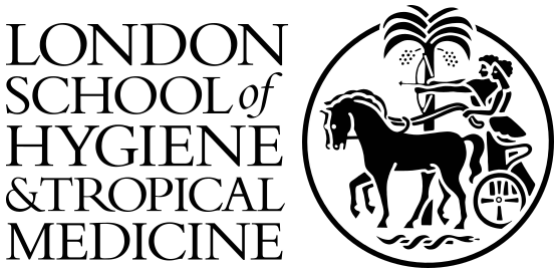

Title: The global burden of multi-drug resistant latent tuberculosis: recent trends and estimates using mathematical modelling

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Abstract

Background

To end the global tuberculosis epidemic, latent tuberculosis infection (LTBI) must be tackled. All recommended standard LTBI treatments contain drugs to which multi-drug resistant (MDR-) *Mycobacterium tuberculosis* are resistant. Hence knowledge of the MDR-*M.tb* global LTBI burden will inform TB elimination policy-making.

Methods

By fitting a flexible statistical model to TB drug resistance surveillance and survey data collated by the World Health Organisation, we estimated national trends in the proportion of new TB cases that were MDR-TB. This was used as a proxy for the proportion of new infections due to MDR-*M.tb* and multiplied ARI trends from previous LTBI estimate work to generate MDR-*M.tb* ARI trends. These were used within a new cohort model to estimate changing levels of latent infection with MDR-*M.tb* (MDR-LTBI). We report global and national prevalence of MDR-LTBI, as well as estimating recent infection levels and making predictions of the future burden in 2035 and 2050.

Findings

We found that 19 [95% uncertainty interval (UI): 16-22] million individuals carried MDR-LTBI in 2014. This represented 0·28% [95% UI: 0·24-0·31%] of the global population and 1·2% [95% UI: 1·0-1·4%] of all LTBI. Country prevalence ranged from 0·002% to 3·8% of the population. In those aged less than 15 years, the proportion of LTBI that is MDR was 2·9% [95% UI: 2·6-3·1%] (risk ratio compared to those over 15 years = 2·65 [95% UI: 2·11-3·25]). Recent MDR-*M.tb* infection meant that 1·9 [95% UI: 1·7-2·3] million individuals globally in 2015 were at high risk of MDR-TB disease.

Interpretation

We estimate that three in every 1,000 people globally carry MDR-LTBI, resulting in one in every 83 individuals with LTBI carrying MDR-*M.tb*, and one in every 34 in those less than 15 years old. With current trends the proportion of LTBI that is MDR will increase, posing serious challenges for LTBI management, a cornerstone of TB elimination strategies.

Funding

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Introduction

The complex natural history of the world's biggest infectious disease killer, *Mycobacterium tuberculosis* (*M.tb),* means that for ultimate control those latently infected must be targeted.[1,2] Currently, latent tuberculosis infection (LTBI) is defined as "a state of persistent immune response to stimulation by *M. tb* antigens with no evidence of clinically manifest active TB".[3] It has been estimated that 23% of the world's population could have LTBI and that even without ongoing transmission after 2014, reactivation disease would overwhelm the 2035 End TB Targets.[4] Hence, understanding and targeting LTBI is a priority for TB elimination efforts,[2] as recognised by the 2018 UN High Level Meeting on TB.[5]

Antimicrobial resistance (AMR) is an increasingly serious threat to global public health.[6] Multidrug-resistant (MDR) strains of *M.tb*, which are resistant to both key first line TB drugs (rifampicin and isoniazid) cause approximately one in four of all AMR deaths.[7] In 2017, MDR-TB contributed to over 10% of TB deaths globally.[8] MDR-TB patients experience low rates of appropriate diagnosis, low treatment success, and unacceptably long treatment regimens (>18months). MDR-TB already accounts for a disproportionally large fraction of the financial burden for TB control programmes. Preventing an increase of MDR-TB from a growing reservoir of MDR-LTBI (i.e. LTBI caused by MDR-*M.tb* strains) is therefore critical for the success of any TB control programme.

