C^- \ / \ A^+/A^- = C^+A^-/C^-A^+,$$

where C and A represent TB incidence in children and adults respectively, and $^+$ represents those detected to have MDR/RR-TB disease while $^-$ represents those with TB (who received a drug sensitivity test result) that is not MDR/RR-TB.

In general, if transmission of TB changes over time we expect to see a change in the number of new cases sooner in children than in adults because of the reactivation effect from the latent reservoir in adults. If transmission were to change over a given time period by a proportion α for drug-sensitive TB (DS-TB) and □ for MDR/RR-TB (where $-1<\alpha,\square<\infty$), then we would expect that change to be less than or equal in adults for both DS-TB and MDR/RR-TB (aα and b□ respectively, where $0<=a,b<=1$).

So, for example, if DS-TB were to increase by 10% ($\alpha=0{\cdot}1$) in children due to an increase in transmission, then we would expect that change to be less in adults (because a proportion of these are a result of reactivation, which won't be immediately affected), say 80% (in which case $a=0{\cdot}8$). If the original incidence for children and adults was given by C^- and A^- respectively as before, then the new incidence would be given by $(1+0{\cdot}1)C^-$ and $(1+0{\cdot}8*0{\cdot}1)A^-$. A similar logic follows for changes in MDR/RR-TB incidence. Here we say that the reactivation effect is greater if a is smaller.

The change in odds ratio over time ($\Delta OR=OR_{time\ 2}-OR_{time\ 1}$) then becomes

$$\Delta OR = (1+\square)C^+(1+a\alpha)A^-/(1+\alpha)C^-(1+b\square)A^+ \ - \ C^+A^-/C^-A^+,$$

$$= C^+A^-[(1+\square)(1+a\alpha) \ - \ (1+\alpha)(1+b\square)] \ / \ (1+\alpha)\,(1+b\square)C^-A^+.$$

So whether the odds ratio increases or decreases is given by

$\text{sign}(\Delta OR) = (1+\square)(1+a\alpha) - (1+\alpha)(1+b\square)$.

We then compare the relative magnitudes of $(1+\square)(1+a\alpha)$ and $(1+\alpha)(1+b\square)$, considering whether transmission is increasing or decreasing for both DS-TB and MDR/RR-TB (i.e. sgn(α) and sgn(□) respectively), the comparative magnitude of these changes (i.e. |α| *vs.* |□|) and the comparative magnitude of the reactivation effect (i.e. |a| *vs.* |b|). Modelled on work by Dye,[2] we identify 6 possible scenarios (table S1).

- Scenario 1: If $\alpha>0$ and $\square<0$, then $(1+a\alpha)<(1+\alpha)$ and $(1+\square)<(1+b\square)$, so the OR will always decrease.
- Scenario 2: If $\alpha>0$ and $\square>0$, then $(1+a\alpha)<(1+\alpha)$ and $(1+\square)>(1+b\square)$, so the OR is more likely to decrease when $|\alpha|\gg|\square|$ or $a\ll b$ (see scenario 5 for when the OR is more likely to increase).
- Scenario 3: If $\alpha<0$ and $\square<0$, then $(1+a\alpha)>(1+\alpha)$ and $(1+\square)<(1+b\square)$, so the OR is more likely to decrease when $|\alpha|\ll|\square|$ or $a\gg b$ (see scenario 6 for when the OR is more likely to increase).
- Scenario 4: If $\alpha<0$ and $\square>0$, then $(1+a\alpha)>(1+\alpha)$ and $(1+\square)>(1+b\square)$, so the OR will always increase.
- Scenario 5: If $\alpha>0$ and $\square>0$, then $(1+a\alpha)<(1+\alpha)$ and $(1+\square)>(1+b\square)$, so the OR is more likely to increase when $|\alpha|\ll|\square|$ or $a\gg b$ (see scenario 2 for when the OR is more likely to decrease).
- Scenario 6: If $\alpha<0$ and $\square<0$, then $(1+a\alpha)>(1+\alpha)$ and $(1+\square)<(1+b\square)$, so the OR is more likely to increase when $|\alpha|\gg|\square|$ or $a\ll b$ (see scenario 3 for when the OR is more likely to decrease).

Table S1: *Potential scenarios indicated by changes in the odds ratio (OR) in children vs. adults. These include whether transmission is increasing or decreasing for DS-TB and* MDR/RR-*TB, how the magnitude in this change compares for DS-TB vs.* MDR/RR-*TB, and whether the reactivation effect (that sees changes in new cases amongst adults as a result of changing transmission lag behind changes in new cases amongst children) is greater for DS-TB or* MDR/RR-*TB, i.e. whether a is less than or greater than b. Arrows indicate whether transmission is increasing (↑) or decreasing (↓), where multiple arrows indicate a greater change in transmission is likely (but not guaranteed) to have taken place. The reactivation effect is likely (but also not guaranteed) to be either greater for DS-TB (>) or* MDR/RR-*TB (<), unless it is not possible to say (-).*

		DS-TB transmission	MDR/RR-TB transmission	Reactivation effect
OR decrease	Scenario 1	↑	↓	-
	Scenario 2	↑↑	↑	>
	Scenario 3	↓	↓↓	<
OR increase	Scenario 4	↓	↑	-
	Scenario 5	↑	↑↑	<
	Scenario 6	↓↓	↓	>

It is worth noting that, because better data exists for trends in DS-TB, we can often rule out a number of possible explanations for changing ORs in our analysis and draw conclusions more simply than we otherwise might.

