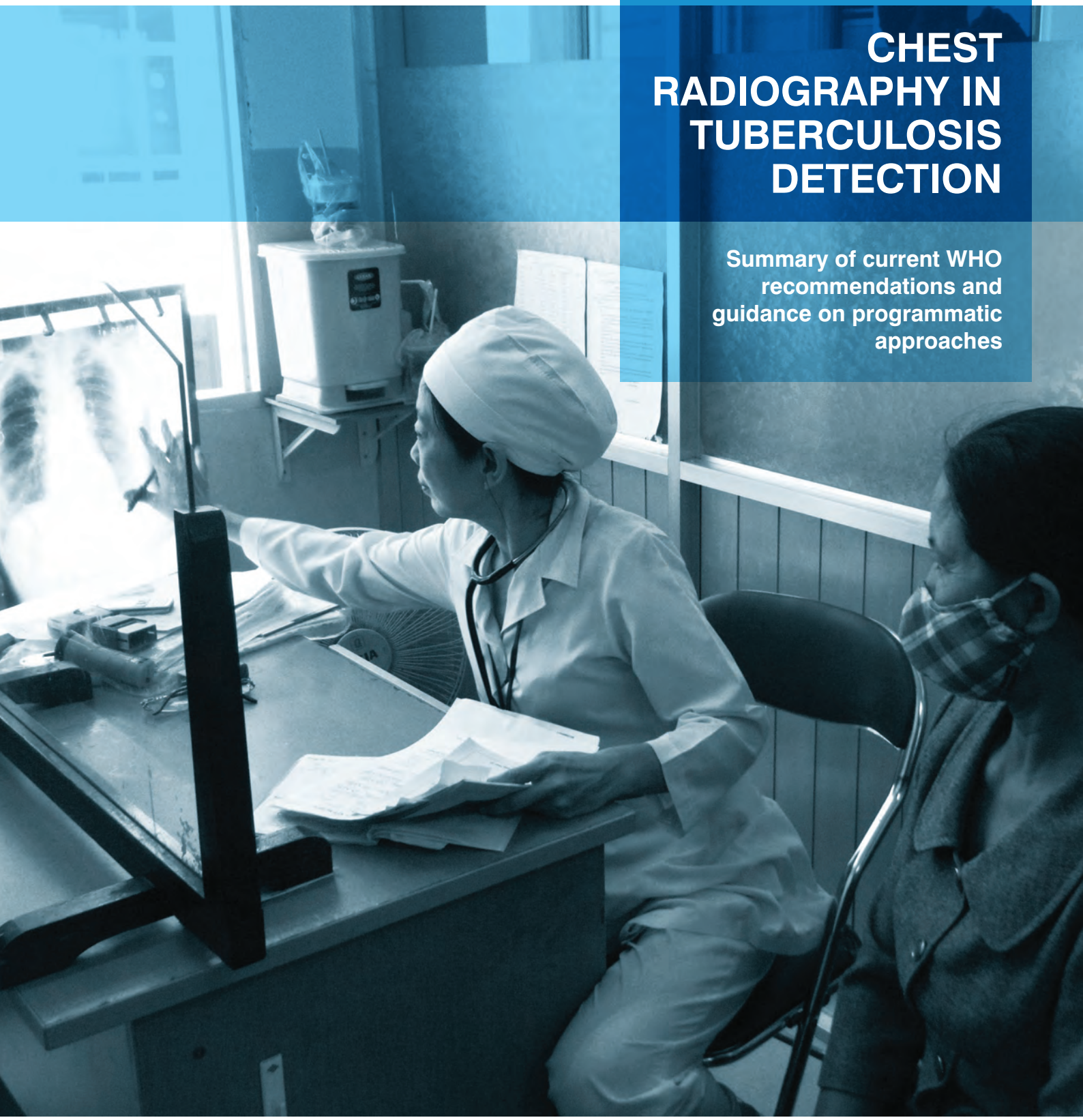
CHEST RADIOGRAPHY IN TUBERCULOSIS DETECTION

Summary of current WHO recommendations and guidance on programmatic approaches



THE END TB STRATEGY

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Preface

The End TB Strategy puts renewed emphasis on the need to ensure early and correct diagnosis for all people with tuberculosis (TB) ***(1)***. Important progress has been made in improving laboratory services in recent decades. New bacteriological tests for TB diagnosis have become available and their use is now being scaled up *(2, 3)*. Efforts have been made to ensure that people who seek care and have symptoms consistent with TB are correctly triaged and evaluated for TB. Systematic screening for active TB in high-risk groups is being implemented and scaled up in several places *(4, 5)*. However, despite these efforts, many people with TB remain undiagnosed or are diagnosed only after long delays *(6)*.

Chest radiography, or chest X-ray (CXR), is an important tool for triaging and screening for pulmonary TB, and it is also useful to aid diagnosis when pulmonary TB cannot be confirmed bacteriologically. Although recent diagnostic strategies have given specific prominence to bacteriology, CXR can be used for selecting individuals for referral for bacteriological examination, and the role of radiology remains important when bacteriological tests cannot provide a clear answer. Access to high-quality radiography is limited in many settings. Ensuring the wider and quality-assured use of CXR for TB detection in combination with laboratory-based diagnostic tests recommended by the World Health Organization (WHO), can contribute to earlier TB diagnosis and potentially to closing the TB case-detection gap when used as part of algorithms within a framework of health-system and laboratory strengthening.

