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Reporting and management of childhood multidrug-resistant TB in Europe and Central Asia: Report of a Regional WHO meeting

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SUMMARY

BACKGROUND: As the WHO European Region has the highest proportion of multidrug-resistant tuberculosis (MDR-TB) among total incident TB cases, many children and adolescents are at risk of MDR-TB infection and disease.

METHODS: We performed an electronic survey of clinicians and TB programme personnel who attended the 2020 Regional Consultation on child and adolescent TB organised by the WHO Regional Office. We characterised access to diagnostics and drugs, and practices in the prevention and management of child and adolescent MDR-TB.

RESULTS: Children and adolescents are inconsistently represented in national guidelines and budgets; child-friendly drug formulations for MDR-TB treatment are insufficiently available in 57% of countries, and 32% of countries reported paediatric drug stock-outs. The novel drugs, bedaquiline and delamanid, are accessible by respectively 80% and 60% of respondent countries. Respondents were asked how many children were diagnosed with MDR-TB in 2019, and a comparison of this number to modelled estimates of incidence (to identify the case detection gap) and WHO notifications (to identify the case reporting gap) showed substantial differences in both comparisons.

CONCLUSIONS: Better representation of this patient group in guidelines and budgets, greater access to drugs and improved reporting are essential to reach TB elimination in this Region.

KEY WORDS: childhood and adolescent tuberculosis; multidrug-resistant tuberculosis; WHO European Region; public health; child health

Historically, child and adolescent tuberculosis (TB) has been under-recognised and under-funded in programmatic care and research. There is now increasing awareness of age-specific challenges in diagnosing, treating, and preventing TB in children and adolescents.

Adequate data collection and notification are key in informing national TB programmes (NTPs), setting programmatic priorities, and selecting appropriate policies.[1] There is a large gap between official notifications of rifampicin-resistant TB (RR-TB) cases, i.e., those reported through WHO since 2017,[2] and the number of cases estimated using mathematical modelling. This could be a result of both a case detection gap and a case notification gap.[3–5] Two recent modelling studies estimated that multidrug-resistant TB (MDR-TB; defined as disease caused by an isoniazid- and rifampicin-resistant *Mycobacterium tuberculosis*),[6] affects between 25,000 and 32,000 children (<15 years) globally every year.[3,4] Around one tenth of these estimated cases are reported to the WHO via official notification channels.[2] It is estimated that 17% of all new TB cases in the WHO European Region are MDR/RR-TB, representing the highest proportion in any WHO region.[2] Mathematical models estimate that 2,120 children in the Region developed MDR-TB in 2017 (16% of the total incident TB cases in children in that year).[3]

There are several reasons why children with MDR-TB may not be appropriately diagnosed, treated, and reported. Microbiological confirmation may be complicated by paucibacillary disease that decreases the probability of a positive result on microscopy, culture or molecular testing.[7] While a clinical diagnosis can be made if a child has clinical or radiological features of TB and has been exposed to a confirmed MDR-TB case,[8] clinicians may be unable to initiate MDR-TB treatment without a culture-confirmed diagnosis. In addition to the diagnostic obstacles, there are few second-line drugs to treat resistant forms of TB available in formulations suitable for children, such as dissolvable tablets with a pleasant taste.[9] Finally, preventive therapy for MDR-TB, although likely as important in controlling the epidemic as it is for drug-susceptible disease, is not well studied or standardised.

Addressing the child and adolescent TB epidemic requires greater focus by NTPs and increased public health prioritisation. In January 2020, the WHO Regional Office for Europe conducted a region-wide consultation to enhance joint national strategies to overcome regional child and adolescent MDR-TB challenges. Here, we present results from the survey distributed to the Member State representatives prior to the consultation. In addition to questions about the management of MDR-TB in this age group, we asked NTP personnel of Member States to provide the number of children and adolescents diagnosed with MDR-TB in their country and used these survey-reported childhood MDR-TB cases as an indication of the true number of

diagnosed patients. We evaluated diagnostic and reporting gaps by comparing these survey-reported numbers to modelled incidence estimates and official WHO notifications. A comparison of these three different data sources on the MDR-TB burden in children and adolescents in the Region will provide a more detailed picture of where cases are missed and will help understand the true burden of paediatric MDR-TB in the Region.