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 OR as a measure of the relative risk of local transmission of MDR/RR-*M.tb* versus DS-*M.tb* is likely not valid. Low rates of local transmission mean that changes in the OR reflect

changes that are happening outside the country. An increase in migration in these countries could, along with a potential increase in per capita rates of MDR/RR-TB, also result in an increase in adults at risk of MDR/RR-TB, resulting in a lower OR but breaking the link to local MDR/RR-TB transmission. We therefore advise interpreting results for these settings with caution.

Data set

Table S2: *Countries with at least 1 paediatric MDR- (pre-2016) or RR-TB (post-2016) case in both 2000-2011 and 2012-2018, identifying years with age disaggregation with and without paediatric cases.*

Country	**Year/s with paediatric case/s**	**Year/s without paediatric case/s**	**2000-2011**			**2012-2018**			**P-value for change in OR over time**
			Number of cases tested (and identified in [ ]) for isoniazid and rifampin* resistance		**Pooled odds ratio (95% CI)**	**Number of cases tested (and identified in [ ]) for isoniazid and rifampin* resistance**		**Pooled odds ratio (95% CI)**	
			Age<15 years	**Age≥15 years**		**Age<15 years**	**Age≥15 years**		
Austria	2006, 2012	2000-2005, 2007, 2008, 2011, 2013-2015	188 [4]	5722 [107]	1·14 (0·42-3·13)	39 [1]	1429 [70]	0·51 (0·07-3·78)	0·453
Belarus	2011, 2014-2017	2010	4 [3]	1564 [716]	3·55 (0·37-34·23)	68 [24]	10 473 [4,865]	0·63 (0·38-1·04	0·111
Belgium	2002, 2003, 2005, 2012-2014	2001, 2004, 2006-2008, 2011, 2015	263 [3]	6789 [137]	0·56 (0·18-1·78)	90 [4]	2729 [48]	2·16 (0·76-6·13)	0·074
Germany	2001-2008, 2011, 2015	2012-2014	819 [29]	33 128 [725]	1·64 (1·12-2·39)	223 [2]	10 291 [341]	0·26 (0·07-1·07)	0·001
Kazakhstan	2011-2013, 2015		117 [45]	12,006 [4,530]	1·03 (0·71-1·50)	546 [156]	31 395 [16,205]	0·38 (0·31-0·45)	<0·001
Latvia	2002-2006, 2008, 2012	2007, 2011, 2013-2016, 2017	128 [18]	7,877 [1,203]	0·91 (0·55-1·50)	23 [1]	3470 [415]	0·34 (0·05-2·49)	0·280

Namibia	2008, 2015		20 [4]	1269 [86]	3·44 (1·13-10·51)	72 [3]	3071 [141]	0·90 (0·28-2·91)	0·104
Netherlands	2002, 2011, 2016	2000, 2001, 2003-2008, 2012-2015, 2017	172 [2]	7098 [75]	1·10 (0·27-4·52)	56 [1]	2629 [58]	0·81 (0·11-5·92)	0·799
Poland	2011, 2012, 2016	2013-2015, 2017	22 [1]	4971 [40]	5·87 (0·77-44·70)	75 [2]	25 236 [240]	2·85 (0·70-11·69)	0·584
Republic of Moldova	2006, 2011, 2012, 2015-2017		23 [6]	5241 [2,200]	0·49 (0·19-1·24)	24 [8]	8167 [3,150]	0·80 (0·34-1·86)	0·445
Spain	2002, 2015	2003-2005	54 [1]	2732 [46]	1·10 (0·15-8·14)	47 [1]	783 [39]	0·42 (0·06-3·09)	0·506
Sweden	2002, 2007, 2011, 2014	2000, 2001, 2003-2006, 2008, 2012, 2013, 2015, 2017	113 [4]	3781 [73]	1·86 (0·67-5·19)	84 [4]	1784 [54]	1·60 (0·57-4·53)	0·839
Switzerland	2005, 2012	2000-2004, 2006, 2008, 2011, 2013-2015	93 [1]	4110 [58]	0·76 (0·10-5·54)	33 [1]	1175 [41]	0·86 (0·12-6·48)	0·929
United Kingdom	2001-2008, 2011, 2012	2000, 2013-2015, 2017	930 [20]	41,843 [439]	2·07 (1·32-3·26)	263 [7]	15,062 [225]	1·80 (0·84-3·87)	0·756
United States of America	2005, 2007, 2011-2014	2015-2017	613 [18]	27,279 [347]	2·35 (1·45-3·80)	618 [6]	35,579 [545]	0·63 (0·28-1·42)	0·003
Uzbekistan	2011, 2017	2005	5 [2]	1316 [451]	1·28 (0·21-7·68)	199 [21]	6,327 [1,836]	0·29 (0·18-0·46)	0·143

*rifampin only for 2016-2018.

DS-TB incidence

We use the WHO global TB database[15] directly to present, for comparison, averaged estimated TB incidence of all forms for countries where the age-disaggregated drug resistance data were available over both time periods. In all 16 countries except Sweden, estimated TB incidence declined between 2000-2011 and 2012-2018 (Table S3), suggesting that DS-TB transmission decreased between the two timepoints.

