WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment

ANNEX 1.

Methods and Expert Panels

THE END TB STRATEGY

World Health Organization

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This publication forms part of the WHO guideline entitled *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014)**.**

Annex 1. Methods and Expert Panels

1. Methods used to develop the guidelines

In conformity with the process recommended by the Guideline Review Committee,[1] three expert groups were established: 1) a Guideline Steering Group, composed of WHO staff; 2) the Guideline Development Group (GDG), including a guideline methodologist, external content experts, national TB programme managers, other implementers, academics, researchers and representatives of patients and civil society; and 3) the External Review Group (ERG), composed of peer-reviewers. The draft guidelines also underwent a public consultation in which feedback was provided by other individuals who volunteered to comment on the revision following a call in July 2019.

The WHO Guideline Steering Group prepared the background document for the guidelines, which detailed the three PICO questions defining the scope of the update; the trial data and evidence review required for the process; draft changes to the wording of existing recommendations and accompanying remarks to improve clarity and the implementation of the guidance; and the composition of the expert panels. The scoping document was submitted to the Guideline Review Committee and approved. The background material inclusive of the biographies of the GDG members were placed on a public website.[2]

A list of potential outcomes of interest for each PICO question was circulated to all members of the GDG, who scored the importance of each outcome on an incremental scale from 1 to 9: 1–3: "not important"; 4–6: "important"; and 7–9: "critical". The average of the scores for each outcome was used to prioritize the outcome and to select the most important outcomes for each PICO question. Nearly all outcomes proposed were ultimately scored as "critical"; only emergence of drug resistance for PICO 6 was deemed "important" according to the average score (see also the GRADE tables in the online **Annexes 2** and **3**).

GDG meetings were conducted as two 2-hour webinars between 15 and 19 July 2019, each of which was repeated for the convenience of GDG members in different time-zones (i.e. 4 webinars in total). Evidence summary tables were drafted for each of the PICO questions using the GRADE ("grading of recommendations assessment, development and evaluation") approach and circulated to the group ahead of the webinars. The meetings were co-chaired by a technical expert and a guideline methodologist who facilitated the discussions to reach consensus, which was defined as unanimous or majority agreement. The GDG agreed in advance that for a recommendation to be made, and should consensus not be reached, approval was required by at least 60% of the GDG participants. The estimates and the judgements on the quality of evidence were reviewed by the GDG members during the online discussions. GRADE evidence-to-decision tables were used to guide discussions on benefits and harm, the quality of the evidence, cost, feasibility, acceptability, equity, values and preferences1. The direction of the recommendations and their strength (strong or conditional) were determined by these factors. GRADEpro was used to document the decisions made.[3]

As part of the 2019 update of the guidelines, the wording of the recommendations from the previous guidance was reviewed for clarity, applicability in different settings, and alignment to other WHO guidance. The guideline contents are structured to follow the cascade of care in the programmatic management of LTBI: identification of populations at risk (adults and children living with HIV, adult and child contacts of people with TB and other risk groups); ruling out of active TB disease; testing for LTBI; providing treatment; managing adverse events; supporting adherence to and completion of treatment; and monitoring and evaluation. The recommendation text is followed by sections that summarise the evidence (justification), discuss their rationale, and highlight key considerations on implementation and monitoring and evaluation. Recommendations that remained valid were retained, with or without slight rewording (see **Supplementary Table** in the main document). The guidelines and the supporting documents were reviewed and endorsed by all GDG members. Remarks from the External Review Group and the public consultation were assessed by the WHO Guideline Steering Group

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[1] WHO handbook for guideline development. 2nd ed. Geneva, World Health Organization; 2014. Available from: http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf

[2] https://www.who.int/tb/publications/2019/Backgrounddocument2019revision_WHOLTBIguidelines.pdf

[3] GRADEpro – Guideline Development Tool. Available from: http://www.guidelinedevelopment.org/

and incorporated in the final version of the guidelines. Final approval of the guidelines by the Guideline Review Committee was received on 17 January 2020.

