WHO Policy Update on TB Screening for Early Case Finding: Recommended Tools and Algorithms

MODULE 1

Acknowledgements

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Introduction

This module discusses the World Health Organization's (WHO) recommended tools and algorithms for systematic screening for TB in different populations.

Course Outline

- → Overview of WHO recommendations on systematic screening for TB
- → Introduction to WHO-recommended screening tools for TB
- → Review of TB screening algorithms for the general population
- → Recommended screening tools and algorithms for people with HIV
- → Recommended screening tools and algorithms for children
- → Scoping the national TB context
- Summary

Learning Objectives

By the end of this module, participants should be able to:

- Understand the requirements and role of systematic screening in the global TB response.
- Describe the advantages and disadvantages of each of the WHO-recommended screening tools.
- Recognize the different TB screening algorithms appropriate for the general population, persons living with HIV, and children.
- Describe the current TB situation in the country, including screening and diagnostic practices.

TB Context

Global TB Situation

10 million people fall ill with TB every year.

Only 5.8 million of these people were diagnosed and notified.

1.5 million people die from TB each year—making it the world’s top infectious killer.

TB is the leading cause of death of people with HIV and a major contributor to antimicrobial resistance.

WHO Recommendations for Systematic Screening

WHO Guidelines on Systematic Screening

Systematic screening for TB disease is defined as:

*The **systematic identification of people at risk for TB disease,** in a predetermined target group, by assessment using tests, examinations, or other procedures that can be applied **rapidly.***

From the WHO Consolidated Guidelines on Tuberculosis

- Screening tests should efficiently distinguish people likely to have TB disease from those who are unlikely to have TB disease.
- In those screened positive, diagnosis needs to be established by **evaluation using one or more diagnostic tests** and by **clinical assessment,** which together have high accuracy.

Role of TB Screening in Overall TB Care

- Addressing the case detection gap—finding the “missing millions”
  - Globally in 2020, 5.8 million people were diagnosed and treated for TB, out of estimated 10 million cases—**significant 18% drop from 2019.**
  - The COVID-19 pandemic has made the problem much worse, with a predicted 4 to 16 percent increase in TB deaths over the next 5 years, according to a modeling study done by Stop TB.
  - Progress still lags in achieving targets from the UN High Level Meeting, 2018.
- Reaching the most vulnerable groups
  - Those with highest risk for TB often have the least access to care.
- Initiating TB preventive treatment
  - Systematic screening for TB disease is an essential first step in initiating TB preventive treatment in eligible populations.

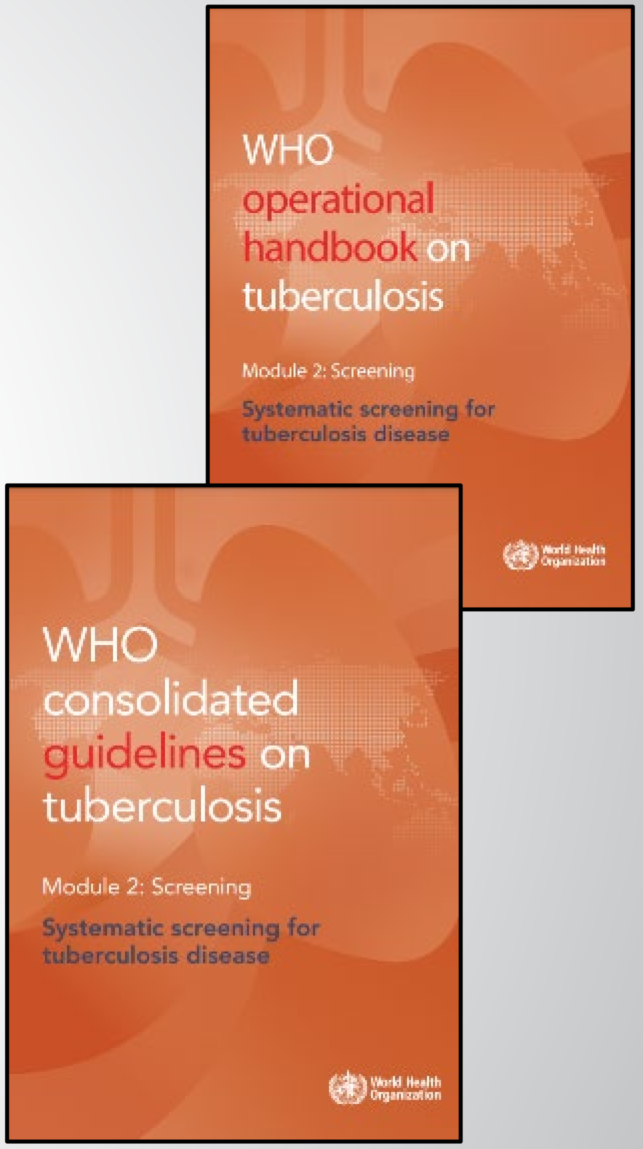
WHO Recommendation on Population to be Screened