Table S3: *Average estimated TB incidence (all forms, taken from the WHO database) in both 2000-2011 and 2012-2018, and change indicated by ↑ (increasing) or ↓ (decreasing).*

Country	**Average estimated total TB incidence (per 100,000 population)**		**Change in estimated TB incidence**
	2000-2011	**2012-2018**	
Austria	12	8	↓
Belarus	70	50	↓
Belgium	12	9	↓
Germany	8	7	↓
Kazakhstan	171	89	↓
Latvia	71	42	↓
Namibia	804	486	↓
Netherlands	8	6	↓
Poland	26	19	↓
Republic of Moldova	120	111	↓
Spain	19	12	↓
Sweden	6	8	↑
Switzerland	8	7	↓
United Kingdom	14	11	↓
United States of America	5	3	↓
Uzbekistan	108	81	↓

MDR/RR-TB incidence

Table S4*: Percentage of new TB cases that are MDR/RR-TB in countries with at least 1 paediatric MDR/RR-TB case in both 2000-2011 and 2012-2018. Using a two-proportion z-test (with a 95% cut-off) we identify where there is strong evidence for a change in incidence (*↑ or ↓*) or no evidence (-).*

Country	**New TB patients that are MDR/RR-TB (%)**		**Change in % of new patients that are MDR/RR-TB**
	2000-2011	**2012-2018**	
Austria	1·6	2·6	↑

Belarus	32·7	35·6	-
Belgium	1·4	1·6	-
Germany	1·4	1·7	-
Kazakhstan	29·3	24·4	↓
Latvia	10·5	8·8	↓
Namibia	3·8	4·3	-
Netherlands	1·0	1·6	↑
Poland	0·6	0·6	-
Republic of Moldova	23·5	26·8	↑
Spain	0·7	3·9	↑
Sweden	1·6	2·8	↑
Switzerland	0·9	2·2	↑
United Kingdom	0·9	1·3	↑
United States of America	1·1	1·2	↑
Uzbekistan	20·5	9·9	↓

We use these estimates of changes in DS- and MDR/RR-TB incidence, along with changes in the odds ratio, to identify possible implications for recent MDR/RR-TB transmission in the main text.

Sensitivity calculations

We conducted three separate sensitivity analyses. Firstly, instead of comparing the OR over two different time periods we compared only the first and last year of age-disaggregated data with a paediatric case for each country, recognising that the time periods for which this data are available differ by country. This meant a reduction in sample size for individual countries, but it might be able to detect change that is more gradual over time. Secondly, we assumed that all previously treated cases were adult, and removed these from the age-disaggregated total to account for the effect of resistance acquisition through previous treatment. Lastly, we removed data points which considered RR-TB cases (present from 2016 onwards) to determine whether our results were affected by differences in MDR-*M.tb* transmission compared to RR-*M.tb* transmission.

Time period

It was difficult to compare different time periods for inclusion in our analysis, as this required the inclusion and exclusion of different countries each time. However, a comparison of the OR for the first and last year that countries had data for showed that, in general, survey sample sizes were indeed too small to detect change (see Table S5). While data were available for a total 26 countries for comparison, in only Kazakhstan and Tajikistan did 95% confidence intervals not overlap, showing evidence for a decrease in the OR.

Table S5*: Countries with at least 2 years with 1 or more paediatric MDR- (pre-2016) or RR-TB (post-2016) case, identifying data in the oldest and most recent years.*

Country	Year	Odds ratio (95% confidence interval)	Number of cases age<15 years tested (and identified in []) for	Number of cases age≥15 years tested (and identified in []) for

			isoniazid and rifampin* resistance	isoniazid and rifampin* resistance
Australia	2005	2.9 (0.5-17.0)	25 [1]	789 [11]
	2011	2.1 (0.5-9.2)	33 [2]	690 [21]
Austria	2006	14.5 (3.8-54.8)	27 [4]	505 [6]
	2012	1.1 (0.1-9.0)	13 [1]	379 [26]
Belarus	2011	3.6 (0.4-34.7)	4 [3]	1340 [609]
	2015	0.9 (0.4-2.0)	25 [11]	2744 [1264]
Belgium	2002	1.5 (0.2-11.3)	27 [1]	779 [20]
	2014	3.7 (0.4-31.6)	18 [1]	516 [8]
Finland	2012	54.3 (3.4-870.1)	3 [1]	219 [2]
	2014	37.8 (2.0-717.2)	2 [1]	155 [4]
Georgia	2013	0.4 (0.1-3.2)	12 [1]	2144 [383]
	2017	0.3 (0.0-2.6)	16 [1]	1963 [323]
Germany	2001	1.1 (0.3-3.4)	107 [3]	4027 [107]
	2015	1.2 (0.3-4.9)	46 [2]	2981 [112]
Kazakhstan	2011	1.0 (0.7-1.5)	117 [45]	12006 [4530]
	2015	0.4 (0.3-0.6)	392 [62]	8595 [2659]
Latvia	2002	1.3 (0.5-3.6)	22 [5]	1220 [221]
	2012	1.0 (0.1-8.7)	7 [1]	759 [105]
Lithuania	2006	0.7 (0.1-6.1)	7 [1]	1780 [331]
	2011	2.8 (0.6-12.7)	7 [3]	1396 [293]
Namibia	2008	3.4 (1.1-10.5)	20 [4]	1269 [86]
	2015	0.9 (0.3-2.9)	72 [3]	3071 [141]
Netherlands	2002	32.3 (2.0-532.7)	24 [1]	744 [1]
	2016	5.4 (0.6-46.3)	9 [1]	574 [13]
Norway	2000	13.4 (1.1-169.3)	7 [1]	163 [2]
	2008	7.1 (0.7-74.5)	11 [1]	216 [3]
Peru	2014	0.6 (0.3-0.9)	414 [17]	17893 [1278]
	2016	0.8 (0.5-1.2)	350 [27]	14962 [1430]
Poland	2011	5.9 (0.8-44.7)	22 [1]	4971 [40]

