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What is the True Tuberculosis Mortality Burden? Differences in estimates by the World Health Organization and the Global Burden of Disease study

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Key Words:	tuberculosis, mortality, epidemiology, estimates, burden

Table 1. Basic characteristics of the models and methodology used by the World Health Organization and the Global Burden of Disease study to obtain country specific and global TB mortality estimates.

	WHO	**GBD**
Overall model strategy	Several internally consistent models	Cause Of Death Ensemble approach (mix effects regression)
Data sources included in models:		
Vital registration data	Yes	Yes
Mortality surveillance data	Yes	Yes
Verbal autopsies	No	Yes
Prevalence surveys	Yes	No
Specific case fatality ratios	Yes	No
Data stratified by HIV status	Yes	Yes
Data stratified by age	Yes (two groups)	Yes
Data stratified by sex	Yes (adults)	Yes
Population	UN estimates	GBD estimates
Methods published?	Yes	Yes
Uncertainty incorporated	Yes	Yes

Table 2. Global absolute differences in TB attributable number of deaths during 2015, as estimated by the World Health Organization and the Global Burden of Disease Study, by sex, age group and HIV status.

		# deaths (GBD)	# deaths (WHO)	Difference	% difference (WHO ref)	% difference (GBD ref)
Total	HIV+TB only	211604	389042	177438	-84%	46%
	TB only	1111312	1379440	268128	-24%	19%
	Total TB	**1322916**	**1768482**	**445566**	**-34%**	**25%**
Adults	HIV+TB only	177567	348026	170458	-96%	49%
	TB only	1075691	1210620	134929	-13%	11%
	Total TB	1253257	1558645	305388	-24%	20%
Children	HIV+TB only	34037	41016	6979	-21%	17%
	TB only	35621	168821	133199	-374%	79%
	Total TB	69659	209837	140178	-201%	67%
Female*	HIV+TB only	78110	143496	65386	-84%	45%
	TB only	367764	352488	15276	4%	-4%
	Total TB	445874	495984	50110	-11%	10%
Male*	HIV+TB only	99457	204471	105013	-106%	51%
	TB only	707927	858132	150205	-21%	18%
	Total TB	807383	1062603	255219	-32%	24%

*Sex stratification was only possible among adults (WHO does not provide sex stratification in people <15 years of age).