Worryingly, MDR-*M.tb* are resistant to all currently recommended therapies prescribed to reduce the risk of progression to active disease for people with LTBI who are not known contacts of an MDR-TB patient.[3] The priority population for LTBI testing and preventative therapy is currently household contacts of TB cases,[9] likely to be infected by their household member, but in high incidence settings, infection may also frequently occur outside of the home.[10] Due to such external transmission,[11] and low detection (<30%) of MDR-TB cases,[8] a substantial proportion of MDR-LTBI individuals will not have had recognized MDR-TB contacts and standard preventive therapy could be less effective. All current LTBI diagnostics rely on measuring immune response,[9] and cannot determine the strain, nor resistances, of any infecting *M.tb*. Hence, estimating MDR-LTBI levels can help inform estimates of standard LTBI therapy efficacy. These estimates can also help guide usage of tailored preventive treatment for contacts of MDR-TB patients[3,12] and setting specific demand for new regimens (which include levofloxacin and delamanid), currently being tested.[13-15]

In addition, as overall TB incidence and annual risk of infection (ARI) of TB decrease, there will be fewer people infected with LTBI (DS or MDR) which is thought to partially protect against *M.tb* reinfection.[16-18] If the TB epidemic becomes increasingly driven by MDR transmission, the presence of an existing "protective" primary DS-LTBI infection is less likely, which could further facilitate an increasing MDR-TB burden in the younger generation.[19] Hence, a decrease in total LTBI prevalence going forward may facilitate an increased proportion of LTBI that is MDR.

No direct data on levels of MDR-LTBI exist as we cannot currently isolate any infecting *M.tb* bacteria and so cannot test for resistance. Hence, a modelling approach is the only way to estimate this metric of TB burden. We developed a new mathematical model which follows cohorts over time, applying historical ARIs estimated by a previous study[4] to track who becomes infected with LTBI. Capturing trends in the proportion of new TB cases that are MDR as a proxy for the proportion ARI that is MDR,[20] allowed us to estimate trends in MDR-*M.tb* infection risk and hence the proportion of each cohort with LTBI that carried MDR-*M.tb.* Using this we could estimate global MDR-LTBI levels.

Methods

Countries included

138 countries had both data on MDR levels in newly treated patients (survey or surveillance data) from the WHO Drug Resistance Surveillance (DRS) Project, and were included in the original total LTBI estimates.[4] These countries account for 93% and 96% of the total incident TB and MDR-TB burden in 2016 respectively, and include 28 of the 30 high MDR-TB burden countries.[8] The two high MDR-TB burden countries that we excluded had no WHO DRS data (Angola and the Democratic Republic of the Congo) and each contributed <1·5% of the estimated global incident MDR-TB burden in 2016[8]. All details of country selection are given in the appendix.

Trends in MDR-M.tb annual risk of infection (ARI)

In order to estimate the burden of MDR-LTBI we needed trends in the annual risk of infection (ARI) with MDR-*M.tb*. Previous work combined tuberculin skin test (TST) surveys with prevalence data and a revised Styblo rule to generate ARI with all *M.tb* for 168 countries.[4] A previous systematic review showed that levels of MDR-TB in children and treatment-naïve adults with TB was a reflection of the current local MDR transmission.[20] Hence, we used the proportion of MDR-TB in new TB cases reported to the WHO as a proxy for the proportion of ARI with *M.tb* that was with MDR-*M.tb*. Fitting trends in the country-level proportions of MDR-TB in new TB cases (see below) to the WHO DRS data was used to provide 200 samples from the posterior of potential fits. These were multiplied by the total ARI with *M.tb* trend estimates from previous work,[4] to give ARI with either *M.tb* strains not resistant to both rifampicin and isoniazid (drug susceptible, DS-) and MDR-*M.tb*.

To capture the changing proportion of new TB cases that are MDR we fitted a flexible statistical model to the WHO DRS data for MDR levels in new TB cases for each country over time using a Bayesian Markov chain Monte Carlo (MCMC) approach with the *RStan* package in R (appendix).[21] This model allows for increases, stabilisation, and also subsequent decreases in the MDR proportion over time. In the absence of extensive timeseries data (see appendix for a time plot of WHO data), this was fitted with informative priors, reflecting three data-based assumptions about MDR trend characteristics, to constrain the potential pattern of MDR-TB increase.