	2016	6.8 (0.9-53.4)	13 [1]	4223 [51]
Portugal	2005	5.2 (0.6-42.2)	11 [1]	1599 [30]
	2011	4.1 (0.5-32.5)	13 [1]	1454 [29]
Republic of Moldova	2006	0.5 (0.2-1.6)	15 [4]	2864 [1201]
	2017	0.6 (0.1-6.0)	4 [1]	1949 [678]
Romania	2015	1.3 (0.4-4.3)	38 [3]	8525 [519]
	2017	0.5 (0.1-3.9)	33 [1]	7776 [436]
Spain	2002	3.8 (0.4-33.1)	7 [1]	476 [20]
	2015	0.4 (0.1-3.1)	47 [1]	783 [39]
Sweden	2002	10.2 (1.0-106.5)	12 [1]	341 [3]
	2014	8.3 (2.2-30.7)	24 [4]	297 [7]
Switzerland	2005	7.3 (0.8-69.2)	16 [1]	441 [4]
	2012	6.4 (0.7-58.1)	9 [1]	364 [7]
Tajikistan	2014	1.5 (0.9-2.7)	73 [16]	2292 [355]
	2017	0.3 (0.2-0.4)	346 [24]	2738 [619]
Turkey	2012	0.3 (0.0-2.2)	59 [1]	5324 [290]
	2017	1.8 (0.7-4.5)	66 [5]	5394 [234]
United Kingdom	2001	1.7 (0.2-12.9)	79 [1]	3101 [23]
	2012	4.9 (2.2-10.9)	103 [7]	5048 [74]
United States of America	2005	2.1 (0.9-5.3)	208 [5]	10164 [116]
	2014	0.8 (0.1-6.0)	85 [1]	5721 [82]
Uzbekistan	2011	1.2 (0.2-7.2)	5 [2]	1032 [370]
	2017	0.3 (0.2-0.5)	199 [21]	6327 [1836]

*rifampin only for 2016-2018.

Retreatment status

As with previous analyses,[11] we have calculated the OR based on both new and retreated patients. This is because age disaggregation is not recorded by treatment status in our data. However, the majority of retreatment cases are likely to be in adults, as children are unlikely to have had the opportunity to be previously treated for TB. One method to account for this is to remove all retreatment cases (treatment status data is recorded separately) from the total age-disaggregated cases for adults. If we do this we see that the ORs increase significantly, with all regions except FSU having an OR of greater than 1 (see Figure S1). At the same time, the number of countries with ORs significantly greater than 1 increases, to include Germany, Namibia, Poland, Sweden, the UK and the USA (although we note that Kazakhstan and Tajikistan still have ORs significantly less

than 1). In terms of changing ORs over time, our results are not noticeably affected; the only change is in the weakening of the evidence for the USA's decrease in OR (see Figure S2).

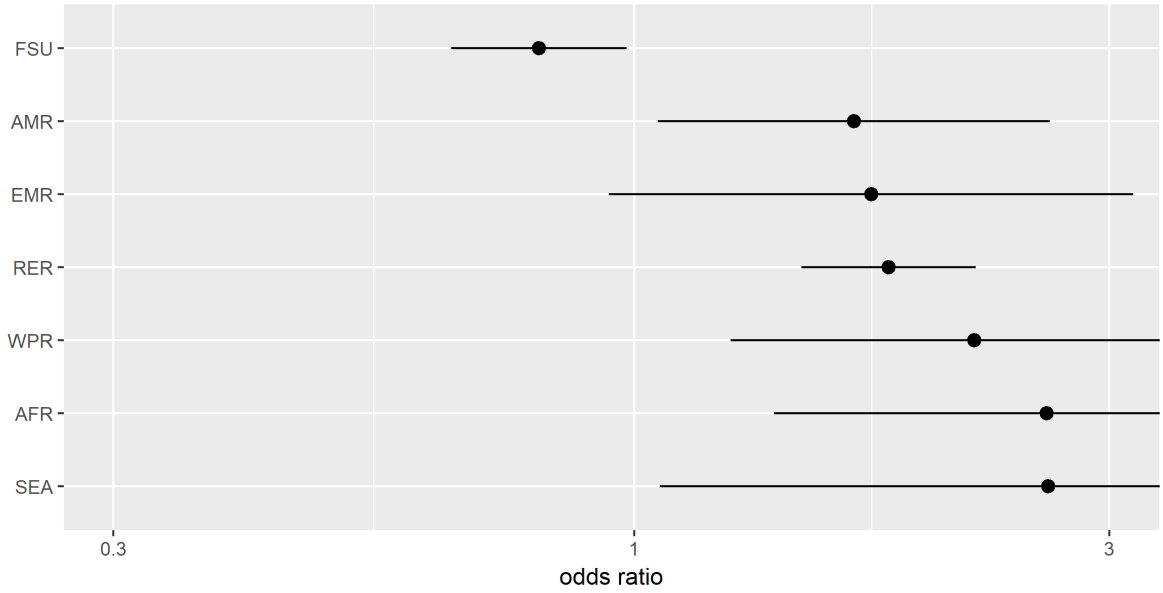


Figure S1: *Forest plot showing odds ratios for multidrug- or rifampin-resistant tuberculosis in children (<15 years) versus adults (>15 years) by WHO region, with the European Region separated into Former Soviet Union (FSU) and the rest of Europe (EUR). Data among new cases only are presented.*