2. Certainty in the estimates of effect and strength of the recommendations

The certainty in the estimates of effect (or quality of evidence) and the strength of the recommendations were assessed with the GRADE method.[4] The certainty in the body of evidence is defined as the degree of confidence that the estimates of effect (desirable or undesirable) are close to the actual effects of interest. The usefulness of an estimate of effect depends on the level of confidence in that estimate: the higher the certainty in the evidence, the more likely a strong recommendation can be made. A decision on the strength of the evidence also depends on other factors. The strength of a recommendation reflects the degree of confidence of the GDG that the desirable effects outweigh the undesirable effects. The desirable effects included beneficial health outcomes (e.g. prevention and early diagnosis of TB, reduced TB-related morbidity and mortality), a smaller burden of TB and more savings; whereas the undesirable effects include harm, a greater burden and more costs. The "burdens" included adherence to the recommendations by programmes, patients and caregivers – formal or informal – such as more frequent tests and taking additional medications.

The certainty in the estimates of effect (quality of evidence) was categorized into four levels:

High The GDG is very confident that the true effect lies close to that of the estimate of the effect.

Moderate The GDG is moderately confident that the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low The confidence of the GDG in the effect estimate is limited: the true effect may be substantially different.

Very low The GDG has very little confidence in the effect estimate: the true effect is likely to be substantially different.

The recommendations are either strong or conditional:

A *strong recommendation* is one for which the GDG was confident that the desirable effects of adhering to it would outweigh the undesirable effects. This could be either in favour of or against an intervention.

A *conditional recommendation* is one for which the GDG concluded that the desirable effects of adhering to it would probably outweigh the undesirable effects, but the GDG was not confident about the trade-off. The reasons for lack of confidence included: absence of high-quality evidence (few data to support the recommendation); imprecise estimates of benefit or harm (new evidence might change the ratio of risk to benefit); uncertainty or variation in the value of the outcomes for different individuals (applicable only to a specific group, population or setting); and small benefits or benefits that might not be worth the cost (including the cost of implementing the recommendation).

3. Publication, implementation, evaluation and expiry

These guidelines were prepared in accordance with the requirements of the Guideline Review Committee (17). The guidelines will be published on the WHO website for free download as part of a comprehensive *WHO consolidated guidelines on tuberculosis* and will be communicated widely at international and regional conferences and meetings of programme managers in all regions. In early 2020 WHO will release an operational guide with more practical details to support programmatic implementation of the revised recommendations.

National programmes will be supported by WHO and technical and funding partners to prepare a national plan for programmatic LTBI management, including prioritization of groups at high risk on the basis of local epidemiology and the characteristics of the health system. Implementers should create a conducive policy and programmatic environment, including national and local policies and standard operating procedures to

[4] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924–6.

facilitate implementation of the recommendations in these guidelines. This should include promoting universal health coverage and offering public financing for LTBI management. Furthermore, dedicated resources should be allocated, including for staff development and service delivery in the community. Training of frontline healthcare staff and students on critical areas such as identification of populations at risk, administering LTBI tests, choice of treatment, counselling and management of adverse reactions is important. National programmes should ensure meaningful engagement with affected populations, their communities, the private sector, other relevant health programmes and ministries in both planning and implementing the interventions. The process should facilitate articulation with other guidance on relevant risk factors for TB, such as diabetes, undernutrition and tobacco smoking, and access to comprehensive care for people with these co-existing risks.

The uptake of these WHO recommendations will be monitored in the annual data collection of WHO Global TB Data Monitoring. WHO will update the guidelines 5 years after their publication or earlier if new evidence becomes available that necessitates a revision.