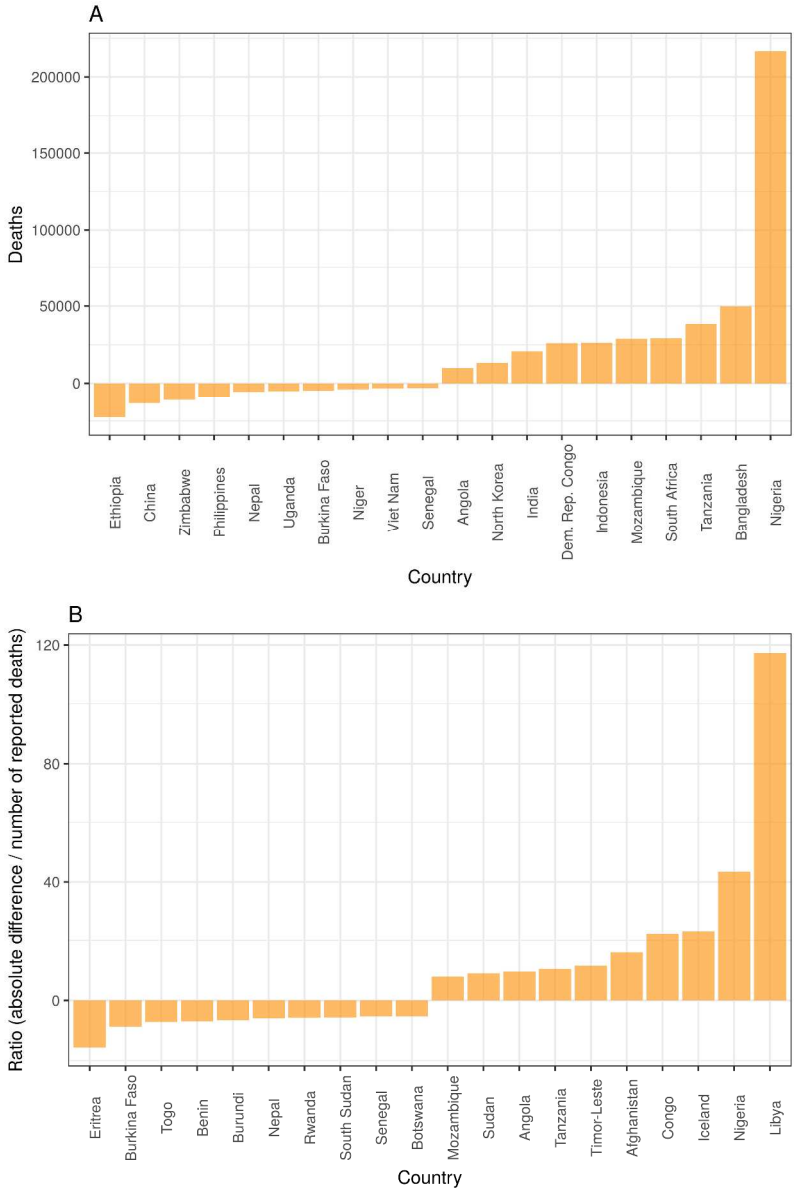
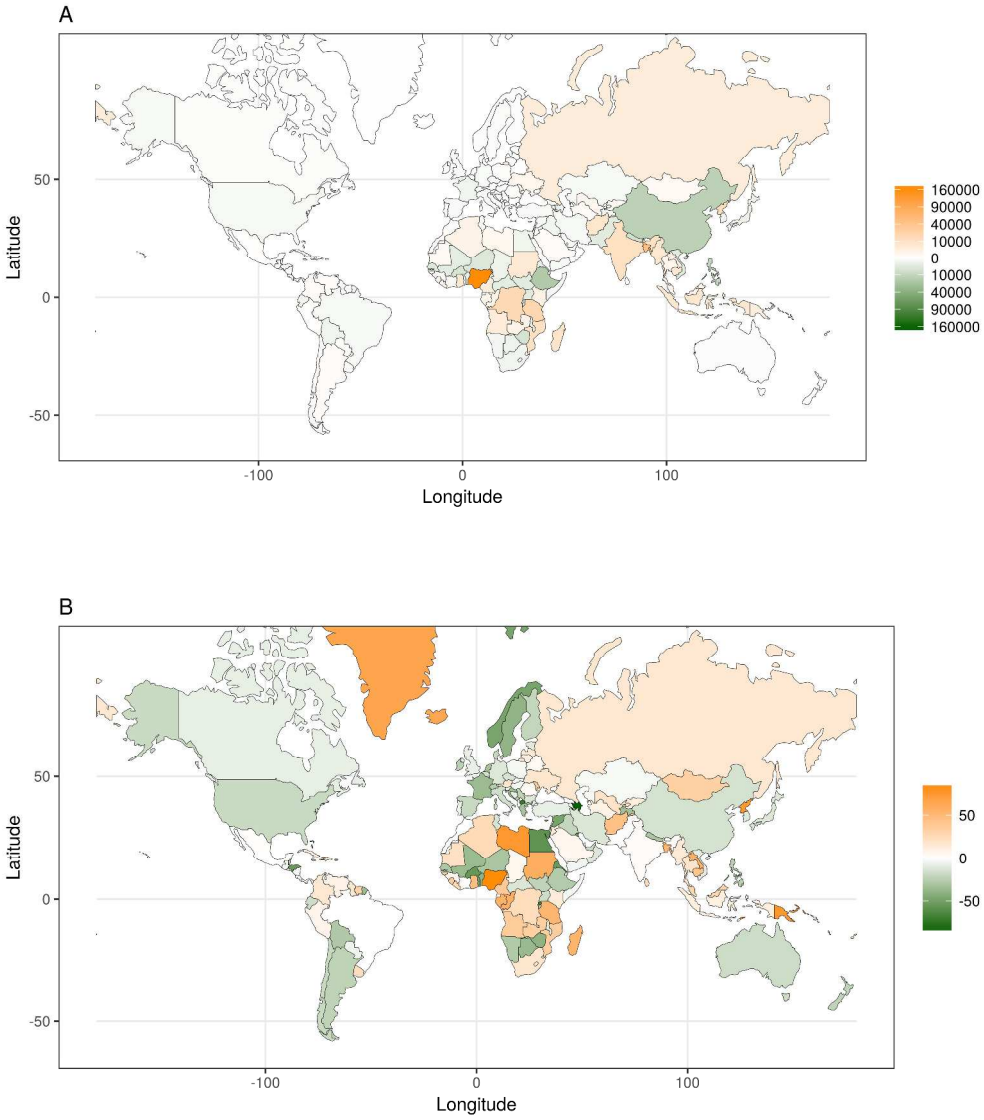


Figure 1. Ranking by (A) magnitude of absolute difference between World Health Organization and Global Burden of Disease study estimates and (B) the ratio of the absolute difference and number of reported deaths by country.



(A) Absolute differences (log scale) and (B) Standardized differences in World Health Organization's and Global Burden of Disease study's number of TB deaths estimates by country (year 2015).

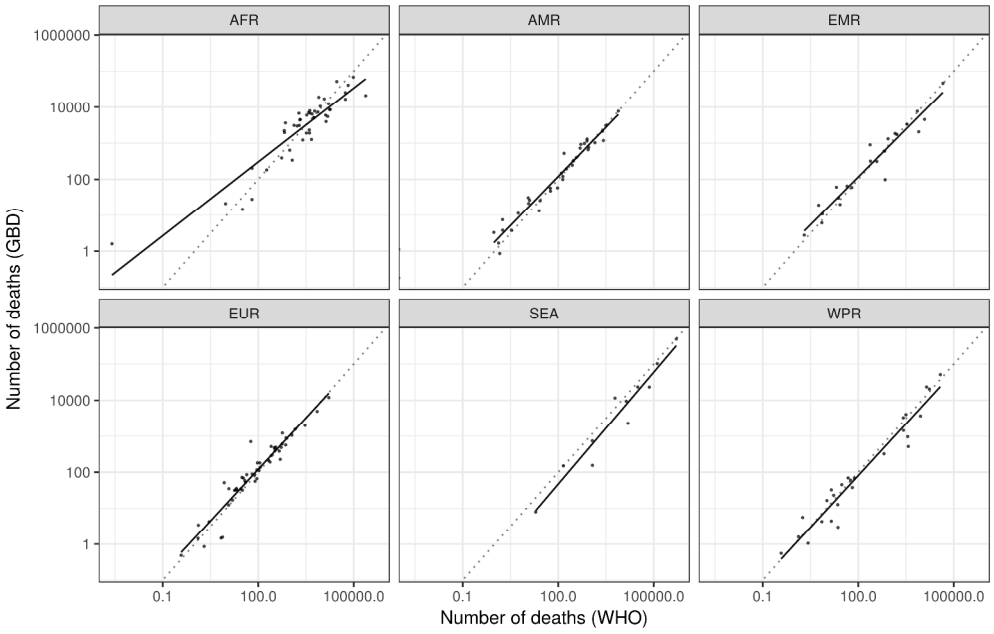


Figure 3. Correlation between World Health Organization's and Global Burden of Disease study's estimated number of TB deaths by UN world region.
*number of deaths in log scale.