Firstly, we assumed that it was very unlikely that detectable levels of MDR-TB could have appeared in any country before 1970 (see appendix for references). To capture this time constraint, the model fitted, for each country, a time when the proportion of new cases that were MDR-TB was assumed to appear at measurable levels. The prior for this parameter was normally distributed with a mean of 1985 and a 95% range between 1970 and 2000. This matches a previous modelling study's assumption that "transmissible" MDR-*M.tb* strains arose 20-60 years before 2013.[22]

Secondly, the rate of increase in proportion of new cases that were MDR was governed by two parameters (*b* and *c*, see appendix) that were scaled to prevent too rapid an increase while still capturing the wide range of MDR levels (including some very low rates of increase). Thirdly, we ensured that our model did not allow for a "peak and crash" in the proportion with MDR-TB. The details for the choice of priors and plots of the trends generated by these assumptions are given in the appendix.

Estimating LTBI burden

The estimates of both DS- and MDR-*M.tb* ARI were inputted into a new cohort model, tracking the proportion of individuals at each age group infected with DS- or MDR-*M.tb* (appendix) from 1934 to 2014. The initial conditions are calculated assuming a constant ARI pre-1934, and there is assumed to be no MDR-TB before 1960 (appendix). We present the estimates of LTBI in 2014 as this is the final time point in the ARI trends.[4] Protection against reinfection is taken to have a mean of 79%.[16] We included all available WHO DRS data in the fitting process, i.e. trends in proportion of new TB that is MDR used WHO MDR-TB data up to 2018 (single data point from Togo).

Specifically, the burden we aim to characterise here is of the number of individuals with a persistent immune response to stimulation by *M.tb* antigens without evidence of clinically manifested active TB.[3] We report the resistance status of the last infecting strain (e.g. MDR- or DS-*M.tb*) taking into account protection against reinfection, ignoring dual infections, and, in the absence of a quantitative alternative, assuming lifelong infection.

Recent levels of infection

We used model output to estimate the population infected with MDR-*M.tb* within the last two years (2013-2014) who would therefore be at a higher risk of progressing to active MDR-TB. These were chosen as these are the last two years for which we had modelled ARI trends from previous work.[4]

Risk ratio by age

We calculated the risk ratio for those under 15 years old having MDR-LTBI conditional on having LTBI, compared with those 15 or more years old. We chose 15 years old as the cut-off to match previous LTBI age segregated estimates and as this is a standard cut-off in TB natural history, as reflected in the WHO data.[8]

Burden of disease in 2035 and 2050

To estimate the contribution of these levels of MDR-LTBI to disease burden in 2035 and 2050, we assumed no *M. tb* transmission after 2014. Using UN Population Division demographic projections[23] we then estimated the MDR-LTBI burden in 2035 and 2050 and the level of MDR-TB disease (incidence) assuming a 0.03% per year remote activation rate, and explored this value in a sensitivity analysis.[24] We compared this to the WHO End TB targets of less than ten TB cases per 100,000 population by 2035, and the Stop TB target of less than one TB case per million population by 2050.[1]

MDR-LTBI data coverage

To compare how well-informed by resistance data our MDR-LTBI estimates were, we used the cohort model to determine the proportion of LTBI in 2014 that originated in each 5-year time block in the past (e.g. 20% of those with LTBI in 2014 were infected in 2000 – 2005 in country X). The sum of all proportions from five year time blocks that had any WHO DRS data for that country gave the data coverage value (appendix). This gave a metric that combined the contribution of a time period to MDR-LTBI burden with whether data was present in that time to compare availability of MDR data by setting. The higher the value, the greater the overlap between contribution of a time period to MDR-LTBI burden and data availability.

Sensitivity analyses

There is an ongoing debate as to the fitness costs associated with the appearance of resistance within *M.tb*.[25,26] We undertook sensitivity analysis applying a 40% fitness cost[25] to the protection from reinfection (from 78% to 47%), and separately to the rate of reactivation (from 0.03% to 0.018%/year), in those with MDR-LTBI. We also undertook a sensitivity analysis on trend shape: allowing for more flexible dynamics in MDR-ARI in a subset of countries with sufficient data and a potential "peak and crash" in their proportion of all TB disease that was MDR (see appendix for details).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Trends in levels of MDR-TB

Model fits for all 138 countries gave estimates of the proportion of new TB cases that are MDR-TB that closely matched the WHO data (see appendix for individual country trends). Examples of model fits for countries in the WHO South-East Asia region are shown in figure 1. Here the substantial uncertainty associated with the lack of data prior to 1990 can be seen, as well as the rising trend in the proportion of new cases that are MDR-TB across all countries.