METHODS

Region-wide consultation

The WHO Regional Office for Europe convened a regional 2-day consultation on child and adolescent MDR-TB in January 2020, inviting NTP representatives from the 53 Member States to attend.

Questionnaire

We administered the survey (Supplementary Data S1) using Google Forms in English and Russian in January 2020. As this was a quality improvement initiative to explore regional differences in child and adolescent MDR-TB prevention and care, ethical approval was not sought. We obtained non-human subjects research determination from the Institutional Review Board at Harvard Medical School, Boston, MA, USA (IRB21-1396) for the secondary analysis comparing different data sources of diagnosed children and adolescents with MDR-TB. The 36 questions of the survey focused on the following five topics: 1) programmatic aspects, 2) management of MDR-TB in children and adolescents, 3) availability of therapeutics and diagnostics, 4) practices in screening and contact tracing, and 5) preventive therapy practices. Participants were also asked to provide numbers of children and adolescents they had diagnosed with culture-confirmed MDR-TB in 2018. For this study, we defined a child as a person aged <15 years and an adolescent as a person aged 15 to <20 years. We piloted the questionnaire with three clinical and programmatic experts (two native English speakers and one native Russian speaker) within the Region. In the case of multiple responses per country (i.e., when two representatives per country attended) discordant responses were reconciled through discussion with the representatives.

Data analysis

We used descriptive statistics to analyse the survey results. Analyses were performed in R v3.6.1 (R Computing, Vienna, Austria) using the *tidyverse*, *ggplot,* and *tmap* packages.[10–12] To explore the differences between numbers of child MDR-TB patients reported through the survey and those reported to the WHO, we extracted public TB notification data from the WHO.[2] For comparison, we also obtained estimates of MDR-TB incidence (modelled incidence estimates) in children from a mathematical modelling study for 2014.[3] Since we assumed the drug resistance proportions of the total paediatric TB incidence to be less dynamic than the overall estimate, we applied the MDR-TB proportions from the 2014 modelling study to the 2018 paediatric TB incidence as estimated by the WHO.

High-priority tuberculosis countries

Among the member states of the WHO Regional Office for Europe, 18 are considered TB high-priority countries.[13] These are Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan. Our analysis on access to rapid diagnostics and treatment agents was stratified by high-priority country.

RESULTS

Respondents

Of the 58 participants who attended the regional consultation, 36 (62%) participants responded to the online survey, providing responses from 29 (88%) of the 33 participating Member States (Fig S1A). Participants were national WHO correspondents and comprised 22 paediatric TB physicians nominated by their NTP (61%), 13 epidemiologists at state or academic institutions involved in the NTP (36%) and one civil society/patient representative. We excluded the patient representative response (Ukraine), as the survey was targeted at NTP staff, leading to responses from 28 countries. Half of the respondents were from countries within the European Union (EU)/European Economic Area (EEA).

Reported child and adolescent tuberculosis in national guidelines

We queried the presence of key programmatic documents in Member States. Of 28 countries, 22 (79%) indicated the presence of a national strategic plan (Fig S2A), and 19 (68%) had updated this plan since 2015 (Fig S2B). Twenty-seven countries (96%) had a national child and adolescent TB guideline, 13 of these as a separate document and 14 as part of the main TB

guideline (Fig S2C). Nineteen (68%) countries with a national guideline had updated their guideline in the past 4 years (Fig S2D). The majority of Member States included both children and adolescents, while four (14%) discussed only children <15 years in their national guidelines (Fig S2E). Only nine (32%) Member States reported having a separate budget dedicated to child and adolescent TB (Fig S2F).