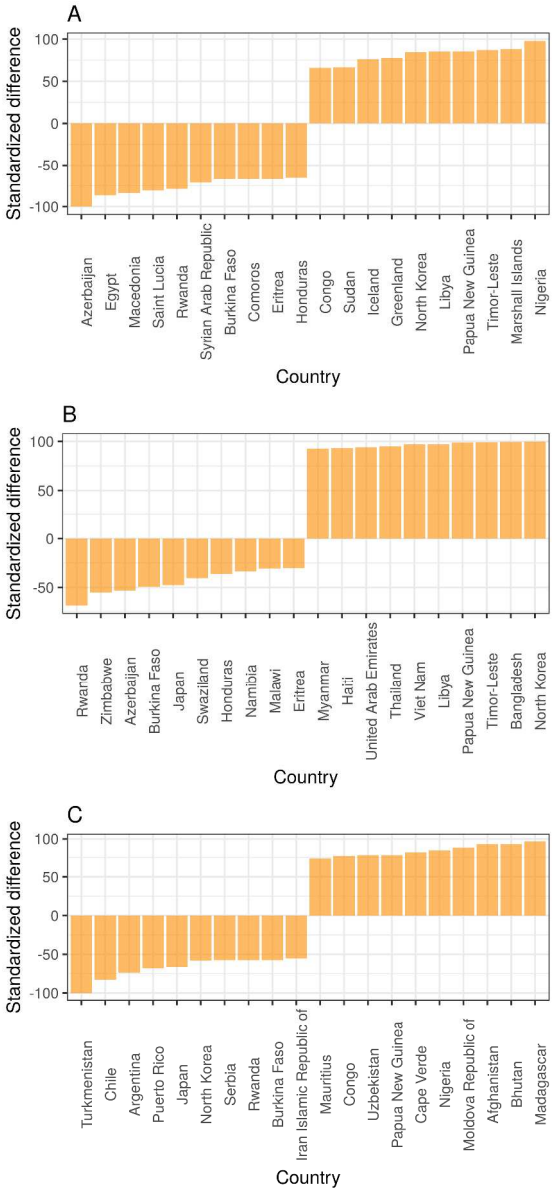


Figure 4. Ranking by magnitude of standardized difference (re-scaled) of World Health Organization and Global Burden of Disease Study TB mortality estimates among a) all tuberculosis deaths (all ages, all types) b) childhood TB deaths (all types) c) HIV-TB deaths (all ages) by country.
* When both WHO and GBD study estimated fewer than 5 deaths for a given subgroup, we removed those countries from the rankings of standardized difference.

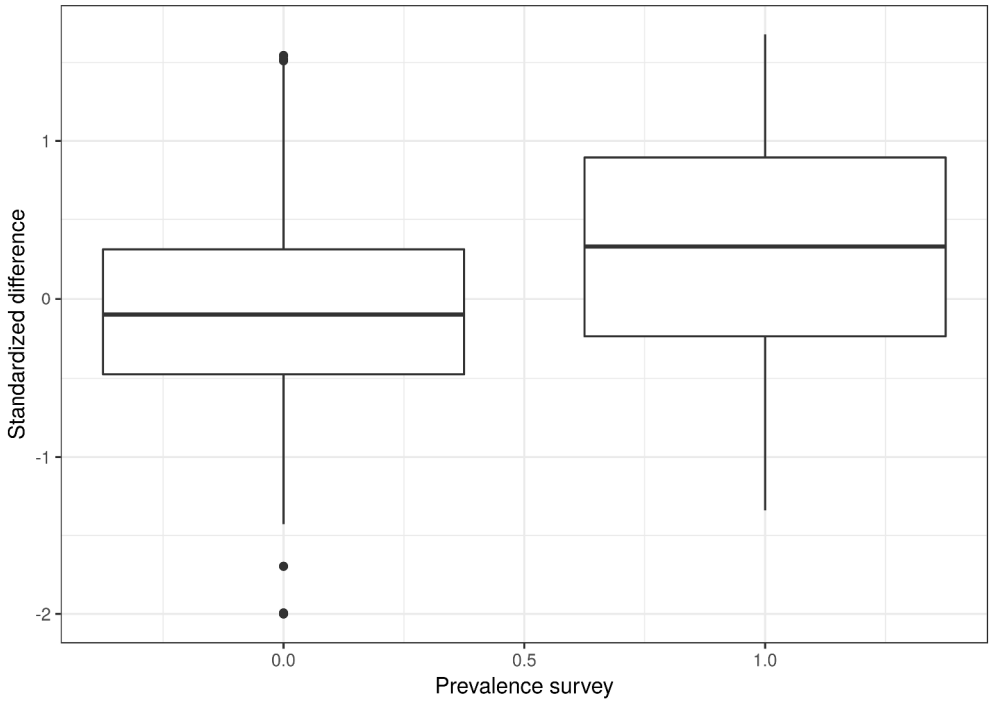


Figure 6. Standardized difference in mortality estimates by World Health Organization and Global Burden of Disease study by having had a nationwide prevalence survey in the country (2009-2015) (1) or not (0).
* Boxes represent 25th-75th percentile, horizontal line represents median value.

