Meeting Minutes: UNAIDS Reference Group Meeting on Estimating Tuberculosis deaths among PLHIV

Date: 13 May 2024
Time: 16:00-18:00 SAST
Location: Online
Chairs: Cari van Schalkwyk; Leigh Johnson
Participants: Listed at the end of this document
Minutes Prepared by: Yuri Munsamy, SACEMA

Background

Keith Sabin opened the meeting highlighting the value for country-specific information on the cause of death among people living with HIV (PLHIV) to support programmes at addressing causes of deaths among PLHIV.
The approach is to rely on existing methods, estimates, and technical groups to achieve the UNAIDS Reference Group's workstream goal: Producing estimated tuberculosis (TB) deaths among PLHIV as an output from Spectrum model and incorporating these estimates into routine HIV estimates outputs to improve access to TB deaths estimates to HIV programme teams.

Meeting objectives

Cari van Schalkwyk introduced the objectives of the meeting:

- Review existing methods for estimating TB burden and deaths due to TB among PLHIV.
- Review the availability of routine surveillance data on TB burden or deaths in settings with high HIV burden.
- Assess the suitability and feasibility of implementing models or TB deaths estimates outputs in the Spectrum model used by country teams to produce national HIV estimates.
- Plan coordinated development of improved country-specific estimation methods in collaboration with TB expert groups.

Meeting Agenda

Two organisations that provide global estimates of TB deaths among PLHIV were approached to present an overview of their methods. The agenda was as follows:

1. IHME Global Burden of Disease (GBD) study estimates of TB deaths among PLHIV by **Hmwe Kyu**, IHME
2. WHO estimates of TB Mortality in People Living with HIV and Adjustments for COVID Disruption, by **Mathieu Bastard and Nim Pathy**, WHO
3. Discussion, chaired by **Leigh Johnson**

1. *IHME Global Burden of Disease (GBD) study estimates of TB deaths among PLHIV by Hmwe Kyu, IHME*

Data sources and calculations to estimate TB-HIV deaths

Data Type	Description	Statistical methods and calculations
TB notification data from WHO	Used to determine the proportion of TB cases that are HIV positive.	**Equation for HIV TB Proportion** $$P_{c,y} = \frac{\text{HIV positive TB cases}}{\text{Total TB cases}}$$ This proportion is estimated using notification data, applying a mixed effects regression model with random effects at the super-region (representing groupings of regions), region, and country levels. The adult HIV death rate covariate is used to facilitate predictions for countries and years without data.
Vital registration data (mostly from high-income countries)	Used for countries that have directly coded causes of death for HIV-TB and TB.	**Relative Risk (RR) Estimation** $$RR_{c,y} = \frac{\text{TB deaths in PLHIV}}{\text{TB deaths in HIV negative individuals}}$$ Calculated by country *c* and year *y* using directly coded death data. The median of these relative risks is used in further calculations to estimate the fraction of TB deaths among PLHIV.
TB mortality estimates	Derived from various sources including vital registration, verbal autopsy, mortality surveillance, and tissue sample diagnoses.	**TB Deaths Among PLHIV** TB deaths among PLHIV = TB no-HIV deaths x $D_{c,y}/(1-D_{c,y})$ Where, $D_{c,y}$ = Proportion of TB deaths with HIV by country and year, calculated as $P_{c,y}RR/(P_{c,y}RR+1-P_{c,y})$ where RR is the median relative risk. The results are adjusted for age, sex, and location patterns using HIV mortality estimates.
Estimated HIV mortality by age and sex	Used to split HIV-TB deaths by age and sex	Use GBD estimates of HIV deaths by age and sex to split HIV-TB by age and sex. Cap HIV-TB deaths at 45% of total HIV deaths based on finding from systematic review.

For countries or regions lacking direct data on TB deaths among people without HIV, estimates are supplemented using regional patterns and covariates to predict TB mortality. While most data originate from the publicly available WHO mortality database and undergo processing for comparability, additional data are sometimes provided by countries through the GBD collaborator network.

Resulting TB-HIV deaths are distributed as drug susceptible, multi-drug resistant and extensively drug resistant TB-HIV deaths using:

- Proportions of drug resistance from routine surveillance and surveys reported to WHO.
- Relative risks of deaths according to drug resistance from systematic reviews.

Results, shown as point estimates and 95% uncertainty intervals based on 1000 draws, are available on the GHDx website: https://ghdx.healthdata.org/.