Reported availability of diagnostic tools and drugs

Respondents from 26 out of 28 countries (93%) had access to rapid molecular testing on the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) platform (Fig 1A). Only 15 (54%) countries were able to include the new drugs, bedaquiline and delamanid, in paediatric MDR-TB treatment regimens (Fig 1B), the majority (10/15) of which are considered high-priority TB countries.[13] Most countries (23/28, 82%) did not use the shorter MDR-TB regimen under operational research conditions (Fig 1C). Nine (32%) countries reported stock-outs for any paediatric TB drug in 2019 (Fig 1D). Drug stock-outs were experienced by both TB high-priority and non-high-priority countries. Overall, 16 (57%) countries indicated insufficient child-friendly second-line TB drug formulations in their country (Fig 1E). More non high-priority than high-priority countries (10 vs. 6) reported insufficient availability of child-friendly drugs than TB. Countries specified that several critical drugs for MDR-TB treatment regimens were not readily available in the WHO European Region (Fig 1F). The WHO has recently reclassified agents for the treatment of MDR-TB into three groups.[14] Among WHO Group A agents, levofloxacin was the only drug available in all countries. High proportions (≥80%) of respondents had access to other Group A and B agents, such as bedaquiline, linezolid, moxifloxacin, clofazimine and cycloserine. Access to Group C agents was sparser, with the exception of pyrazinamide and ethambutol.

Reported management of MDR-TB disease and infection

Lengthy MDR-TB hospitalisation durations were reported, predominantly in countries of the former Soviet Union (Figs 2A and B). Children were hospitalised for a median of 8 weeks (interquartile range [IQR] 5–22) and adolescents for 9 weeks (IQR 8–17). Respondents from two Member States said that children were hospitalised for 90 and 108 weeks, i.e., the duration of a full conventional MDR-TB treatment course.

The approach to active case-finding among children exposed to MDR-TB cases was similar across countries (Fig 2C). Most countries reported using either Mantoux only (tuberculin skin test; 8 countries) or interferon-gamma release assays (1 country) or a

combination of the two (17 countries) for screening for preventive therapy in exposed individuals. Preventive treatment of childhood MDR-TB contacts comprised a fluoroquinolone-containing regimen (reported by nine countries) or was designed according to the resistance profile of the index case (eight countries). In terms of programmatic documents, 14 Member States (50%) had a policy on treating children and adolescents who are exposed to an index case with MDR-TB (Fig S1B). When asked whether clinicians treat MDR-TB childhood contacts, we found that preventive therapy was provided in some or most cases (68%) (Fig S1C). Provision of preventive therapy was more common in non-high priority countries (12/13, 31%) than in high-priority countries (4/13, 45%).

Comparison of data sources of paediatric MDR-TB burden

Given the previously observed discrepancy between TB notifications and modelled incidence estimates in EU countries, we surveyed respondents on the total diagnosed childhood RR/MDR-TB cases in these countries in 2018.[5] We compared these numbers (survey-reported cases) to two different data sources, first, to the modelled incidence estimates by Dodd et al.[3] and second, to the WHO notified cases (WHO notifications).[2]

Survey-reported cases and modelled MDR-TB incidence

We calculated the proportion of RR/MDR-TB cases of total TB incidence in 2014, the year the estimate modelling was performed, and applied this proportion to the total incidence in 2018.[3] We observed a stark difference between the modelled incidence estimates and the survey-reported paediatric RR/MDR-TB cases for high-priority countries, with an average difference of 121 cases (range 659) (Fig 3A). The modelled incidence estimates in all these countries indicated higher MDR-TB numbers than the survey responses. In other countries of the Region, the mean difference was 1 case (range 4).