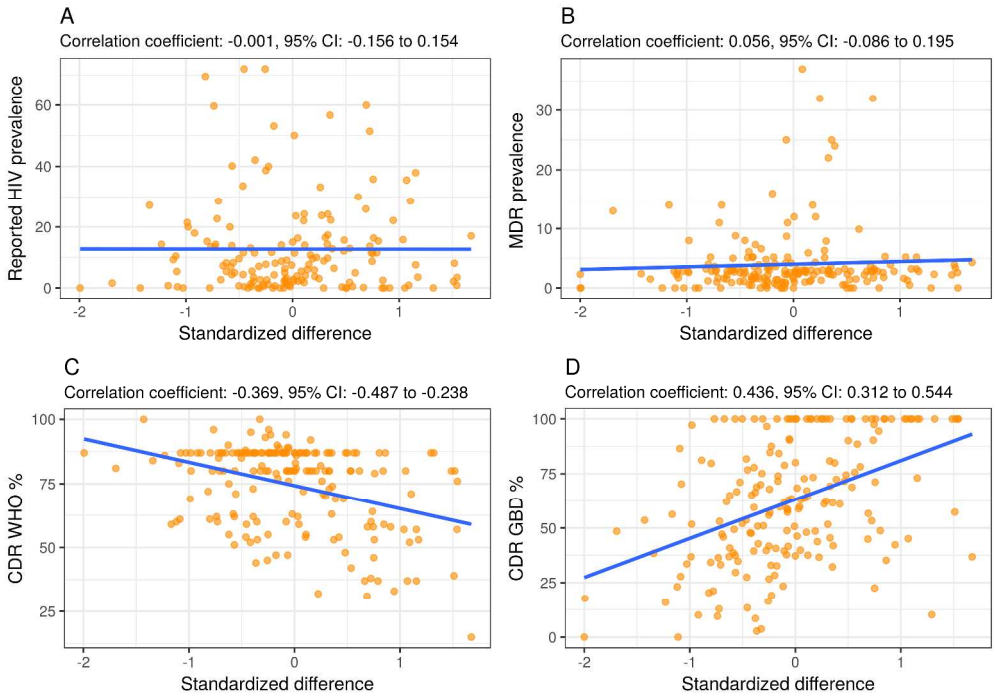


Figure 5. Ecological association of standardized difference in mortality estimates by the World Health Organization and Institute for Health Metrics and Evaluation with a) HIV prevalence b) MDR prevalence (WHO) c) Estimated Case Detection Rate by WHO d) Estimated case detection rate (based on GBD incidence data)

* Line represents linear regression line.

Title: What is the True Tuberculosis Mortality Burden? Differences in estimates by the World Health Organization and the Global Burden of Disease study

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ABSTRACT

Background

The World Health Organization (WHO) and the Global Burden of Disease (GBD) study at Institute for Health Metrics and Evaluation (IHME) periodically provide global estimates of tuberculosis mortality. We compared the 2015 WHO and GBD tuberculosis mortality estimates and explored which factors might drive thedifferences.

Methods

We extracted the number of estimated tuberculosis-attributable deaths, disaggregated by age, HIV status, sex, and country from publicly available WHO and GBD datasets for the year 2015. We “standardized” differences between sources by adjusting each country’s difference in absolute number of deaths by the average number of deaths estimated by both sources.

Results

For 195 countries with estimates from both institutions, WHO estimated 1,768,482 deaths attributable to TB, whereas GBD estimated 1,322,916 deaths, a difference of 445,567 deaths or 29% of the average of the two estimates. The countries with the largest absolute differences in deaths were Nigeria (216,621), Bangladesh (49,863) and Tanzania (38,272). The standardized difference was not associated with HIV prevalence, prevalence of multidrug resistance or global region, but did show s correlation with the case detection rate as estimated by WHO (r=-0.37, 95%CI: -048; -0.24) or, inversely, with case detection rate based on GBD data (r=0.42, 95%CI: 0.31; 0.54). Countries with a recent national prevalence survey had higher standardized differences (higher estimates by WHO) than those without (p=0.006). After exclusion of countries with recent prevalence surveys the overall correlation between both estimates was r=0.991.

Conclusions

A few countries account for the large global discrepancy in TB mortality estimates. The differences are due to the methodological approaches used by WHO and GBD. The use and interpretation of prevalence survey data and case detection rates seem to play a role in the observed differences.

Keywords: tuberculosis; mortality; death; burden; estimates; epidemiology; Global Burden of Disease, World Health Organization;

KEY MESSAGES

- Given the contribution of tuberculosis as a global cause of death, being the main infectious cause of death in several settings, the precise assessment of its burden is critical to prioritize health interventions at national level and globally.
- We identify a list of countries for which tuberculosis mortality figures should be carefully reviewed. Our findings suggest that the methodology and different data sources used by WHO and GBD might be driving the differences in TB mortality estimates.
- A global difference of nearly 450,000 deaths (and country differences higher than 10,000 deaths) hinders the assessment of the End-TB programmatic targets in some countries.
- These findings urge both institutions to take a closer look at the modelling approaches where differences are largest, in order to understand the true burden of TB in those settings. These results also call for investment in the development and / or improvement of high quality vital registration systems around the world.