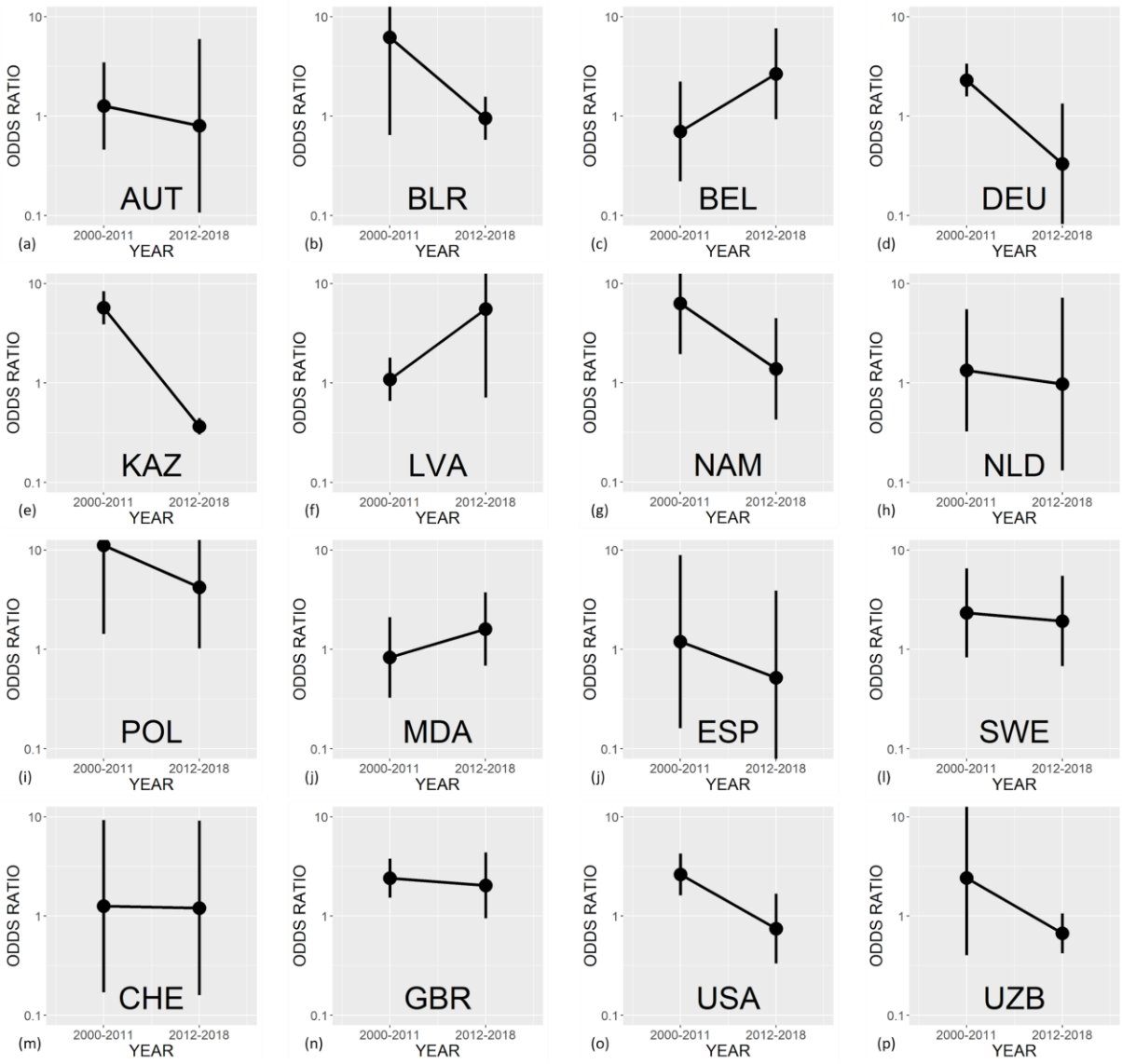


Figure S2: *trends over time in odds ratios for multidrug- or rifampicin-resistant tuberculosis disease in children (<15 years) versus adults (≥15 years) using 95% confidence intervals for new patients only, for (a) Austria, (b) Belarus, (c) Belgium, (d) Germany, (e) Kazakhstan, (f) Latvia, (g) Namibia, (h) Netherlands, (i) Poland, (j) Republic of Moldova, (k) Spain, (l) Sweden, (m) Switzerland, (n) United Kingdom, (o) United States of America and (p) Uzbekistan.*