Limitations

- The 45% cap is based on an outdated systematic review (<2010) of verbal autopsy data, which has sensitivity/specificity limitations.
- *Limitation raised during discussion*: the method does not account for higher screening rates among PLHIV, which may bias the prevalence of HIV among notified TB cases.

2. *WHO estimates of TB Mortality in People Living with HIV and Adjustments for COVID Disruption, by Mathieu Bastard and Nim Pathy, WHO*

WHO measures the burden of TB disease in terms of incidence and mortality using data gathered through surveillance systems (case notifications, deaths in vital registration systems) and prevalence surveys.

Different approaches are used to estimate TB deaths by country according to the data available:

- For countries with high-quality vital registration data, estimates of TB deaths among HIV-negative people with HIV are taken directly from cause of death information recorded in death registries (Blue countries in Figure 1).
- For other countries without high-quality registration data, TB deaths among HIV-negative and PLHIV are estimated based on (1) estimates of TB incidence derived from available TB burden data, (2) estimates of TB treatment coverage derived from TB case notification and estimated burden, and (3) estimates of TB case fatality rate conditional on treatment status. (Yellow countries in Figure 1).
- For countries that experienced large case finding disruptions during Covid-19, TB death estimates are based on a new dynamic model that was created to reflect the impacts of annual changes in case finding on mortality rates (Triangles in Figure 1).

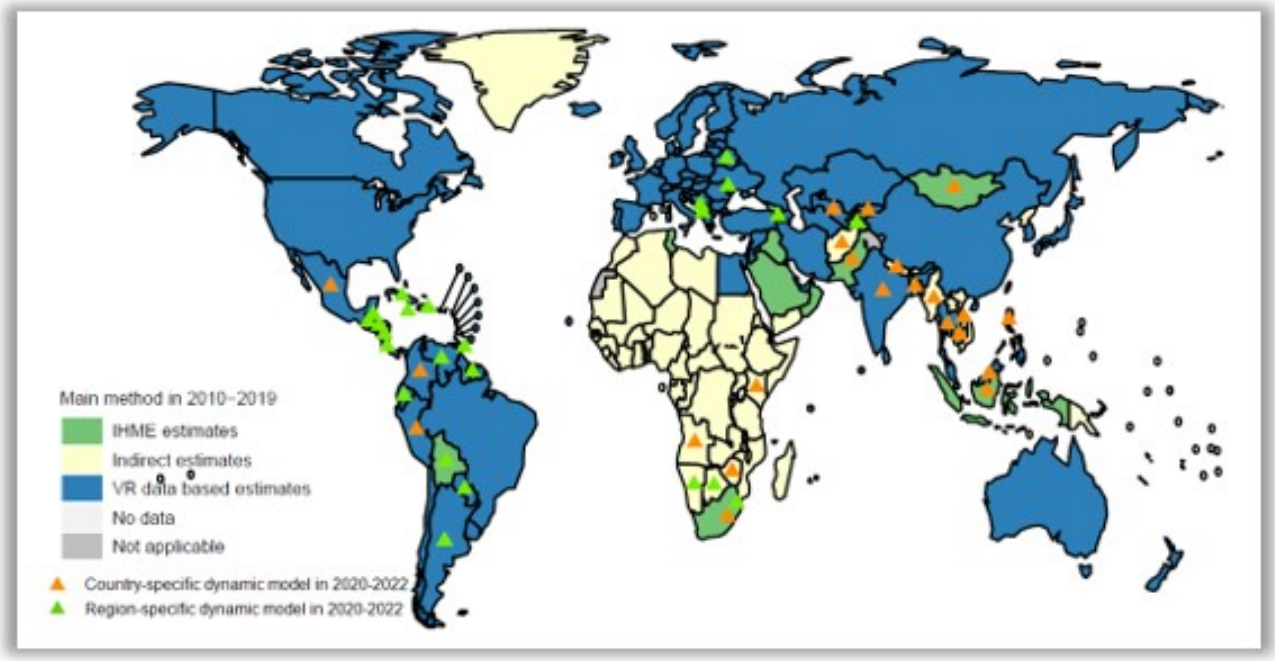

Figure 1: Methods used to estimate global TB burden

Estimating TB Mortality Among PLHIV

Method 1: Product of TB incidence and case fatality ratios

1. *Estimate TB Incidence in PLHIV*

TB Incidence in PLHIV (I_{PLHIV}) is estimated by multiplying estimated TB incidence in the total population by the prevalence of HIV in TB cases derived from various sources, including:

- surveys
- routine testing data with sufficient coverage reported to WHO
- sentinel data
- UNAIDS estimates to derive prevalence of HIV and TB from the prevalence of HIV in the general population.