INTRODUCTION

Mycobacterium tuberculosis is the single infectious agent that caused the largest number of deaths in 2016. It has been a major cause of death in previous centuries and potentially, in the history of humankind.[1,2] In the pre-chemotherapy era, the 10-year case fatality of smear-positive tuberculosis (TB) ranged from 53% to 86%, with 3 years duration on average from onset of disease to death.[3] Since a considerable proportion of TB cases are not diagnosed and many of the deaths among diagnosed patients are not accurately assigned,[4] global mortality figures are estimates derived from mathematical and statistical models. The World Health Organization (WHO) estimated that in 2015, there were 10.4 million new cases and 1.7 million deaths attributable to TB.[2] This alarming mortality burden attributed to TB in 2015 represents a 20% increase from 2014, driven not by a true upward trend, but based on newly available data from notifying countries and refinement of the modelling approach.[2,5]

Over the last 20 years, the Institute of Health Metrics and Evaluation (IHME) at University of Washington in Seattle, has developed a methodology to quantify the burden of multiple communicable and non-communicable diseases, injuries and risk factors, with the underlying objective of guiding international and local policy making.[6] The Global Burden of Disease (GBD) study, a broad international collaborative effort by IHME, periodically provides estimates on different key indicators of burden of disease assessment, including those related to TB. A comparison of the authoritative TB estimates by WHO and GBD for 2013 showed that global mortality figures were reasonably similar (WHO: 1.3 million deaths and GBD: 1.4 million deaths), although important differences existed at national and regional levels.[7,8] Interestingly, global estimates for TB deaths among HIV-uninfected people were considerably different: 0.9 vs 1.3 million as estimated by WHO and GBD, respectively. The available information for the year 2015 shows bigger discrepancies. Recently released estimates by GBD for 2015 amount to 1.3 million deaths (1.1 among HIV negative cases, range 0.9-1.4),[9,10]

which is significantly different to 1.8 million (1.4 among HIV negative cases, range 1.2-1.6) estimated by WHO for the same year.

TB mortality estimates vary due to the different underlying assumptions used in the two approaches. Although neither institution used to release much detail on their exact methods, since 2015 the WHO has included a specific appendix in their annual Global Tuberculosis Report in which the main assumptions underlying their TB mortality models are specified.[2] General information on the GBD approach for mortality has been published by GBD,[9,11] and TB-specific methodology for their 2015 estimates has recently been released.[10]

Burden of disease assessment is critical to prioritize health policy and planning at country level and globally. We sought to provide a detailed comparison of the 2015 WHO and GBD TB mortality estimates and explore which factors might drive the observed differences at national, regional and global level.

METHODS

Data sources and management

Data from the Global Burden of Disease 2015, GBD2015 iteration, were downloaded in December 2016 using the data health tool, available at http://ghdx.healthdata.org/gbd-results-tool. Variables included: number of deaths and mortality rate, disaggregated by age, HIV status, sex, and country. Data from WHO were downloaded from http://www.who.int/tb/country/data/download/en/ (global TB burden, case notifications and TB treatment outcomes datasets) in December 2016. Since WHO did not include data stratified by sex and age, additional disaggregated data by these two variables were requested and obtained from the Global TB Department.

A master dataset containing raw data from both sources was created and is freely available online for the sake of transparency and reproducibility. All source code is also freely available at www.github.com/joebrew/tb_mortality.

Data analysis

We described absolute differences in TB mortality estimates by both methods by age (adults vs children), sex, HIV status and global region. In addition, we described the differences in TB mortality estimates by both methods as the ratio between the estimated and reported numbers of deaths. Since the absolute difference in deaths might be driven by country's TB burden, we standardized the differences in mortality estimates by adjusting each country's difference in absolute number of deaths by the average number of deaths estimated by WHO and GBD using the formulae: (a-b)/((a+b)/2), where a and b are the numbers of deaths estimated by WHO and GBD respectively. This standardization yielded a metric (standardized difference) that takes into account the TB burden in the country. Since its scale cannot easily be interpreted, for plotting country rankings we rescaled this metric to a -100 to +100 scale, using the relative difference as a proportion of the maximum value obtained, yielding a positive score for a given country when WHO estimates were higher than GBD's and vice versa. Therefore, a score of +100 or -100 would represent the maximum difference in TB deaths observed between WHO and GBD relative to the average number of estimated deaths. When both estimated fewer than 5 deaths for a given subgroup, we removed those countries from the rankings of standardized difference. In a sensitivity analysis we explored whether the standardization of the absolute difference in number of TB deaths (WHO-GBD) by reported number TB deaths yielded different results with regards to potential drivers of the difference (**online supplementary material**).

Methods used by WHO and GBD to estimate TB mortality

The methods by which WHO estimated TB mortality in 2015 have been published in the 2016 Global TB report, released in October 2016.[2] A comprehensive explanation of

these methods is beyond the scope of this analysis. Briefly, the main data sources included direct measurements of mortality from vital registration systems or mortality surveys (145 countries) and indirect estimates obtained through estimated TB incidence and estimated case fatality rates (CFRs) among untreated patients. Mortality among HIV positive individuals was estimated using CFRs derived from previously published HIV-specific CFR data and other assumptions, including being on TB or HIV (antiretroviral) treatment.[2,12–14]

The methodology used in the GBD study to estimate TB mortality has recently been released.[10].[9] TB mortality has been estimated in a different fashion for HIV negative and positive individuals. For HIV negative individuals, the GBD study uses data sources from vital registration data, verbal autopsies and mortality surveillance data. These data sources were then modelled using different modelling strategies (mixed effects models and spatiotemporal Gaussian process regression models), as part of the cause of death ensemble modelling (CODEm) strategy.[10] Mortality among HIV-positive individuals was estimated based on the calculation of on the fraction of TB/HIV deaths among all TB deaths using data from countries with high quality vital registration data. It entails estimating the proportion of HIV positive TB cases among all TB patients, as well as the relative risks of TB death among patients TB and HIV. Further details are given in the methods section as well as in the appendix 1 of the article on global burden of TB from GBD2015.[10] A general comparison of the different approaches by WHO and GBD is given in **table 1**.