New WHO guidelines and an operational handbook were released on March 22, 2021.

Systematic screening for TB disease is **strongly** recommended among:

Household and close contacts of TB patients	People living with HIV	Miners exposed to silica dust	Prisoners	Internally Displaced Persons (IDP)

The question is: using what tools, algorithms, and implementation models; **and** how often should screening occur?
TB preventive treatment should be provided to those identified to have TB through subsequent diagnosis and clinical evaluation.



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WHO Recommendation on Population to be Screened

Systematic screening for TB disease is also **conditionally** recommended among:

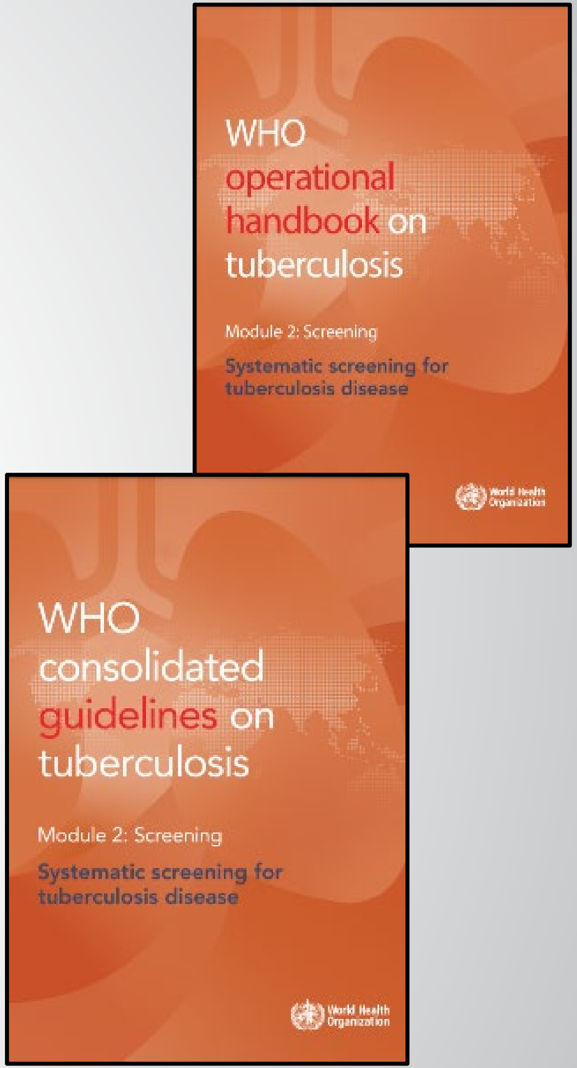
- People with untreated fibrotic lesions on a chest X-ray
- People with TB risk factors who are seeking health care, in settings with ≥0.1 percent TB prevalence
- People with malnourishment, diabetes, history of TB, chronic lung disease, and others
- Populations with structural risk factors for TB and limited access to health care
- Urban poor, homeless, refugees, migrants, and other vulnerable or marginalized groups
- General population in settings with ≥0.5 percent TB prevalence