Estimates of MDR-LTBI

We estimate a global prevalence of MDR-LTBI in 2014 of 0·28% [95% uncertainty interval (UI): 0·24-0·31%] (table 1, figure 2), representing 19 [95% UI: 16-22] million individuals with MDR-LTBI in 2014 (table 2). Of the global LTBI burden, 1·2% [95% UI: 1·0-1·4%] is due to MDR-*M.tb*. Combined with our estimates of DS-LTBI prevalence, total LTBI estimates match previous modelling,[4] validating the new cohort model approach used here.

Geographical heterogeneity in the prevalence of MDR-LTBI was substantial, with the lowest estimate in the Region of the Americas (0·05% [95% UI: 0·04-0·06%], table 1, figure 2). Variation in the estimates within the West Pacific Region was large. Reflecting the data showing an increasing proportion of new cases being MDR-TB, across the six regions we estimate that there has been a substantial increase in MDR-LTBI since 1990 (figure 2).

The estimates for prevalence of MDR-LTBI by country (figure 3 and appendix), show that most countries with estimates have a prevalence of MDR-TB of less than 1%, whilst countries in Eastern Europe and Central Asia have a prevalence of above 1·5%. Among the top-30 MDR burden countries, Kazakhstan had the highest percentage of LTBI that is MDR at 17·5% [95% UI: 6·5-22·9%] (appendix). China (~6 million), India (~4 million) and Russia (~1·8 million) had the highest absolute numbers of individuals with MDR-LTBI (appendix).

In children, the global percentage of LTBI that is MDR (<15 years old) is more than double that in the total population at 2·9% [95% UI: 2·6-3·1%] (table 1), with the highest relative rate in the European region (14·1% [95% UI: 13·1-15·2%] in children, vs. 2·8% [95% UI: 1·6-3·9%] in the total population). Aggregating by WHO region shows that in all regions there is a peak in MDR-*M.tb* infection between 20 and 35 years old (figure 4). The risk ratio for MDR-LTBI by age (i.e. the ratio of the proportion of those with LTBI that was MDR in those < 15 years old vs. those > 15 years old) was 2·65 [95% UI: 2·11-3·25].

The number of individuals with recent MDR-LTBI infections in the past two years were estimated at 1·9 [95% UI: 1·7-2·3] million individuals, or 0·03% [95% UI: 0·02%-0·03%] of the global population in 2014. This population is at high risk of progressing to active MDR-TB. In children, we estimate that 0·6 [95% UI: 0·6-0·8] million individuals aged < 15 years old were recently infected with MDR-TB in 2014.

Future projections of MDR-LTBI in 2035 remain high even assuming no ongoing transmission from 2015: 14 [95% UI: 12-16] million, decreasing to 11 [95% UI: 10-12] million by 2050 (see appendix for a map of the prevalence). MDR-TB disease incidence from this latent pool would be 0·48 [95% UI: 0·42-0·53] per million per year in 2035 and 0·34 [95% UI: 0·30-0·38] per million per year in 2050. These estimates do not exceed the 2035 WHO End TB or 2050 Stop TB targets (< one TB case per million) by 2050.[1]

Metric for data coverage

The mean and range of the metric for data coverage across all countries and model fits was 0·56 [0 - 1]. Fourteen countries had median metric values of 1 suggesting that data was available within all contributing time periods. Four countries had zero metric values as they only had data after 2014. The best data coverage for the 30 high MDR burden countries was in Russia, Thailand and Uzbekistan (median metric values 0·87 – 0·99), whilst only one had a median metric value below 0·25: Zimbabwe (appendix). The top four countries in terms of number with MDR-LTBI (appendix) had median metric values above 0·5.