In order to explore what drivers could account for the observed differences, we analysed the association of the per-country standardized difference metric with potentially explanatory variables including case detection rate (CDR) as estimated by WHO, calculated CDR based on GBD data using incident cases estimated by IHME divided by the reported cases by countries, HIV burden using reported prevalence of HIV among new TB cases, prevalence of multidrug resistance TB among new cases as

reported by WHO, availability of recent nationwide prevalence survey results, and WHO region. Correlation coefficients were calculated and regression lines were plotted for each variable. Since all countries with available WHO and GBD estimates were included, no random error was taken into account except for the correlations; neither did we consider reported uncertainty for the per-country or aggregated estimates.

RESULTS

Mortality estimates for 2015 from both WHO and GBD were available for 195 countries. WHO estimated TB mortality for 23 additional countries, which accounted for 238 deaths in total. Among those 195 countries with estimates from both institutions, WHO estimated 1,768,482 deaths attributable to TB, whereas GBD estimated 1,322,916 deaths, resulting in a difference of 445,567 deaths (25.2% reduced mortality if taking WHO as the reference, or 33.7% increased mortality if GBD is the reference). This difference in TB mortality was higher in people living with HIV (211,604 by GBD vs 389,042 by WHO), where WHO estimated 84% more deaths attributable to TB than did GBD. The relative difference in number of deaths was especially high for children (<15 years of age), where WHO estimated three times more deaths than did GBD (209,837 vs 69,659 number of deaths by WHO and GBD respectively). In both estimates there were almost twice as many deaths estimated among adult men than among women with the smallest relative differences among HIV negative women (**table 2**).

For 86 (44.1%) of 195 countries WHO estimated a higher number of TB deaths than did GBD. The 10 countries with the largest absolute differences in total number of TB deaths were (by decreasing magnitude of the difference): Nigeria (216,621 deaths difference), Bangladesh (49,863), Tanzania (38,272), South Africa (29,108), Mozambique (28,909), Indonesia (26,121), Democratic Republic of Congo (26,010), India (20,696), North Korea (13,218), and Angola (9,910). The top-10 countries in which GBD estimated higher number of deaths than WHO were: Ethiopia (22,650),

China (13,538), Zimbabwe (11,082), Philippines (9,436), Nepal (5,477), Uganda (5,081), Burkina Faso (4,837), Niger (3,758), Viet Nam (3,252), and Senegal (3,147) **(figure 1A). Figure 2A** shows how the largest differences in terms of absolute number of deaths were concentrated in few countries, with Nigeria alone accounting for almost half of the difference in estimated global TB mortality between the two methods. In fact, the correlation of TB mortality estimates between both methods was very good for most countries and regions (**figure 3**), with an overall correlation coefficient of 0.92.

After standardization, the countries with highest difference in estimates were Azerbaijan (-100.0), Nigeria (99.9) and Marshall Islands (91.2). The differences in absolute number of childhood TB deaths estimates were largest in India (59,508), Nigeria (32,004) and Indonesia (12,752). After standardization, the magnitude of this difference was greatest in North Korea (100.0), Bangladesh (99.4) and Timor Leste (99.1). Regarding differences in TB-HIV deaths (all ages), Nigeria (52,805), South Africa (29,594) and Indonesia (19,480) were the countries with highest differences in absolute numbers, and Turkmenistan (-100), Chile (-82.7) and Argentina (-73.7) showed the largest standardized differences (**figure 4 and supplementary table 1**). In nine countries, the difference between WHO and GBD estimates of number of deaths was more than 10 times than the number reported by the country: Libya (117 times higher), Nigeria (43), Iceland (23), Congo (22), Afghanistan (16), Eritrea (13), Timor-Leste (11) and Tanzania (11) (**figure 1B**). In the online supplementary material, the **interactive map** shows all indicators of this descriptive analysis by country.

After standardization of the absolute differences in mortality estimates for the WHO-GBD averaged estimate we found no associations with the following potential drivers of this difference: reported HIV prevalence among new TB cases (r = -0.001, 95% CI: -0.16; 0.15) and multidrug/rifampicin resistance prevalence (r= 0.06, 95% CI: -0.09; 0.20). There was an association with case detection rate (as estimated by WHO), (r = -0.37, 95% CI: -0.49; -0.24) which showed an inverse association when using CDR

based on GBD-estimated number of incident cases (r= 0.44, 95% CI: 0.31; 0.54) (**figure 5**) and with case fatality rate as estimated by WHO (r= 0.37, 95% CI: -0.49; -.24). Countries that conducted a national prevalence survey between 2009 and 2015 had a higher median standardized difference than those that did not (0.330 vs -0.104, respectively) (**figure 6)**. In other words, in those countries for which national prevalence survey data were available, WHO tended to estimate higher numbers of TB deaths (p=0.006). For the 19 countries that had national prevalence surveys, WHO estimated rather low CDRs, being below 75% for all except two countries (China and Rwanda). Removing the 19 countries with a prevalence survey, the correlation between WHO and GBD number of deaths estimates improved from r=0.92 to r=0.99.