Survey-reported cases and WHO notifications

Some countries that relayed case numbers in the survey (Russian Federation, Kazakhstan, Azerbaijan) did not report any paediatric RR/MDR-TB cases to WHO in 2018 (Fig 3B). Among high-priority countries, 7 out of 12 had discrepancies, with a mean difference of 11 cases (range 50) between survey-reported cases and WHO notifications. Four out of these seven countries had reported more cases in the survey than via the WHO notification system (mean –26.5 cases, range 49), and three had reported more to the WHO than in the survey (mean 8 cases, range 14). The gap between RR/MDR-TB cases diagnosed in the countries and those reported to the

WHO via official channels was much smaller than the gap observed between diagnosed cases and modelled estimates of MDR-TB.

DISCUSSION

The survey identified several recent programmatic improvements for child and adolescent MDR-TB management. The high access to Xpert MTB/RIF is an important milestone and the inclusion of child and adolescent TB in national strategic plans, guidelines and budgets has increased compared to a previous survey.[15] Access to child-friendly, second-line drug formulations and the outdated practice of long periods of hospitalisations for MDR-TB treatment of children and adolescents are identified as two major hurdles in improving TB care for this age group.

Our results highlight the substantial discrepancy between modelled estimates of MDR-TB incidence and cases reported by country representatives through the survey, and also between survey responses and cases notified to the WHO. This highlights a steady loss of information between true incidence estimates (i.e., modelled incidence), diagnosed case counts (i.e., reported in this survey) and notified case counts (i.e., official WHO notifications). Official WHO notification data are critical for assessing and appraising the paediatric RR/MDR-TB situation in countries. The WHO has reported age-stratified (under and over 15 years of age) incidence estimates since 2012, and RR-TB notifications in children are available since 2017. Our observation of a gap between survey-reported cases and WHO notifications represents an actionable finding that can be addressed by NTP managers and stakeholders in the reporting hierarchy to ensure all children and adolescents are included in reporting systems.

The detection gap between modelled incidence estimates and diagnosed cases seen in our data is in line with previous findings.[3,4] Limited access to rapid molecular testing, and lower performance of microbiological diagnostics for paediatric TB and drug resistance challenge the detection of active cases in children.[16] The widespread availability of Xpert reported is promising, as this enables rapid detection of rifampicin resistance within hours.[17] A fundamental change would be to close the large detection gap for paediatric MDR-TB; this will necessarily require improved microbiological diagnostics and increasing numbers of children diagnosed clinically without microbiological confirmation.[18,19]

Lack of access to child-friendly drug formulations has previously been reported as a central challenge in paediatric MDR-TB,[15] as well as adult TB[20] management by WHO European countries. In the present study, we observed that large numbers of countries experience frequent drug stock-outs and do not have ready access to critical MDR-TB drugs,

including the new agents bedaquiline and delamanid. Both manufacturer- and country-level barriers to their use have been identified and partnerships with industry through compassionate use programmes have been initiated to permit ready access to these two drugs.[21,22]

The practice of lengthy hospitalisation of children and adolescents with MDR-TB is controversial and usually unnecessary. The hospital payment mechanisms may explain this in places where hospitals and departments are reimbursed at higher inpatient treatment rates than ambulatory care.[23] Further research is required to better understand the factors contributing to the continued use of this practice, given the impact on the lives of children and their families, along with resulting increased treatment costs. Advocacy by all stakeholders, including civil society, to reduce hospitalisation is also needed to change practice, along with the introduction of better incentives by funders and governments.

This study has limitations. First, it relies on the accuracy of responses provided by NTP representatives, which may have been affected by recall bias, or be otherwise error prone. The survey results reflect the representatives' perspectives and are not a direct analysis of patient data. Second, participants were nominated by their respective NTPs to attend the meeting and this power differential may have introduced bias. A third limitation concerns data completeness. The country representatives who attended and responded to our survey comprised 53% of the WHO European region's total Member States. Fourth, to encourage answers where exact numbers or estimates were likely not available, questions were phrased more qualitatively ('Is Xpert testing widely available?'). Also, the survey-reported numbers of diagnosed MDR-TB cases may be rough estimates or otherwise inaccurately represent the true number diagnosed. The comparison between WHO-notified and survey-reported MDR-TB case numbers was limited to countries that had both data points. Finally, despite developing both English and Russian language versions of the survey, language barriers may have resulted in errors and misunderstanding.