Sensitivity analyses

Reducing the protective effect of MDR-LTBI to reinfection by 40% resulted in a < 1% difference to all our results on MDR-LTBI prevalence (appendix). The risk ratio for MDR-LTBI by age decreased slightly to 2·47 [95% UI: 2·03-2.97]. A 40% fitness cost affecting progression from MDR-LTBI to active disease (reactivation) reduced TB disease incidence from the stable MDR-LTBI pool to 0·29 [95% UI: 0·25-0·32] and 0·20 [95% UI: 0·18-0·23] per million with MDR-TB in 2035 and 2050 respectively. Allowing for more flexible dynamics resulted in a pre-1995 peak (i.e. before data was available) in the proportion of new TB that is MDR in the three countries included (China, India and the USA). This increased overall MDR-LTBI estimates but had limited impact on the MDR-LTBI estimates in those aged less than 15 years (appendix).

Discussion

We estimate that in 2014 the global prevalence of MDR-LTBI was 0·28% [95% UI: 0·24-0·31%] with substantial variation by geography and age group. The proportion of LTBI that is MDR was 1·2% [95% UI: 1·0-1·4%], but more than double this at 2·9% [95% UI: 2·6-3·1%] in children (< 15 years old). We estimated that if all transmission stopped in 2015, reactivation cases from MDR-LTBI alone would not exceed the one per million target for TB elimination by 2050, but would alone contribute approximately a third of the target.[1] For all WHO regions we found that the levels of MDR-LTBI are increasing.

Our analysis suggests that MDR-LTBI prevalence currently peaks in 20 – 35 year olds. This reflects the combination of lower LTBI prevalence in younger age groups due to lower cumulative exposure time, but an increase in the proportion of *M.tb* infections that are MDR from the early 1990s. A high burden of MDR-LTBI in children has been estimated previously, but the latter model assumed a constant ARI and did not consider other age groups.[27] We showed that children have double the chance of having LTBI that is MDR compared to adults, which is worrying given their higher rates of progression to disease and lower probability of appropriate diagnosis or treatment for MDR-TB compared to adults.[28] For future MDR-TB burden, these children also represent a long-persistent reservoir for MDR-TB disease, in the absence of substantial and effective roll-out of new LTBI preventative therapy programmes. This higher burden is driven by the increasing proportion of ARI that is due to MDR-TB, within the globally decreasing TB-ARI trend. Hence, children are more likely to be infected with MDR-*M.tb* bacteria than the current generation of adults were. Indeed, the current generation of adults are partially "protected" from the current TB-ARI by higher levels of DS-LTBI,[16-18] and hence are less likely to have MDR-LTBI. The public health implications of this are that, independently of MDR-TB contacts, LTBI infection cases in children should be considered at a higher risk of being MDR.

Our top-ranked WHO global regions by MDR-LTBI prevalence (European and Western Pacific) in 2014 matched the ranking for proportion of new cases with MDR-TB in the WHO 2018 Global TB report.[8] These estimates, alongside country level values, should help to guide preventative therapy in some settings: high levels of MDR-*M.tb* infection in LTBI in high incidence settings may suggest that standard LTBI preventative therapy should be given with even more caution to household contacts and that possible second-line therapies, such as those currently under trial,[13-15] should be considered.

Our estimated trends in MDR-LTBI at the WHO regional level were all increasing, as has been estimated previously for China[29] and for isoniazid-resistant latent infection in Lesotho[30], despite WHO estimates suggesting that MDR-TB incidence is currently relatively stable. Our aim was to characterize historical patterns of change in MDR-ARI to inform MDR-LTBI burden rather than to determine current trajectories in MDR-TB incidence.

We have created a generalisable approach to combine historical data from country-level with generally informative priors on MDR appearance to estimate global MDR-LTBI levels. We used informative priors to capture the timings of isoniazid and rifampicin usage and limited rates of increase to better support the data available. A strength of our approach is the inclusion of a range of trajectories in the proportion of new TB cases that are MDR. Our model was also able to track infection by age, which highlights the increasing burden in younger age groups. We also included sensitivity analyses around the impact of MDR on protection from reinfection and rate of reactivation, finding that the former had little effect on our results whilst the latter reduced our predicted MDR-TB incidence by approximately 40% (in line with the assumed parameter reduction). This highlights the importance of determining this parameter for forecast analysis.