Standardization of the absolute difference in number of TB deaths (WHO-GBD) by reported number of deaths yielded associations with potential drivers of the mortality difference of similar direction and magnitude (**Supplementary figure 1**). There was again a negative correlation between standardized difference and WHO-estimated CDR (r=-0.32, 95%CI -0.45;-0.18); the positive correlation with CDR based on GBD-estimated number of deaths disappeared (r= 0.09, 95%CI -0.06; 0.24). Also countries with prevalence surveys had a higher mean standardized difference (mean 3.5) than those without (0.88) (**Supplementary figure 2**).

DISCUSSION

Despite using different approaches, the latest estimates of TB mortality by WHO and IHME are similar for most countries in the world. The global TB mortality estimates are nonetheless quite different due to large differences for a small number of countries. Twelve countries showed a difference in their TB mortality of more than 10,000 deaths: Nigeria, Bangladesh, Tanzania, South Africa, Mozambique, Indonesia, Democratic Republic of Congo, India, North Korea, Ethiopia, China, Zimbabwe. Only for the latter three countries, IHME estimated higher numbers of deaths than did WHO. With the

possible exception of some countries with a large TB burden, such as China or India, these absolute differences in estimated number of deaths likely reflect relevant effects of differences in modelling methods and data sources used. This is further supported by absolute differences in estimated numbers of deaths being >10 times larger than the reported numbers of TB deaths for several of these countries. The absolute differences in TB deaths found among HIV positive cases or children are also concentrated in similar countries as for all TB with some exceptions. Nonetheless the standardized differences are different, reflecting the specific HIV burden and demographic characteristics of the countries. In addition, the lack of reliable data sources for children adds uncertainly to paediatric TB death estimates.[15]

HIV prevalence among new TB cases, as a proxy for HIV/TB burden in the country and prevalence of MDR-TB did not seem to be determinant factors for the differences observed. We did find an association with the case detection rate as estimated by WHO or GBD: the lower the CDR as estimated by WHO, the larger the standardized difference between WHO and GBD estimates. This association also existed, but in opposite direction, for CDR using GBD's-estimated numbers of cases. The association with CFR as estimated by WHO is likely due to the association with CDR. In addition, differences in the estimation of TB deaths seemed to be driven by the availability of national prevalence survey data. When removing the countries with recent prevalence survey data, the correlation of WHO and GBD estimates came close to 100%.

Several differences in methodology used by WHO and GBD may account for the differences in mortality estimates. For countries with poor vital registration and disease reporting systems, any method for estimating TB mortality has to deal with two information gaps that cannot be directly observed: the number of individuals with TB disease who are never diagnosed and/or reported, and the death rate due to TB among these individuals. The former is reflected in the CDR that is generally expressed as the ratio of the number of TB patients reported and the number of estimated incident

TB cases over a given period. The latter is referred to as the case fatality rate (CFR). Both approaches (from GBD and WHO) have different ways of taking these two variables into account.

The WHO uses three main strategies to account for the undiagnosed cases: for high income countries, notifications are adjusted by a standard factor, and for low- and middle-income countries, either data from prevalence surveys are used or notification data are combined with expert opinion. Nine other countries use data from capture-recapture analyses or from inventory studies. For 74 countries, expert opinion was used. This approach, which is not based on observational data, has clear limitations and introduces a high degree of uncertainty in the estimates. For 19 countries the CDR was based on findings from national prevalence surveys (and for India from one regional prevalence survey), which, according to WHO, represent 62% of all TB incidence.[2] Prevalence surveys have generally lowered the case detection rate estimated by WHO compared to the previous estimate.[2] In fact this happened for Tanzania and Nigeria, two of the three countries with highest absolute differences. The association of low CDR with higher mortality estimated by WHO might thus be driven by the countries that had a prevalence survey.

The use of data from prevalence surveys also has implications for the way CFRs are applied to obtain estimated numbers of deaths. Half or more of the patients detected in prevalence surveys are asymptomatic[2], and their true CFR may be lower than that for patients with TB symptoms. For Nigeria and Tanzania, which account for 57% of the total global difference in TB mortality estimates, the CDR estimate was lowered as result of their prevalence surveys. If TB mortality is lower among asymptomatic than among symptomatic cases detected through prevalence surveys, WHO might be overestimating true TB mortality in those countries. In addition, in countries without reliable vital registration systems, case fatality rates are derived from the product of TB incidence and CFR (for treated and untreated). However, no adjustment is made for

setting specific CFR, which we believe might vary depending on the specific country health profile.

Estimating TB deaths among HIV patients is complex since people living with HIV who die from TB are registered as HIV deaths, and the intermediate causes are not always registered. For countries with VR systems or mortality surveys, GBD study uses different algorithms that help to identify garbage codes from the death certificates (assigned codes that are not real causes of death) and redistribute to the most plausible causes. This process adds certain uncertainty to data even in countries with good quality VR systems. In addition, GBD uses verbal autopsy data as one of the sources for estimating TB mortality. Verbal autopsies provide poor quality estimates and have limited sensitivity and specificity for TB against clinical diagnosis or autopsy findings, especially in high HIV infection prevalence settings.[4,16–18] Clinical (premortem) diagnosis itself has shown a high degree of discrepancy with autopsy findings for TB diagnosis.[19–21] If clinicians fail to diagnose TB premortem, it is likely that verbal autopsy data is even less accurate. Indeed, two recent studies comparing verbal autopsy and classical autopsy findings for TB diagnosis showed that verbal autopsies over- or underestimated the true burden of TB in two sub-Saharan settings.[17,18] The decision to not include verbal autopsy data from countries with HIV prevalence above 5% will minimize this source of error, but further studies are needed to validate verbal autopsy findings (against autopsy findings) and see whether its systematic use plays a role in underestimating or overestimating TB mortality.

