World Health Organization

Rapid communication on systematic screening for tuberculosis

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Background

Tuberculosis (TB) is the leading cause of death from a single infectious agent even if is largely curable and preventable. In 2019 an estimated 2.9 million of the 10 million people who fell ill with TB were not diagnosed or reported to the World Health Organization[1]. The Political Declaration adopted by the United Nations General Assembly in September 2018 commits, amongst others, to diagnosing and treating 40 million people with TB. In order to achieve these ambitious targets, there is an urgent need to deploy strategies to improve diagnosis and initiation of care for people with TB. One of them is systematic screening for TB disease, which is included in the End TB Strategy as a central component of its first pillar to ensure early diagnosis for all with TB.

To facilitate the implementation of TB screening at the country level, the World Health Organization (WHO) published guidelines on screening for TB in 2013[2]. Since then, there have been important new studies evaluating the impact of screening interventions on both individual-level and community-level outcomes related to TB, as well as new research evaluating innovative tools for screening for TB among important populations at high risk for TB disease, including the use of computer-aided detection of TB on digital radiographs, C-reactive protein and WHO-approved rapid molecular diagnostic tests for TB.

In the light of these new developments and according to the request by Member States in 2020 WHO convened a Guideline Development Group (GDG) to examine the evidence in order to update the *Systematic screening for active tuberculosis: principles and recommendations* of 2013. The Group met in virtual sessions between June and October 2020 and proposed several new recommendations related to TB screening. The preparation and review of the new *WHO consolidated guidelines on tuberculosis: Module 2: Screening – systematic screening for tuberculosis disease* are in process and they are scheduled to be released in March 2021, alongside an operational handbook. WHO gratefully acknowledges the work of the GDG members, the evidence reviewers, national TB and HIV programmes, WHO colleagues, technical and funding partners, civil society, patients and all others who contributed to the data to inform this guideline update.

This Rapid Communication is being issued to help national TB programmes and other stakeholders prepare for the changes that will be introduced with the new guidelines on TB screening.

Key findings

Chest radiography for TB screening

Chest radiography ("chest X-ray" or CXR) has a long history of use for TB screening and triage of people being evaluated for TB. In addition, recent studies have shown that a substantial proportion of people with TB disease do not present with symptoms and TB is detected through CXR alone [3,4,5]. Data on the use of CXR as a screening tool for detection of TB disease in several populations including the general public, people living with HIV, contacts of TB patients under 15 years of age and other high-risk groups were reviewed. Across all populations considered, CXR was found to be a sensitive screening tool that, while lacking sufficient specificity to confirm a TB diagnosis, has an important role in the early detection of TB

[1] Global Tuberculosis Report 2020 https://www.who.int/tb/publications/global_report/en/
[2] Systematic screening for active tuberculosis: principles and recommendations 2013 https://www.who.int/tb/tbscreening/en/
[3] Onozaki et al. Trop Med Int Health 2015 Sep;20(9):1128-1145. doi: 10.1111/tmi.12534.
[4] Law et al. *Trop Med Int Health* 2020 Nov;25(11):1308-1327. doi: 10.1111/tmi.13485.
[5] Frascella et al. Clin Infect Dis. 2020 Sep 16;ciaa1402. doi: 10.1093/cid/ciaa1402.

in children and adults at higher risk of TB, as well as to reduce the population burden of TB disease when combined with early treatment and other public health action.

Computer-aided detection software for the automated interpretation of chest radiography for screening and triage of TB

While chest radiography is widely used in the clinical evaluation of TB, the inter-reader variability of human interpreters is substantial and access to trained radiologists is limited in many resource-constrained settings. In recent years computer-aided detection (CAD) software packages have been developed and introduced in the market to automate the interpretation of digital CXR images and produce a numerical score indicating the likelihood of TB.

Three independent evaluations of CAD were undertaken for both the screening and triage use cases. Each evaluation considered all three CAD technologies that were CE marked at the start of 2020 and available on the market. Diagnostic accuracy measurements (sensitivity and specificity) from these analyses were assessed and compared with human reader interpretation, using bacteriological confirmation of TB as a reference standard. The results were presented blinded to the brand name of the software and the discussion therefore relates to the class of technologies as a whole and is not specific to any particular product. Evaluations showed substantial variation in CAD performance (diagnostic accuracy) across different contexts, implying that the use of CAD may require adjustment for the purpose and setting in which CAD will be implemented. Nonetheless, the diagnostic accuracy and the overall performance of CAD software were similar to the interpretation of digital chest radiography by a human reader, in both the screening and triage contexts.