CONCLUSION

In conclusion, the survey identified shortcomings in NTPs that could be addressed to strengthen health systems for the management of child and adolescent MDR-TB. Although MDR-TB services for this age group in the WHO European Region have improved substantially over the last 5 years, regional strategies to eliminate MDR-TB are unlikely to be successful unless more progress is made.

Acknowledgements

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FIGURES

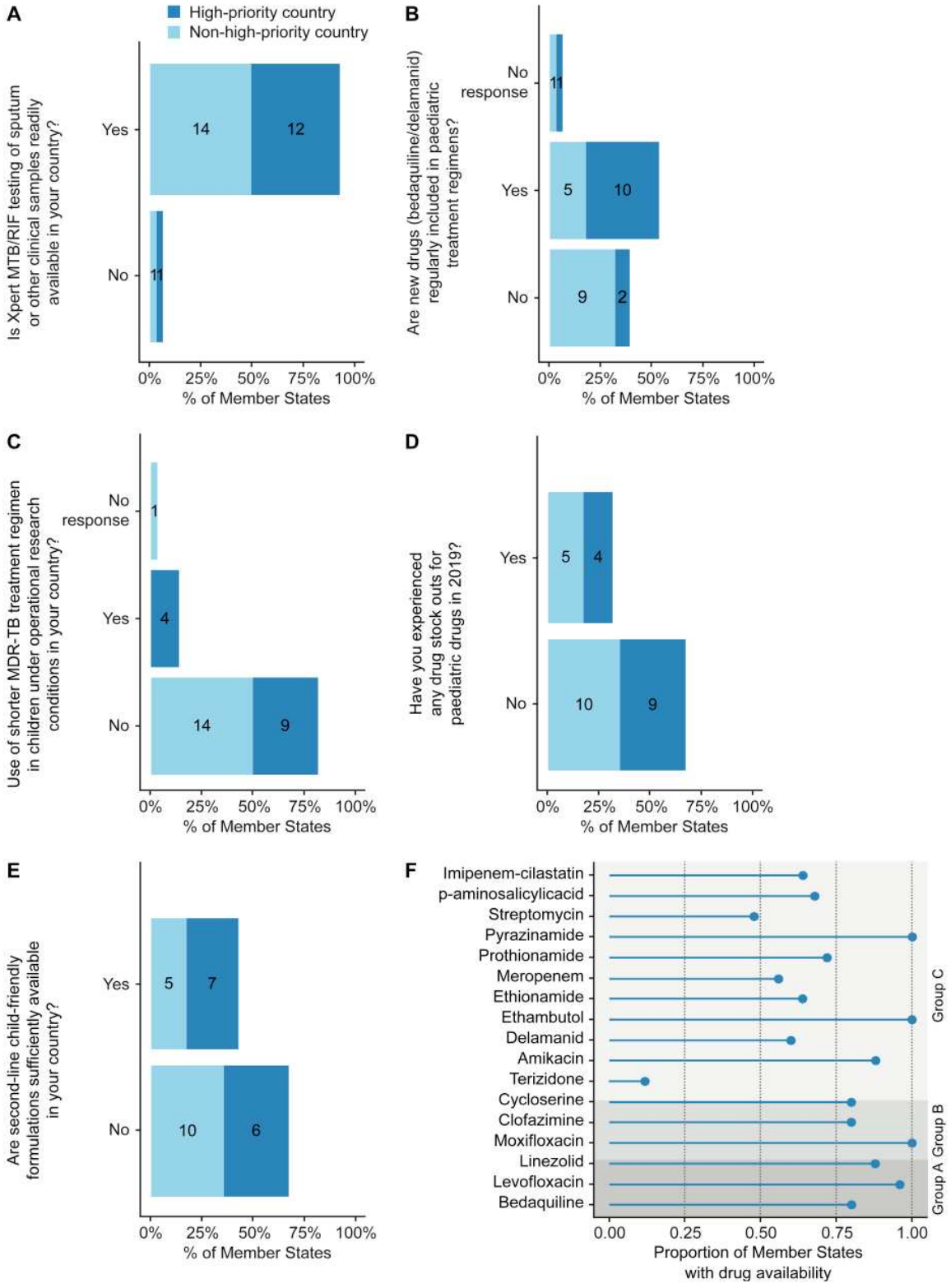
A
High-priority country
Non-high-priority country
Is Xpert MTB/RIF testing of sputum or other clinical samples readily available in your country?
Yes
No
14
12
11
0% 25% 50% 75% 100%
% of Member States
B
Are new drugs (bedaquiline/delamanid) regularly included in paediatric treatment regimens?
No response
Yes
No
11
5
10
9
2
0% 25% 50% 75% 100%
% of Member States
C
Use of shorter MDR-TB treatment regimen in children under operational research conditions in your country?
No response
Yes
No
1
4
14
9
0% 25% 50% 75% 100%
% of Member States
D
Have you experienced any drug stock outs for paediatric drugs in 2019?
Yes
No
5
4
10
9
0% 25% 50% 75% 100%
% of Member States
E
Are second-line child-friendly formulations sufficiently available in your country?
Yes
No
5
7
10
6
0% 25% 50% 75% 100%
% of Member States
F
Imipenem-cilastatin
p-aminosalicylicacid
Streptomycin
Pyrazinamide
Prothionamide
Meropenem
Ethionamide
Ethambutol
Delamanid
Amikacin
Terizidone
Cycloserine
Clofazimine
Moxifloxacin
Linezolid
Levofloxacin
Bedaquiline
Group C
Group B
Group A
0.00 0.25 0.50 0.75 1.00
Proportion of Member States with drug availability