However, this comes with a major caveat; the removal of retreatment cases from the adult-only total is not necessarily a reliable calculation, due to inconsistencies between the treatment status- and age-disaggregated data. For example, in Lesotho in 2014 the data shows that there were 1409 new and 1677 retreatment cases with a DST for both INH and RIF. However, there are only a total of 1861 age-disaggregated cases recorded, so there is a major disparity in the number of cases reported by treatment status compared to by age. This is also reflected in the number of adult MDR/RR-TB cases reported (68) compared to the number of MDR/RR-TB retreatment cases reported (122). Indeed, across all ages, treatment status and countries (those which have any with age-disaggregated data), calculating based on age-disaggregated data gives an incidence of 8·63%, whereas based on treatment-status disaggregated data incidence is 5·99%. Due to the way the data is recorded, this grows more unreliable for RR-TB post-2016. In total, in only 190 out of 691 entries for a given country and year with age-disaggregated data are the number of MDR/RR-TB cases and number of DSTs the same for the age-disaggregated data as for the treatment-status-disaggregated data. We therefore did not make assumptions about age and retreatment status in our main results, but instead offer them here as a caveat, noting that they do not appear to significantly affect our results for trends. However, if we are interested in the odds of MDR/RR-TB in children compared to treatment naïve adults only, more data that is appropriately reconciled is required in order for us to have confidence in this calculation.

MDR- vs. RR-TB

Another aspect to note, of particular relevance when comparing between time periods, is that we compare results for MDR-TB only for the first time period, and both MDR- and RR-TB for the second. This could lead to bias if we expect to see very different rates for INH vs. RR resistance in children compared to adults. This would quantitatively affect our results in the main text in Figure 3 for Belarus, Latvia, Poland, Republic of Moldova, Sweden, the UK and the USA (as well as Netherlands and Uzbekistan, where if we remove RR-TB results we are no longer able to make the comparison). However, in no case is there a qualitative change in our results (see Figure S3).

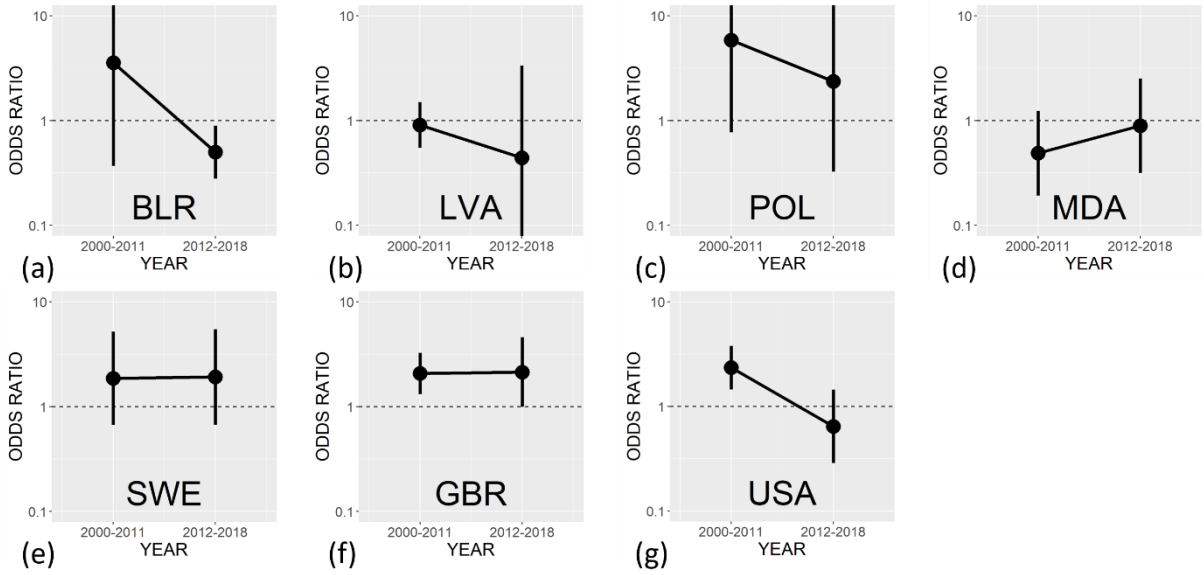
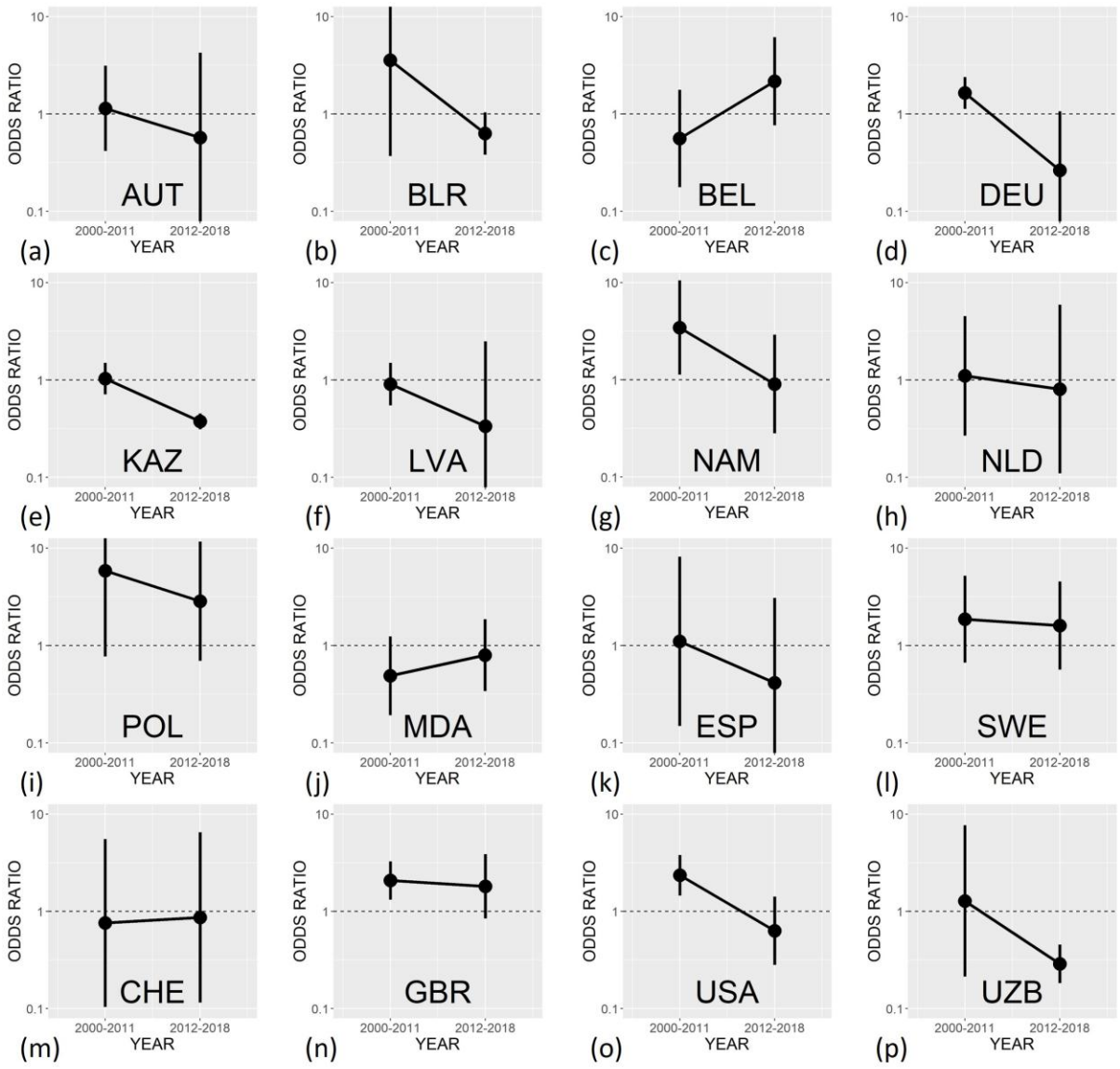