4. Composition of Guideline Development Group and External Review Group[5]

Guideline Development Group

Name	Area of expertise	Sex	Region
Mohammed Al Lawati	Clinical	M	Eastern Mediterranean
Helen Ayles	Trials & content	F	Western Europe
Rolando A. Cedillos	Clinical	M	North America
Padmapriyadarsini Chandrasekaran	Clinical	F	S-E. Asia
Diana Gibb	Epidemiology & trials	F	Western Europe
Yohhei Hamada	Content	M	Western Pacific
Anthony D Harries	Content	M	Western Europe
Alexander Kay	Paediatrics	M	Africa
Nasehi Mahshid	National TB Programme	F	Eastern Mediterranean
Alberto Matteelli	Content & clinical	M	Western Europe
Lindiwe Mvusi (co-chair)	National TB Programme	F	Africa
Kuldeep Singh Sachdeva	National TB programme	M	S-E. Asia
Nandi Siegfried (co-chair)	Guideline methodology	F	Africa
Ezio Távora dos Santos Filho	Gender, equity and rights	M	South America
Marieke van der Werf	Epidemiology	F	Western Europe
Wim Vandevelde	Gender, equity and rights	M	Africa
Irina Vasilyeva	National TB programme	F	Eastern Europe

External Review Group

Name	Area of expertise	Sex	Region
1. Connie Erkens	Public health & content	F	Western Europe
2. Stephen Graham	Paediatrics	M	Western Pacific
3. Giovanni B. Migliori	Public health & content	M	Western Europe
4. Nguyen Viet Nhung	National TB Programme & clinician	M	Western Pacific
5. Rohit Sarin	Clinical	M	S-E. Asia
6. James Seddon	Paediatrics	M	Western Europe
7. Alena Skrahina	National TB Programme & clinical	F	Eastern Europe
8. Carrie Tudor	Nursing	F	Africa

[5] See Acknowledgements in main text for affiliations and countries of experts

5. Declaration of interests and management of potential conflict

The members of the Guideline Development Group (GDG) and External Review Group (ERG) completed a WHO declaration of interests form. All declarations were evaluated by the WHO Guideline Steering Group for any financial conflict of interest that might warrant exclusion from membership or from certain discussions of the GDG. The completed forms were summarised and presented to all GDG members at the first meeting, at which point the members were requested to update their declarations. Intellectual conflict of interest was not considered a motive for exclusion from the GDG as expertise on the topic was considered an important criterion for selection and the diversity and representation in the Group was large enough to balance any individual member's intellectual interest. The biographies of the GDG members were made public alongside the background document outlining the 2019 update on 1 July 2019, ahead of the GDG meetings.

Guideline Development Group

The following GDG members declared no interests that could conflict with the objectives of the guidelines:

- Mohammed Al Lawati, Rolando A. Cedillos, Diana Gibb, Yohhei Hamada, Nasehi Mahshid, Alberto Matteelli, Lindiwe Mvusi, Kuldeep Singh Sachdeva, Irina Vasilyeva.

The following GDG members declared interests that were judged not to conflict with the objectives of the meeting:

- Helen Ayles declared a research grant received by her institution from EDCTP plus in-kind support for a project in which she is principal investigator (QFT test kits at subsidized price from Qiagen and support to try a new, simplified version of the QFT test). Delft diagnostics provide in kind support in order of $100,000 to subsidize the cost of using their digital chest radiography and computer assisted diagnostics. Helen is a member of the Technical Review Panel for the Global Fund, which promotes adherence to the normative guidance of WHO.
- Padmapriyadarsini Chandrasekaran declared research grants received by her employer, the National Institute for research in TB, in Chennai, India, and collaboration, sponsorships and other funding from USAID under model DOTS project. The study is now completed
- Anthony D. Harries is a Senior Advisor at The Union, Paris, was the lead author on a "State of the Art" paper on "Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries" (Int J Tuberc Lung Dis 2019; 23: 241–251). With other UNION colleagues he wrote a review – "Treatment for latent tuberculosis infection in low- and middle-income countries: progress and challenges with implementation and scale-up" – for "Expert Review of Respiratory Medicine" as part of unpaid work. The paper, that was under review at the time of the GDG meeting, deals largely with the programmatic requirements to scale up the WHO LTBI treatment recommendations.
- Alexander Kay declared a research grant received by his organization from UNOPS and the Stop TB Partnership for a "TB Reach" project designed to increase the uptake of preventive therapy in children exposed to TB ($400,000). This work with NTP Eswatini aims to enhance access to preventive therapy among household contacts and includes nurse led community-based TB screening and preventive therapy. Shorter preventive therapy regimen (3RH) is used for children and isoniazid in adults and children living with HIV, however no specific regimen is privileged.
- Nandi Siegfried declared consultation work with WHO.
- Ezio Távora dos Santos Filho declared delivering a talk at the Regional IAS Conference in April 2018 in Mexico City on the need for advanced tools for LTBI treatment, without endorsing any particular study. He also declared that as TB advocate he participated in many discussions with the Global TB Community Advisory Board and the Brazilian National TB CAB on the implementation of new LTBI treatment methods. The Brazilian TB CAB is now raising awareness of 3HP and LTBI. The affected communities may benefit directly from new guidelines.