This analysis has several limitations. The standardisation used for analysing potential drivers of the differences in mortality estimates is based on the adjustment of those estimates by the average number of deaths estimated by both institutions, as a proxy of the true country mortality burden. However, this standardization approach assumes both approaches are equidistant from the true number of TB deaths, which may not be the case. Alternative standardisation by adjustment for reported number of deaths

showed less pronounced associations with GBD-estimated CDR and use by WHO of national prevalence survey data. This standardization may also have introduced bias because the departure of estimated number of deaths from reported number of deaths strongly depends on the CDR and this would have not been taken into account.

Secondly, although in recent years more detail has been provided on the modelling approaches and data sources used, we believe that neither WHO's nor GBD's estimates are fully reproducible using publicly accessible data. This adds a layer of uncertainty on how figures are obtained. Public availability of some input data sources might conflict with confidentiality agreements established by countries or institutions. In addition, GBD and WHO updated estimates supersede the previous ones for any particular year, hindering a comprehensive understanding and retrospective analysis of a specific year's estimates. Lastly, we have not been able to compare of mortality estimates due to MDR-TB or XDR-TB (not provided by GBD), which is a growing problem. We believe that a specific methodology to estimate mortality among this subgroup needs to be incorporated.

The fact that two independent institutions make an important effort to come up with global TB burden indicators must be welcomed and appreciated. We consider that it is beneficial that there is not a single institution claiming full authority on TB or any disease estimates, which allows to further discuss methods, and ultimately improve estimates for relevant public health indicators. Nonetheless, there is a need to provide a clearer picture about the magnitude of TB mortality for some specific countries, as well as to analyse the reasons for the estimation differences between WHO and GBD. There may be elements in both institutions' methodologies that may result in over- or underestimating TB mortality. A global difference of nearly 450,000 deaths (and country differences higher than 10,000 deaths) makes it difficult to assess progress on control efforts directed at reducing mortality in some settings. We recommend both GBD and WHO to take a closer look at the modelling approaches for the countries with

highest absolute differences in TB mortality estimates by both institutions, as well as for those countries which highest differences relative to the size of their reported mortality. Likewise, there is an urgent need to invest in the creation and / or improvement of high quality vital registration systems, which are lacking in many high TB burden countries. Lastly, new tools to diagnose TB as cause of death need to be implemented. Since full post-mortem examination is rarely performed in countries lacking vital registration systems, alternative approaches for TB assessment at death, such as minimally invasive tissue sampling (MITS) based tools, should be explored for monitoring TB mortality surveillance.[22]

Contributors:

ALGB and FC designed the study. JB performed data management and visualizations. ALGB, FC, BW, MB contributed to data analysis and interpretation of the results. ALGB wrote the first version of the manuscript. All authors provided critical review and comments to the manuscript and agree with the content of the final version, as sent to the journal. All authors meet all four criteria for authorship in the ICMJE recommendations.

Declaration of interests:

ALGB is part of the GBD collaborator network. ALGB, FC and MB have participated in taskforces of the Global TB Program at the World Health Organization. BW is former employee of the Stop TB Department (now Global TB Program) at the World Health Organization.

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Tables and Figures

Table 1. Basic characteristics of the models and methodology used by the World Health Organization and Institute of Health Metrics to obtain country specific and global TB mortality estimates.

Table 2. Global absolute differences in TB attributable number of deaths during 2015, as estimated by the World Health Organization and Institute of Health Metrics and Evaluation, by sex and age group.

Figure 1. Ranking by (A) magnitude of absolute difference between World Health Organization and Global Burden of Disease study estimates and (B) the ratio of the absolute difference and number of reported deaths by country.

Figure 2. (A) Absolute differences (log scale) and (B) Standardized differences in World Health Organization's and Global Burden of Disease study's number of TB deaths estimates by country (year 2015).

Figure 3. Correlation between World Health Organization's and Global Burden of Disease study's estimated number of TB deaths by UN world region.

*number of deaths in log scale.

Figure 4. Ranking by magnitude of standardized difference (re-scaled) of World Health Organization and Global Burden of Disease Study TB mortality estimates among a) all tuberculosis deaths (all ages, all types) b) childhood TB deaths (all types) c) HIV-TB deaths (all ages) by country.

* When both WHO and GBD study estimated fewer than 5 deaths for a given subgroup, we removed those countries from the rankings of standardized difference.

Figure 5. Ecological association of standardized difference in mortality estimates by the World Health Organization and Institute for Health Metrics and Evaluation with a) HIV prevalence b) MDR prevalence (WHO) c) Estimated Case Detection Rate by WHO d) Estimated case detection rate (based on GBD incidence data)

* Line represents linear regression line.

Figure 6. Standardized difference in mortality estimates by World Health Organization and Global Burden of Disease study by having had a nationwide prevalence survey in the country (2009-2015) (1) or not (0).

* Boxes represent 25^{th}-75^{th} percentile, horizontal line represents median value.