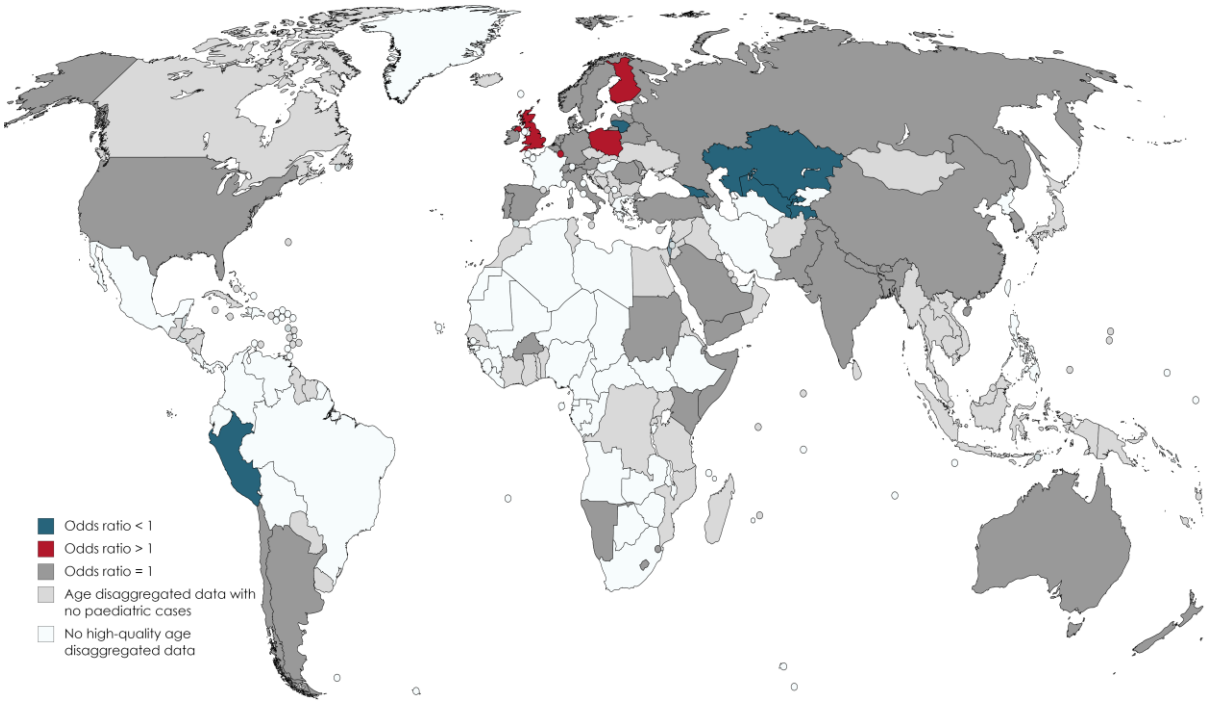
Figure S3: *trends over time in odds ratios for multidrug-resistant tuberculosis disease in children (<15 years) versus adults (≥15 years) using 95% confidence intervals, for (a) Belarus, (b) Latvia, (c) Poland, (d) Republic of Moldova, (e) Sweden, (f) United Kingdom and (g) United States of America.*