For these populations, consideration should be given to:

✓ **Weighing** the benefits and risks of screening

✓ **Considering** opportunity costs for other TB and health interventions

✓ **Prioritizing** risk groups that represent the greatest burden or have the greatest vulnerability in a particular setting



TB Screening Tools Overview

Recommended Tools to Screen
General Population (aged 15+) and High-risk Groups (not HIV+)

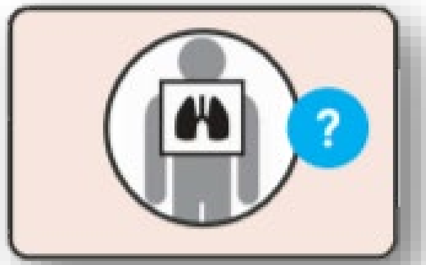
There are **four recommended screening tools** for TB in high-risk populations (and the general population in high burden settings) that are recommended by WHO for all individuals aged 15 years and older:

1. Symptom screening

Cough

Any TB symptom

2. Chest X-ray



3. Computer-aided detection

4. Molecular WHO-recommended rapid diagnostics

Symptom Screening

Screening individuals for symptoms of TB. This could be **any cough, prolonged cough,** or **any TB-associated symptom,** including any cough, hemoptysis, weight loss, fever, or night sweats.

Benefits:

- A suitable and acceptable screening tool in most settings and risk groups
- May be more feasible to implement (fewer resources needed and less costly)
- Non-invasive

Limitations:

- Less sensitive than chest X-ray or molecular tests
- Does not identify asymptomatic or pre-symptomatic individuals, nor people with atypical symptoms.

Screening test	No. of studies (no. of participants)	Sensitivity	No. of studies (no. of participants)	Specificity
WHO target product profile	NA	> 0.90	NA	> 0.70
Prolonged cough (≥ 2 weeks)	40 (6 737)	0.42	40 (1 284 181)	0.94
Any cough	21 (2 734)	0.51	21 (768 291)	0.88
Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss)	28 (3 915)	0.71	28 (460 878)	0.64
Chest radiography (any abnormality)	22 (4 243)	0.94	22 (1 012 752)	0.89
Chest radiography (suggestive abnormality)	19 (2 152)	0.85	19 (464 818)	0.96
Molecular WHO-recommended rapid diagnostic test	5 (337)	0.69	5 (8 619)	0.99

Chest X-ray

Chest X-ray (CXR) is an imaging tool for identifying lung abnormalities. The role of CXR is improving TB notification in high-prevalence settings.

Benefits:

- ✔ A sensitive tool for screening and detecting active pulmonary TB
- ✔ Can identify asymptomatic or presymptomatic people with TB
- ✔ Useful triage tool to improve efficiency of molecular diagnostic testing
- ✔ Can provide differential diagnosis of other lung conditions outside of TB
- ✔ Potential in treatment monitoring

Limitations:

- ✔ Cannot detect extra-pulmonary TB
- ✔ Not very specific
- ✔ Involves exposure to radiation (although risk is minimal)
- ✔ Use and access to CXR is hampered by:
  - Insufficiently trained radiologists
  - Shortage of trained readers (usually physician radiologists) to interpret the images.
  - Intra- and inter-reader variability
  - Limited access to high-quality digital CXR imaging in low-resource settings

WHO recommends the use of CXR as an effective screening test for pulmonary tuberculosis, as well as an aid in the diagnostic pathway to complement bacteriological tests.

Computer-aided Detection Software

Computer-aided detection (CAD) is an interpretation tool for chest X-ray that can provide rapid, automatic interpretation of x-ray results and be used in addition to or in place of human readers.