C-Reactive Protein for screening of people living with HIV

C-Reactive Protein (CRP) is an indicator of inflammation that can be measured using point-of-care tests performed on capillary blood collected via finger-prick. These tests are becoming increasingly available even in low resource settings. The performance of CRP levels against bacteriologically confirmed TB in people living with HIV was assessed using an individual patient data meta-analysis of people screened in high and medium burden settings. CRP was found to have similar sensitivity and higher or similar specificity to symptom screening in all subpopulations tested. CRP offers a clinically significant improvement in accuracy over the WHO four-symptom screen among ambulant people living with HIV who are newly in care and not yet on antiretroviral treatment (ART), a subpopulation for whom the specificity of the four-symptom screen is low.

Molecular WHO-approved rapid diagnostic tests for TB screening

Molecular WHO-approved rapid diagnostic tests for TB (mWRDs; eg Xpert MTB/RIF) were reviewed for use as TB screening tools in people living with HIV and other subgroups at high risk of TB. Evidence shows improved accuracy and effectiveness in people living with HIV and in other high-risk populations in high TB-burden settings, including populations with an estimated TB prevalence below 1%. The evidence is strongest for hospitalized patients with HIV in high TB-burden settings, given the limited value of symptom screening and the grave consequences of missing the opportunity to initiate TB treatment promptly in this patient group.

Key updates

- Community-wide systematic screening using a sensitive tool such as CXR followed by an accurate diagnostic test may be used in settings with TB prevalence even lower than 1% - the threshold proposed in the 2013 guidance - based on evidence of public health benefit at such levels.
- CAD may be used as an alternative to human reader interpretation of plain digital CXR for screening and triage for TB. Its use should be limited to the interpretation of plain CXR for pulmonary TB in individuals aged 15 years or more.
- mWRDs may be used for TB screening to improve the accuracy of symptom screening in high risk populations.
- When scaling up CXR and innovations like CAD, CRP and mWRD for screening, due consideration should be given not to create inequities. mWRD needs to be prioritized for use for diagnostic testing of people with presumptive TB. Implementation of CAD will require thorough consideration of infrastructure requirements including digital radiography equipment, computer availability, internet access, as well as the costs for licence and use of different CAD products.
- In people living with HIV:
    - Screening with CXR improves the sensitivity of the WHO four-symptom screen (cough, fever, weight loss or night sweats) in detecting TB, including in people who attend HIV care services for ART.
    - CRP may be used for TB screening over and above the WHO four-symptom screen in all people living with HIV in high TB-burden settings.
    - mWRDs may be used to screen for TB in all people living with HIV as in other high-risk populations in high TB-burden settings. They offer a distinct opportunity to improve timely diagnosis and treatment in hospitalized patients with HIV in medical wards in high TB-burden setting.

Next steps

- The updated recommendations will be released as the *WHO consolidated guidelines on tuberculosis: Module 2: Screening – systematic screening for tuberculosis disease* in March 2021. These guidelines will replace all previous WHO guidance on tuberculosis screening and will include updated recommendations and detailed results of the evidence review for all questions that guided the analysis. The summary of findings and the evidence to decision tables will be produced in conformity with the GRADE method and made available on the WHO Global TB Programme website.

- The recommendations will be accompanied by updated operational guidance. This will include further details on target populations and tools to use for systematic screening, including revised algorithms and new sections on CXR and CAD, with advice on how to implement CAD and a protocol for calibration of the CAD product to the local conditions where it will be used.

- The release of the new guidance will be followed by a series of WHO webinars for different regions to communicate the new guidelines. The new screening policies will also be included in an online knowledge sharing platform that the Global TB Programme will launch in early 2021 and that will provide access to the guidelines, implementation aids and eLearning tools in one place. The webinars and the platform will support countries to update their national guidelines, train staff, inform programme budgets and facilitate the rapid transition to more effective interventions. National programmes and other stakeholders are encouraged to seek advice from WHO and technical partners before introducing the novelties being recommended in our new guidelines and expanding systematic screening activities.

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