- Marieke van der Werf declared interest of her employer in the topic and that ECDC is working on LTBI.
- Wim Vandevelde declared travel support from the Stop TB Partnership for participation as speaker in TB/HIV symposium at the IAS 2019 in Mexico and that symposium will cover LTBI.

External Review Group

The following ERG members declared no interests that could conflict with the objectives of the guidelines:

- Stephen Graham, Giovanni B. Migliori, Rohit Sarin, Alena Skrahina

The following ERG members declared interests that were judged not to conflict with the policy of WHO or the objectives of the meeting:

- Connie Erkens declared that a study she was involved in on LTBI screening in migrants to the Netherlands received 1,800 QuantiFERON-TB Gold Plus from the manufacturer QIAGEN (value EUR27,000) in 2016–2018.[6] Qiagen had a role in the study design, implementation, data collection and analysis, decision to publish, or preparation of the report.
- James Seddon declared that he is employed by Imperial College, London, UK to carry out research on childhood TB, some of these studies involve the investigation of treatment of LTBI. He also has a grant from Global Trials Scheme (WT/MRC/DFID/HIHR) to carry out a trial of preventive therapy for MDR-TB exposed children. He also has a fellowship from MRC to carry out studies evaluating correlates of risk in MDR-TB exposed children. He is also involved in the TB-CHAMP trial (MDR-TB prevention trial in children under 5 years) and has a personal fellowship to look at correlates of risk using the trial as a research platform. His PhD looked at MDR-TB preventive therapy in an observational cohort of children treated in Cape Town. He collaborates with the UNITAID grant CapTB which includes household contact tracing and preventive therapy. He has been involved in an application as a co-investigator to the NIH for a K43 to look at implementation of 3HR in South Africa. He is collaborating on a modelling exercise (funded by TB-MAC) to look at implementation of different types of LTBI treatment, use of TST and decisions in whom to treat in terms of risk-benefit and cost effectiveness; he has also collaborated on modelling the impact of household contact activities on childhood TB burden. The amounts were not disclosed. He is co-investigator in a NIH R01 study that has been submitted (Implementation of child contact management interventions to prevent TB in children in Cape Town, South Africa); budget US$2.8 million. He has also written reviews on TB infection (including treatment).
- Carrie Tudor declared that she is employed with the International Council of Nurses, which received US$1 million from the Eli Lilly Foundation MDR-TB partnership to train nurses between 2013 and 2019.

Evidence reviewers

The evidence reviewers provided the estimates for the evidence summaries but did not participate in formulating the recommendations for policy. The following reviewer declared interests that were judged not to conflict with the policy of WHO or the objectives of the meeting:

- Lynne M. Mofenson declared that in 2018 she has served as a consultant for WHO on the use of dolutegravir in pregnancy

[6] Spruijt I, Erkens C, Suurmond J, Huisman E, Koenders M, Kouw P, et al. (2019) Implementation of latent tuberculosis infection screening and treatment among newly arriving immigrants in the Netherlands: A mixed methods pilot evaluation. PLoS ONE 14(7): e0219252. https://doi.org/10.1371/journal.pone.0219252

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