This document summarizes WHO's recommendations on using CXR for TB triaging, diagnosis and screening. It also outlines a framework for the strategic planning and use of CXR within national TB programmes (NTP). Moreover, the document provides a brief overview of technical specifications, and quality assurance and safety considerations for CXR. However, because these technical aspects are generic and should be addressed as part of the general strengthening of radiography and imaging services, this document does not go into technical details. General radiography guidance is provided elsewhere *(7-11)*.

The document focuses on CXR, with a major emphasis on detecting pulmonary TB. CXR can be useful for diagnosing other forms of TB (for example, miliary or pericardial TB, or tuberculous effusions) and other imaging techniques are also valuable for TB diagnosis, for example, for extrapulmonary TB, but these topics are not discussed in this document.

The document is mainly intended for NTPs and partners helping with the planning and implementation of national TB care and prevention efforts. It is not intended to be a clinical guide. The recommendations and principles that are summarized in this document need to be adapted to each setting's TB epidemiology and health-system capacity.

Development process

A steering group was established in January 2016, which advised WHO on the scope and content of this document. The members of the steering group were Faiz Ahmad Khan, Sevim Ahmedov, Frank Cobelens, Jacob Creswell, Claudia Denkinger, Christopher Gilpin, Michael Kimerling, Knut Lönnroth, Cecily Miller, YaDiul Mukadi, Ikushi Onozaki and Madhukar Pai.

After consultation with WHO's Guideline Review Committee, it was determined that the document is not a new guideline but a summary of existing WHO recommendations. Therefore, it did not need to follow WHO's guideline development process.

All major WHO publications about TB were reviewed for their relevance to the use of CXR in screening for, triaging and diagnosing TB. Recommendations across all documents were compiled and summarized. An accompanying framework for strategic planning for using CXR within NTPS was developed based on experts' opinions.

No systematic literature review was undertaken during the development of this document. The evidence base for the statements made in this document is the same as for those in the cited WHO guidelines and policy frameworks.

Scenarios for the yield of TB (true positive/true negative and false positive/false negative) for different triaging algorithms were modelled using the ScreenTB tool *(12)* to illustrate how the different placement of CXR in an algorithm influences yields and costs under different epidemiological scenarios. The model outputs that are included in this document should not be used for forecasting TB detection, but are included merely to demonstrate how variations in algorithms influence TB detection and costs. Readers are advised to develop setting-specific scenarios based on the local TB epidemiology and the best data about test accuracy and costs.

A first draft was completed in July 2016 and was circulated to experts (see below) for peer review. Based on comments from the peer review, a second draft was prepared ahead of a global consultation held during 28–29 September 2016. The consultation provided additional inputs on the draft document, and the documented was thereafter finalized.

Acknowledgements

The first draft was prepared by Cecily Miller and Knut Lönnroth. The following persons contributed to the development of the document or peer reviewed it, or both: Faiz Ahmad Khan, Sevim Ahmedov, Farhana Amanullah, Samiha Baghdadi, Draurio Barreira, Adriana Velazquez Berumen, Nils Billo, Annemieke Brands, Grania Brigden, Chen-Yuan Chiang, Maarten van Cleeff, Jacob Creswell, Claudia Denkinger, Anna-Marie Celina Garfin, Nebiat Gebreselassie, Sifrash Meseret Gelaw, Wayne van Gemert, Robert Gie, Steve Graham, Rob van Hest, Philip Hopewell, Bogomil Kohlbrenner, Alexei Korobitsyn, Devesh Gupta, Michael Kimerling, Irwin Law, Partha Pratim Mandal, Guy Marks, Giovanni Batista Migliori, Mahshid Nasehi, Nobuyuki Nishikiori, Pierre-Yves Norval, Kosuke Okada, Ikushi Onozaki, Salah-Eddine Ottmani, Madhukar Pai, Tripti Pande, Mario Raviglione, Maria del Rosario Pérez, Anna Scardigli, Eric Stern, Beat Stoll, Etienne-Leroy Terquem, Belay Tessema, Mukund Uplekar, Diana Weil, William Wells, Marieke van der Werf and Christine Whalen.

Declarations of interests

The following interests were declared by the experts consulted.

Declared interests that were deemed not significant

- Claudia Denkinger: took part in several clinical research projects to evaluate new diagnostic tests against the target product profiles for TB defined through consensus processes led by WHO. These studies were for diagnostic products developed by private sector companies (Cepheid, Epistem, Molbio Diagnostics, Hain Lifescience, Nipro, Becton Dickinson, Alere, YD Diagnostics, Ustar Biotechnologies and Qiagen) that provide access to know-how, equipment and reagents, and contribute through unrestricted donations as per FIND (Foundation for Innovative New Diagnostics) policy.
- Bogomil Kohlbrenner and Beat Stoll: were employed as researchers on a project to develop appropriate medical devices and appropriate training for health workers in the field of tropical medical imaging; it was a philanthropic project.