Benefits:

- Validation studies have shown that CAD performance is similar to, or **better than,** human readers.
- Can be used **in absence** of trained human reader (if not available) and thereby increase case detection from CXR screening interventions
- Can enhance and facilitate human resources capacity when used **with** trained human reader (decision support, prioritization, workflow management)
- Results are provided rapidly (<1 minute), allowing for quick clinical decision-making
- Standardized reporting reduces inter- and intra-reader variability
- Can be used to meet different programmatic goals (e.g., halving the number of confirmation tests required or increase yields)

Limitations:

- Not yet validated nor recommended for use in children <15 years
- May not be as accurate in people with TB scarring but no active disease
- Further research is needed to ensure that CAD performs as well in key populations, such as persons living with HIV.
- A TB CAD product may not give an indication on the presence or absence of other diseases. Even if it does, the accuracy of differential diagnosis is not validated.
- High price and complex pricing structures

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Molecular WHO-recommended Rapid Diagnostics

Molecular WHO-recommended rapid diagnostics (mWRDs) are rapid and sensitive molecular tests suitable for screening. mWRDs include Xpert MTB/RIF, Xpert MTB/RIF Ultra, Truenat, etc.

When used for screening, mWRDs have different accuracy than when they are used for diagnosis, and different predictive values are associated with a positive test and a negative test due to differences in the prevalence of TB in the populations being tested.

Benefits:

- ✔ Highly specific when used for screening (99 percent)
- ✔ Some mWRDs are becoming more decentralized.

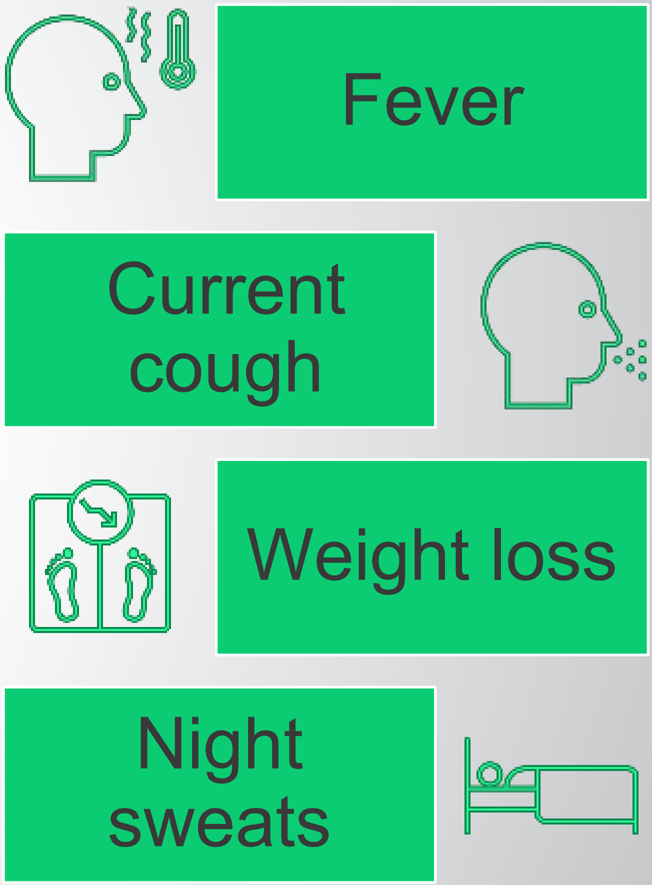
Limitations:

- ✔ Require significant resources (machines, cartridges, consumables)
- ✔ Limited in individuals who cannot produce sputum
- ✔ Can result in false positives when used alone in low-prevalence setting for people living with HIV
- ✔ A negative mWRD cannot be used to exclude TB for people living with HIV.