2. *Estimate TB mortality Among PLHIV*

TB mortality among PLHIV is estimated using:

$$M_{PLHIV} = (I_{PLHIV} - T_{PLHIV}) \times CFR_{PLHIV\ untreated} + T_{PLHIV} \times CFR_{PLHIV\ treated}$$

Where,

- I_{PLHIV}: TB incidence in PLHIV
- T_{PLHIV}: the number of treated TB cases in PLHIV
- $CFR_{PLHIV\ untreated}$: CFR among PLHIV untreated for TB
- $CFR_{PLHIV\ treated}$: CFR among PLHIV treated for TB

Case fatality ratios depend on 1) TB treatment status, 2) ART status, and 3) ART duration (none, <1 year, >=1 year) and were estimated through TB-MAC systematic reviews. Distribution of treated TB into HIV treatment states are based on country-reported TB case notification data. Untreated TB cases with HIV are assumed to be not on ART.

Limitations

- No direct measurement of HIV-associated TB mortality, potentially leading to inaccuracies.
- Reliance on older literature for CFRs, which may not reflect current realities.
- Estimates depend on overall TB incidence and HIV prevalence data, which may be imprecise, particularly in high HIV burden regions.
- *Limitation raised during discussion*: the method does not account for higher screening rates among PLHIV, which may bias the prevalence of HIV among notified TB cases.

Method 2: Dynamical models to account for COVID disruptions

Nim Arinaminpathy presented a new model developed to address the impact of the COVID-19 pandemic on TB services and mortality rates. This model adjusts TB mortality estimates to account for reduced access to TB services and potential increases in mortality due to the pandemic.

- Analyzed annual TB notifications, showing a nearly 20% drop in TB cases reported during the pandemic.
- Developed individual country models for 25-26 countries that accounted for the majority of this global drop. For 23 other countries with significant disruptions but smaller contributions to the global drop, regional-level models were used.
- Adjusted the model to account for reduced TB diagnosis and treatment initiation, which increased the burden of undetected and untreated TB, resulting in increased mortality.

- Included short-term reductions in TB transmission due to lockdowns and medium-term increases in TB mortality and incidence due to delayed diagnoses and treatment interruptions.
- Calibrated the model to pre-pandemic mortality estimates and adjusted for COVID-19 related disruptions.

Limitations

This method has the *same limitations as method 1*, in addition:

- The model does not incorporate drug resistance nor age structure due to limited data availability.
- Uncertainties around the duration and extent of reduced TB transmission during lockdowns.
- Does not include direct impacts of COVID-19 on TB mortality or other distal factors affecting TB determinants.

3. Discussion

- Integration of TB-HIV deaths estimates in Spectrum would ideally involve calculations within Spectrum, to use the latest HIV estimates in this calculation. However, this would lead to a different estimate than the numbers produced by WHO or IHME and communication of divergent estimates would require careful consideration.
- For WHO estimates, this difference would largely be explained by the difference in timelines – WHO estimates are officially launched around November, using HIV estimates from UNAIDS released in July. During the HIV estimates process starting in December, the newest TB estimates would therefore apply to the previous year. IHME estimates are produced every two years, and do not rely on UNAIDS HIV estimates but rather GBD HIV estimates.

Next Steps and Recommendations

- Explore the presentation of three *numbers of TB-HIV deaths* ***or*** *TB-HIV deaths as proportion of HIV-related* deaths in Spectrum, initially displaying for 2021-2023:
    a. Latest WHO estimates
    b. Latest GBD estimates
    c. Values calculated within Spectrum, using PLHIV estimated in Spectrum and the following numbers from WHO:
        i. TB-HIV incidence,
        ii. Proportion treated for TB,
        iii. Case fatality ratios by ART status and duration.

- Investigate the large variation in WHO HIV-TB deaths as a proportion of UNAIDS estimated HIV-related deaths by country.

Meeting Participants

Name	Organisation
Ajay Rangaraj	WHO
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Anand Date	CDC
Annabel Baddeley	WHO
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