Declared interest that were deemed significant for making recommendations to WHO about whether to develop guidelines for computer-aided detection

- Faiz Ahmad Khan and Madhukar Pai: received a research grant to study the diagnostic accuracy of CAD4TB (developed by Delft Imaging Systems, Veenendaal, the Netherlands) in collaboration with Interactive Research & Development, who have purchased equipment from the makers of CAD4TB. The developers of CAD4TB are not collaborators or in any way involved in the research. Faiz Ahmad Khan and Madhukar Pai were invited to present the systematic review on CAD for TB detection, provide comments throughout the meeting, and peer-review draft documents. However, they were not part of the decision to advise WHO on the initiation of a CAD guideline development process.

Abbreviations

AFB	acid-fast bacilli
CAD	computer-aided detection
CXR	chest X-ray or chest radiography
HIV	human immunodeficiency virus
LTBI	latent tuberculosis infection
MTB	Mycobacterium tuberculosis
NTP	national tuberculosis programme
PICO	population, intervention, comparator, outcome
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SSM	sputum-smear microscopy
TB	tuberculosis
WHO	World Health Organization

Definitions

Bacteriologically confirmed TB case: A bacteriologically confirmed case of TB is one from whom a biological specimen tests positive by smear microscopy, culture or WHO-recommended rapid diagnostic (such as the Xpert MTB/RIF assay). All such cases should be notified, regardless of whether TB treatment has started *(13)*.

Clinically diagnosed TB case: A clinically diagnosed case of TB is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of anti-TB treatment. This definition includes cases diagnosed on the basis of abnormalities seen on X-ray or histology suggestive of TB, and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed *(13)*.

Systematic screening for active TB: is the systematic identification of people with suspected active TB in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly *(4)*. Unlike evaluations of those who actively seek care for respiratory symptoms (known as triaging), the systematic screening of individuals for TB is typically initiated by a provider and offered in a systematic way to an apparently healthy target group that has been determined to have a high risk of TB.

Triaging: For the purpose of this document, triaging is defined as the processes of deciding the diagnostic and care pathways for people seeking healthcare, based on their symptoms, signs, risk markers and test results. Triaging involves assessing the likelihood of various differential diagnoses as a basis for making clinical decisions. It can follow more- or less-standardized protocols and algorithms and may be done in multiple steps.

1. INTRODUCTION

1.1 Medical imaging

Medical imaging uses different modalities and processes to image the internal structures of the human body for diagnosis and treatment. Imaging has an important role in healthcare for all population groups. In public health and preventive medicine, as well as in both curative and palliative care, effective clinical decisions depend on correctly screening, triaging and diagnosing patients. The use of imaging services is paramount in correctly screening, confirming and documenting the course of many diseases. With the improved availability of medical equipment, global access to medical imaging has increased considerably, but is still insufficient in many settings *(14)*. Medical imaging is a key element within many evidence-based clinical decision-support algorithms, consistent with overarching evidence-based recommendations for disease management *(14)*. As such, medical imaging should be accessible to all and should not be exclusively a hospital service *(15)*.

1.2 Radiography

Radiography uses X-rays to visualize the internal structures of a patient. X-rays are a form of electromagnetic radiation produced by an X-ray tube. The X-rays pass through the body and are captured behind the patient by film that is sensitive to X-rays or by a digital detector. Different tissues in the body vary in their absorption of X-rays: dense bone absorbs more radiation, but soft tissue allows more to pass through. This variance produces contrasts within the image to give a two-dimensional representation of the three-dimensional structures. As a result, the X-ray image often includes overlapping structures. A thorough knowledge of anatomy is needed to identify an abnormality on an X-ray and understand where it is in the body. Common clinical applications include imaging the chest to assess lung and intrathoracic pathologies; imaging the skeletal system to examine bone structures and diagnose fractures, dislocations or other bone pathologies; imaging the abdomen to assess obstructions or free air or fluid within the abdominal cavity; or imaging the teeth to assess common dental pathologies, such as cavities or abscesses *(14)*.

1.3 Chest X-ray for detecting TB

Chest X-ray (CXR) is a rapid imaging technique that allows lung abnormalities to be identified. CXR is used to diagnose conditions of the thoracic cavity, including the airways, ribs, lungs, heart and diaphragm.

CXR has historically been one of the primary tools for detecting tuberculosis (TB), especially pulmonary TB. CXR has high sensitivity for pulmonary TB and thus is a valuable tool to identify TB as a differential diagnosis for patients, especially when the X-ray is read to identify any abnormality that is consistent with TB. However, CXR has poor specificity; although some CXR abnormalities are rather specific for pulmonary TB (for example, cavities), many CXR abnormalities that are consistent with pulmonary TB are seen also in several other lung pathologies and, therefore, are indicative not only of TB but also of other pathologies. Moreover, there is significant intra- and interobserver variation in the reading of CXRs. Relying only on CXR