Tools for Screening People Living with HIV

The following tools are recommended for screening people living with HIV (for adults and adolescents 10 years and older):

- WHO-recommended four symptom screen (W4SS)
    - Cough, fever, night sweats, weight loss
- C-Reactive Protein (CRP)
    - A point-of-care blood test measuring the occurrence of an indicator (CRP) in the blood.
    - Improves on the accuracy (particularly specificity) of the W4SS for people living with HIV not on antiretroviral therapy (ART)
- Chest X-ray
- Molecular WHO-recommended rapid diagnostic tests



C-Reactive Protein

- A general marker for inflammation, can be performed as a point-of-care test in some settings
- Has similar sensitivity and similar or improved specificity to W4SS in all subgroups of people living with HIV, depending on cut-off
- Represents an improvement in accuracy (particularly specificity) over the W4SS for people living with HIV not on ART

Population	Cut-off > 5 mg/L		Cut-off > 10 mg/L	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
All people living with HIV	90	50	83	65
Inpatients	98	12	97	21
Outpatients on ART	40	80	20	90
Outpatients not on ART	89	54	82	67
≤ 200 CD4 cells/μL[a]	93	40	90	54
Pregnant women living with HIV	70	41	70	54

Tools for TB Screening in Children

There are two groups of children in whom TB screening is **strongly** recommended:

Child contacts of people with TB

Tools **strongly** recommended for screening child contacts (up to 15 years) include:

- Symptom screening (cough, fever, poor weight gain)
    - In young children, reduced playfulness or lethargy may also be considered a symptom.
- Chest X-ray

Children living with HIV

Children with HIV (<10 years) should be screened for TB at every encounter with a health care worker given the risk of TB and of mortality in this group

Tools **strongly** recommended for screening children living with HIV (up to 10 years) include:

- Symptom screening
    - Cough, fever, poor weight gain
- Being a close contact of someone with TB

Children frequently have extrapulmonary TB disease, **health care workers must be aware of symptoms that indicate TB at other sites,** such as lymphatic, abdominal, meningeal, and osteoarticular TB.

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TB Screening Algorithms Overview

Overview of TB Screening Algorithms

Screening algorithms **combine one or several screening tests and diagnostic evaluation** for TB disease. Different configurations of screening tests have different implications for the sensitivity, specificity, and costs of the algorithm.

There are four general types of screening algorithms to be aware of:

1. Single screening algorithm: Uses **only one screening test.** A positive screen result requires diagnostic evaluation.

2. Parallel screening algorithm: Uses **two screening tests in parallel.** A positive result on either or both requires diagnostic evaluation.

3. Sequential positive serial screening algorithm: Uses **two screening tests in sequence.** A positive result on the first screen results in referral to the next screening test.

- Diagnostic evaluation for anyone screening positive on both screening tests.

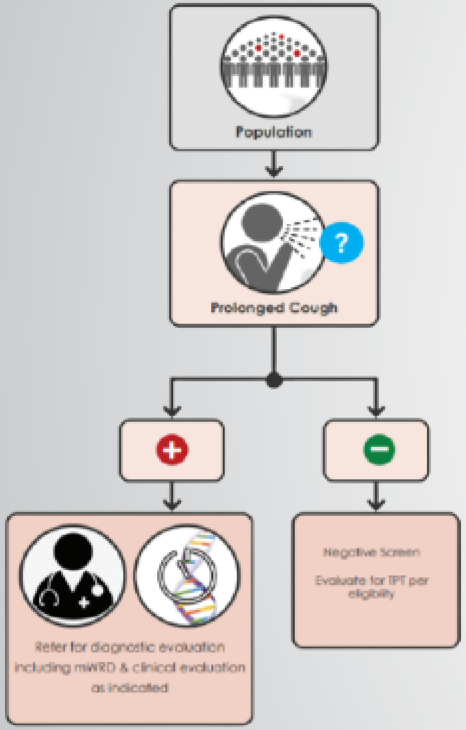
4. Sequential negative serial screening algorithm: Uses **two screening tests**

- A positive result on the first screening test results in referral to diagnostic evaluation.
- A negative result on the first screening test results in referral to the second screening test and diagnostic evaluation if positive on the second screening test.
- It is similar to, but reduces the cost of, parallel and sequential positive screening by limiting the numbers of people referred for a second screening test.