Figure 1 Reported access to rapid diagnostics and treatment agents. Barplots show Member State representatives' responses stratified according to **A)** availability of rapid molecular testing, **B)** uptake of two new drugs in regular paediatric MDR-TB treatment regimens, **C)** use of the shorter MDR-TB regimen, **D)** occurrence of drug stock-outs, and **E-F)** the availability and access to MDR-TB treatment agents. The shaded areas in **(F)** represent the recent WHO reclassification of MDR-TB agents into three groups.[14] The vertical text shows the survey questions. Legend **(A)** indicates whether a Member State is part of the group of 18 TB high-priority countries in the WHO European Region (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan). The number of countries is plotted over the bars in each plot. MDR-TB = multidrug-resistant tuberculosis.

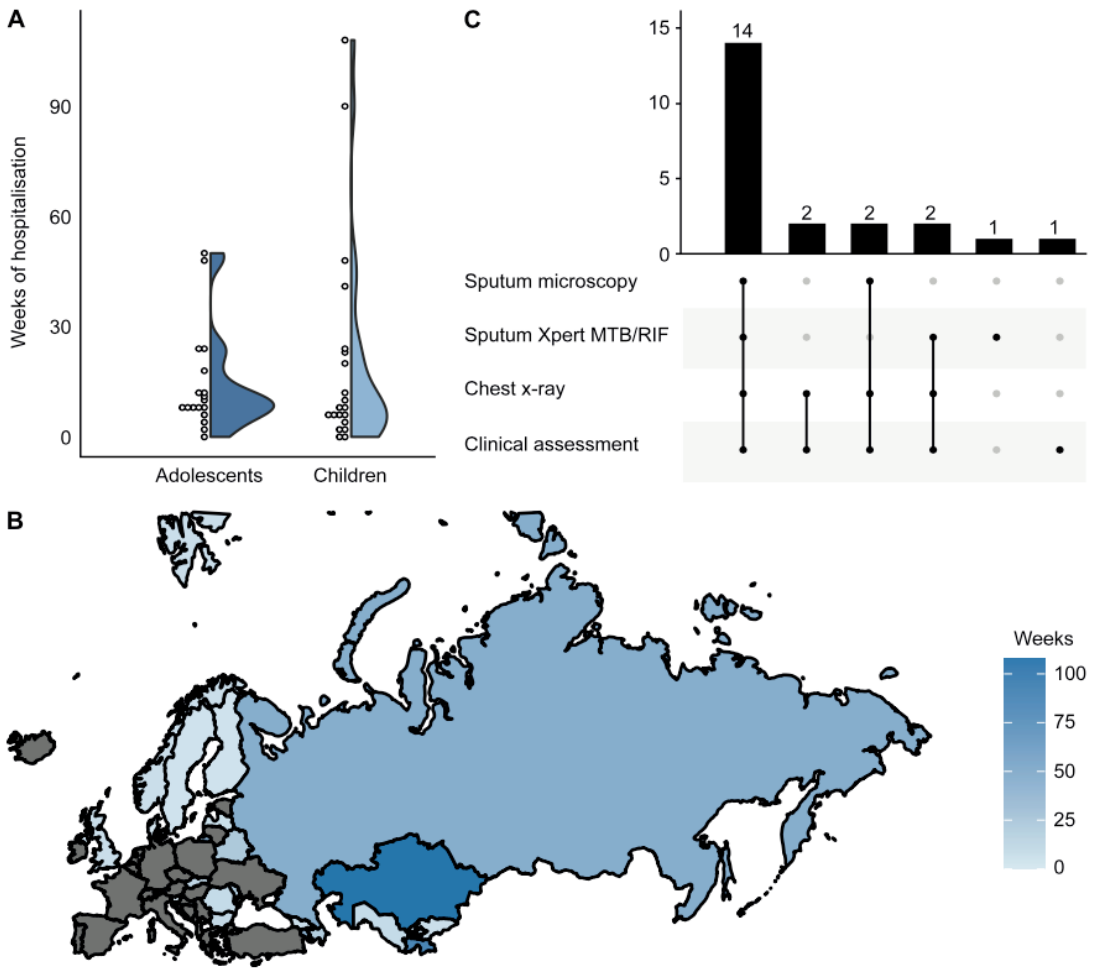

Figure 2 Reported prevention and care of paediatric MDR-TB infection and TB disease. **A)** Violin plot showing the reported length of hospitalisation in weeks for adolescents (15 to <20 years) and children (<15 years). Dots represent individual countries. **B)** Map of the WHO European Region (Greenland not shown) with countries coloured by the length of childhood (<15 years) MDR-TB hospitalisation in weeks. **C)** Intersection plot displaying the different combinations of reported clinical and diagnostic methods for diagnosing child and adolescent. MDR-TB = multidrug-resistant tuberculosis.