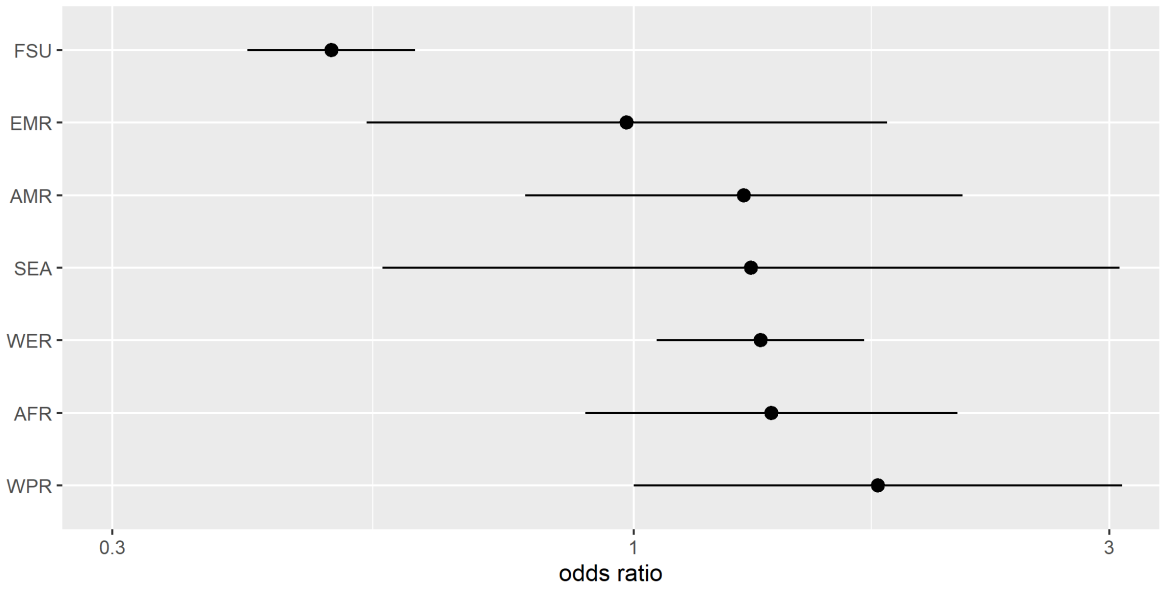
References

1. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland, 2019.
2. Dye C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. *Nat Rev Microbiol* 2009; **7**(1): 81-7.
3. Dye C, Williams BG. Slow Elimination of Multidrug-Resistant Tuberculosis. *Sci Transl Med* 2009; **1**.
4. Jenkins HE, Zignol M, Cohen T. Quantifying the burden and trends of isoniazid resistant tuberculosis, 1994-2009. *PLoS One* 2011; **6**(7): e22927.
5. Zignol M, van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. *Bull World Health Organ* 2012; **90**(2): 111-9D.
6. Cohen T, Jenkins HE, Lu C, McLaughlin M, Floyd K, Zignol M. On the spread and control of MDR-TB epidemics: an examination of trends in anti-tuberculosis drug resistance surveillance data. *Drug Resist Updat* 2014; **17**(4-6): 105-23.
7. Zignol M, Dara M, Dean AS, et al. Drug-resistant tuberculosis in the WHO European Region: an analysis of surveillance data. *Drug Resist Updat* 2013; **16**(6): 108-15.
8. Blondal K, Viiklepp P, Blondal P, Altraja A. Countrywide management of pulmonary tuberculosis reverses increasing incidence. *Int J Tuberc Lung Dis* 2011; **15**(7): 892-8.

9. Global, regional, and national burden of tuberculosis, 1990-2016: results from the Global Burden of Diseases, Injuries, and Risk Factors 2016 Study. *Lancet Infect Dis* 2018; **18**(12): 1329-49.
10. Zignol M, Dean AS, Falzon D, et al. Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *The New England journal of medicine* 2016; **375**(11): 1081-9.
11. Zignol M, Sismanidis C, Falzon D, Glaziou P, Dara M, Floyd K. Multidrug-resistant tuberculosis in children: evidence from global surveillance. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2013; **42**(3): 701-7.
12. Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; **383**(9928): 1572-9.
13. Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. *The Lancet Global health* 2017; **5**(9): e898-e906.
14. Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet* 2015; **385**(9979): 1799-801.
15. World Health Organization. World Health Organization Global TB Database. https://www.who.int/tb/country/data/download/en/ (accessed 12 March 2019).


ODDS RATIO
10
1
0.1
2000-2011
2012-2018
YEAR
AUT
(a)
BLR
(b)
BEL
(c)
DEU
(d)
KAZ
(e)
LVA
(f)
NAM
(g)
NLD
(h)
POL
(i)
MDA
(j)
ESP
(k)
SWE
(l)
CHE
(m)
GBR
(n)
USA
(o)
UZB
(p)


Odds ratio < 1
Odds ratio > 1
Odds ratio = 1
Age disaggregated data with no paediatric cases
No high-quality age disaggregated data


FSU
EMR
AMR
SEA
WER
AFR
WPR
0.3
1
3
odds ratio