However, our analysis has several limitations. The first of these is the reliance on historical trends in proportion of new TB cases that are MDR-TB when little data exists prior to 1990. By setting relatively informative priors (e.g. very unlikely that MDR arose before 1970) and allowing for both quadratic and linear curves we believe we have explored a reasonable area of potential MDR trend space and reflect this in our wide uncertainty ranges, but this was fundamentally limited by the amount and precision of data. We explored this in a sensitivity analysis for a limited set of high MDR burden countries where data indicated a potential peak in MDR-ARI before data was available, by fitting more flexible spline models. While this had an impact on our results, it assumed MDR transmission to rise rapidly from 1970 onwards and pushed the limits of the available data. It is clear, however, that overall MDR-LTBI prevalence is sensitive to data and assumptions of pre-2000 trends, and future work could include past trend determination, especially for China (possibly through phylogenetic analysis) as this contributed most to the observed change in MDR-LTBI prevalence. Our data availability metric shows that most countries in the top 30 MDR countries had good data availability (median metric values above below 0·5). New drug resistance surveys or improved surveillance are needed to estimate levels of recent MDR-TB infection that could then be

used to update our MDR-LTBI estimates. When countries had both survey and surveillance data available, we also did not treat the data differently (e.g. to account for potential underreporting in surveillance).

A second limitation is the homogeneity assumed in the model in terms of contact patterns, strain differences, reactivation rates, spatial variation and population characteristics. By not including differences in mixing patterns by age, we may have missed some age variation: age assortative mixing, combined with changing disease presentation[31] may result in further differences between children and adults. In terms of strain variation, we did show that reduced reactivation rates for MDR-TB had a substantial impact on future MDR incidence suggesting that strain variation differences in reactivation rates could drive differences in MDR incidence globally. For example, future work could estimate variance in MDR-LTBI prevalence by HIV status, which may have consequences for assumed fitness costs to resistance and hence greater levels of MDR-LTBI infection in HIV positive populations. Similarly, we modelled, and averaged surveillance and survey data, at the national level, which for some settings, such as the Russian Federation, may not be appropriate.

We also assume lifelong infection, despite the likelihood that self-cure is possible following *M.tb* infection.[19] Indeed most of the LTBI estimates are based on TST and some TST positives may have cleared their *M.tb* infection, suggesting that the reservoir of true *M.tb* infection for reactivation is smaller than estimated LTBI prevalence (defined through persistent immune response).[32] We also present recent infection levels which are likely to cause the majority of current cases of MDR-TB disease. While our results may overestimate the population carrying MDR-*M.tb*, this is accounted for in our estimates of MDR-TB disease driven by reactivation from MDR-LTBI; the implications for global elimination targets are likely to be robust. We also only modelled MDR, not all rifampicin resistance, as historical data was on MDR- not rifampicin-resistance levels.

A further complexity that we did not explore here was mixed infection as the dynamics of reactivation and mixed strain disease are not fully understood, despite their importance.[33] LTBI was assumed to be with the last successfully infecting strain (e.g. MDR- or DS-*M.tb*, taking into account protection against reinfection). However, given the relatively low ARIs in past decades, potential mixed infections make up a low proportion of all MDR-LTBI, and are unlikely to affect the total number of cases carrying MDR- or DS-LTBI.

Furthermore, in our main analysis we used a single study estimate for the level of protection against reinfection progression conferred by LTBI status,[16] despite there being other varying estimates available.[17,18] This estimate captures potential risk reductions in infection and/or of progressive TB dependent on LTBI status, which are currently not possible to separate. We explored the impact of this parameter by lowering the protection again reinfection for MDR-LTBI in our sensitivity analysis, finding a < 1% change. We did not include a sensitivity analysis for all LTBI as this result, and the impact in previous work[4] of reducing protection from the mean 79% used here to 50% for all LTBI, was so small. The only impact seen in the previous work[4], which was also reflected in the slightly reduced risk ratio for MDR-LTBI by age in our sensitivity analysis, was on the age distribution of recent infections, pushing there to be more in older age groups.

The broader, public health implications of this work are that evidence for the efficacy of current and potential preventative therapies for those potentially carrying MDR-LTBI needs to be strengthened and the recommendations possibly made context specific. Our estimates also provide some idea of the value of a diagnostic test to differentiate between the resistance status of LTBI strains. In terms of future modelling work, there is a need to quantify the rate and proportion of self-clearance of LTBI to better estimate the size of the reactivation reservoir. For future transmission, it will be important to explore the impact of any fitness costs conferred by resistance carriage in *M.tb* on natural history progression, as well as to better determine the trends in MDR-*M.tb* ARI.