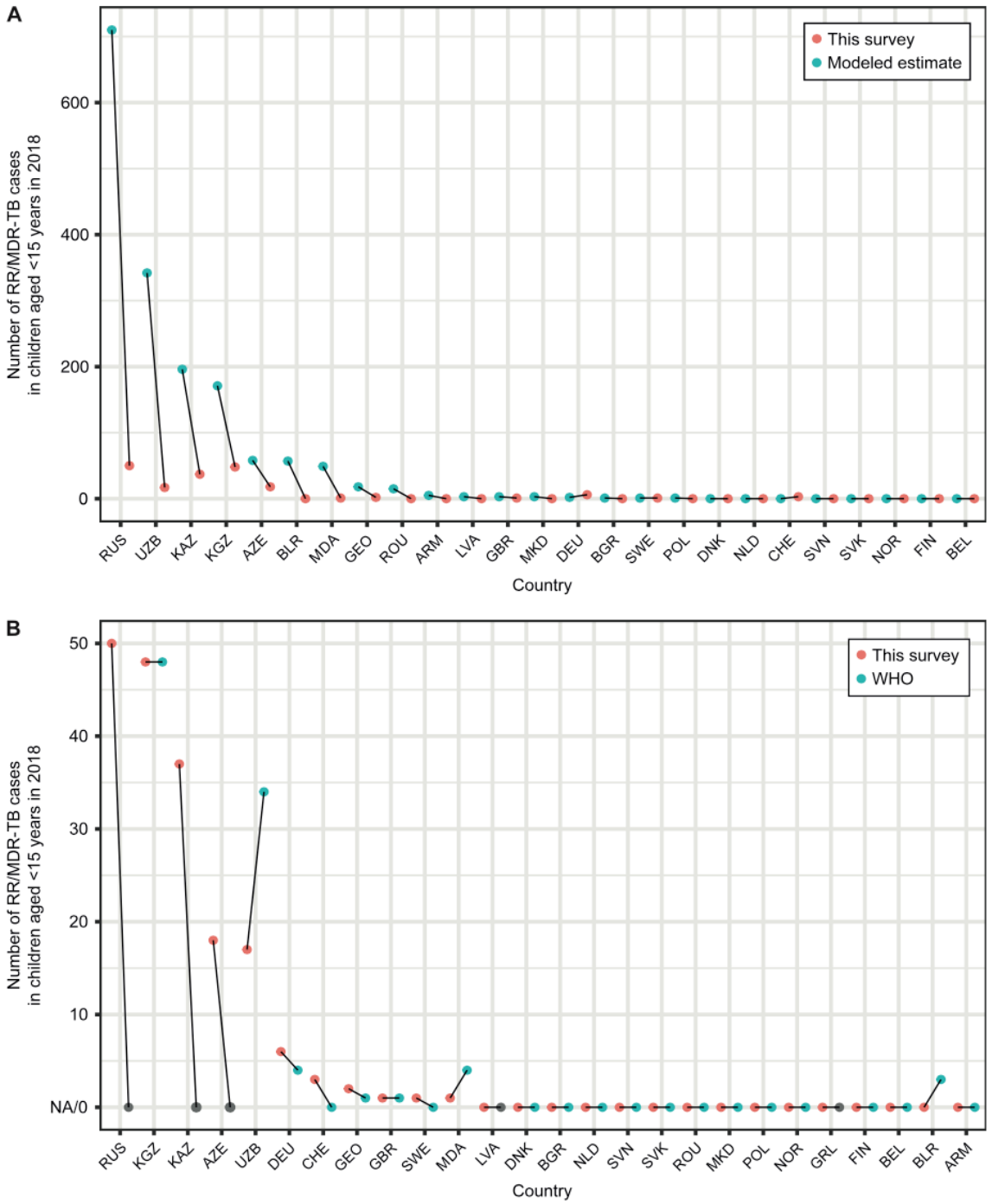

Figure 3 Comparison of paediatric (<15 years) RR/MDR-TB numbers across three data sources. **A)** Line plot comparing RR/MDR-TB cases reported in the survey and case number estimates obtained through mathematical modelling by Dodd et al.[2] **B)** Line plot comparing RR/MDR-TB case reported in the survey and official WHO channels.[1] Grey dots represent datapoints where no numbers were reported. RR/MDR-TB = rifampicin resistant/multidrug-resistant TB; RUS = Russian Federation; UZB = Uzbekistan; KAZ = Kazakhstan; KGZ = Kyrgyzstan; AZE = Azerbaijan; BLR = Belarus; MDA = Republic of Moldova; GEO =

Georgia; ROU = Romania; ARM = Armenia; LVA = Latvia; GBR = United Kingdom of Great Britain and Northern Ireland; MKD = North Macedonia; DEU = Germany; BGR = Bulgaria; SWE = Sweden; POL = Poland; DNK = Denmark; NLD = The Netherlands; CHE = Switzerland; SVN = Slovenia; SVK = Slovakia; NOR = Norway; GRL = Greenland; FIN = Finland; BEL = Belgium.