Conclusions

Our estimates suggest that one in every 83 individuals with LTBI carries an MDR-*M.tb* strain, resulting in nearly three in every 1,000 people globally carrying MDR-LTBI. However, in children the number with LTBI that is MDR is one in every 34 and will be higher still in close contacts of those with MDR-TB. Using WHO data on proportion of new TB cases with MDR, we found that levels of MDR-LTBI are increasing in all WHO regions. With these current trends, the MDR-LTBI proportion will only increase, posing serious challenges for LTBI control, a cornerstone of TB elimination strategies.

Contributors

GMK, RMGJH and PJD conceived and designed the study. GMK led data analysis and modelling, and wrote a first draft of the article. RMGJH, FM, GMK and PJD designed the methodology and critiqued the results. All authors contributed to editing the final draft.

Conflicts of interest

We declare that we have no conflicts of interests.

Ethics committee approval

We required no ethics approval for this study.

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Figure Legends

Figure 1: Median (black line) and 95% uncertainty range (blue shaded area) from 200 model fits to WHO data (red) for the nine included countries from the WHO South-East Asia region. Results for all countries are given in the appendix. Note the varying y axis limits and that although we estimated MDR-LTBI burden in 2014 (hence the cut-off shown here) the model trend was fitted to all WHO DRS data.

Figure 2: MDR-LTBI prevalence over time by WHO region. The black line is the median, with shaded red areas being the 95% uncertainty interval for each region from 200 model fits.

Figure 3: Estimated population prevalence of MDR-LTBI (%). Countries with no data shown in grey. The same mapping at 2035 and 2050 is shown in the appendix.

Figure 4: The percentage of the population in each age group for each of the six WHO regions with MDR-LTBI. The DS-LTBI levels are shown in the appendix. Error bars indicate 95% uncertainty interval.

490 ***Tables***

WHO Region	DS-LTBI prevalence (%)	MDR-LTBI prevalence (%)	LTBI that is MDR (%)	LTBI that is MDR in <15 year olds (%)
African	22·1 [20·1-25·5]	0·23 [0·19-0·29]	1·0 [0·8-1·3]	2·3 [1·9-2·7]
Americas	10·6 [7·3-19·0]	0·05 [0·04-0·06]	0·5 [0·3-0·8]	3·3 [2·8-4·1]
South-East Asia	30·7 [27·7-34·5]	0·31 [0·23-0·41]	1·0 [0·7-1·3]	2·2 [1·9-2·6]
Eastern Mediterranean	16·4 [13·5-20·9]	0·14 [0·08-0·24]	0·9 [0·5-1·5]	2·9 [1·9-3·8]
Western Pacific	26·8 [17·8-39·2]	0·36 [0·26-0·49]	1·3 [0·7-2·2]	3·7 [3·3-4·1]
European	13·5 [9·9-19·8]	0·38 [0·32-0·44]	2·8 [1·6-3·9]	14·1 [13·1-15·2]
GLOBAL	22·9 [20·1-26·1]	0·28 [0·24-0·31]	1·2 [1·0-1·4]	2·9 [2·6-3·1]

491

492 **Table 1: Proportion of population infected with *Mycobacterium tuberculosis* of differing drug resistance**
493 **type, by WHO region, in 2014**. Brackets indicate 95% uncertainty interval.

494

WHO Region	Number with DS-LTBI (thousands)	Number with MDR-LTBI (thousands)
African	155,000 [141,000-179,000]	1,590 [1,310-2,010]
Americas	102,000 [70,700-183,000]	510 [418-624]
South-East Asia	584,000 [527,000-656,000]	5,810 [4,410-7,750]
Eastern Mediterranean	96,000 [78,900-122,000]	837 [481-1,410]
Western Pacific	493,000 [326,000-720,000]	6,620 [4,840-9,000]
European	122,000 [90,100-180,000]	3,440 [2,920-3,990]
GLOBAL	1,580,000 [1,380,000-1,800,000]	19,100 [16,400-21,700]

Table 2: Number (thousands) of individuals infected with *Mycobacterium tuberculosis* of differing drug resistance type, by WHO region, in 2014. Brackets indicate 95% uncertainty interval.