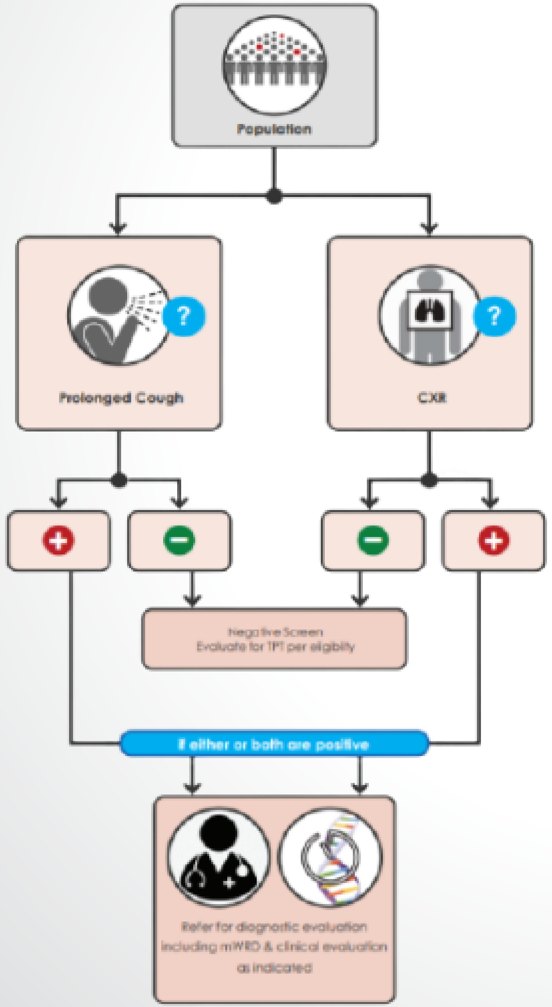
General Population (aged 15+) and High-risk Groups (not HIV+)

Initial screen: Cough and all symptoms
CXR is used as secondary screen and mWRD/clinical evaluation as diagnosis

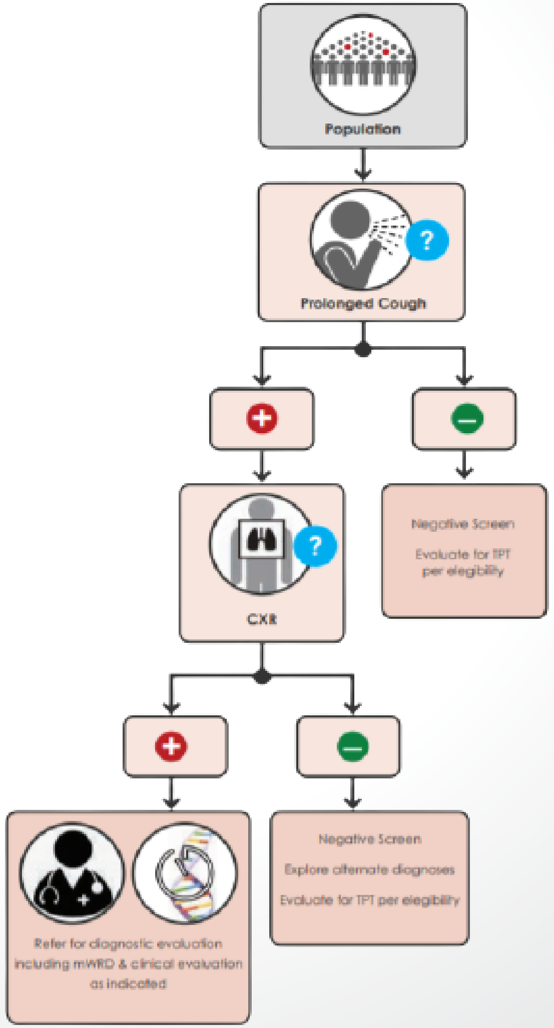
Single screening algorithm



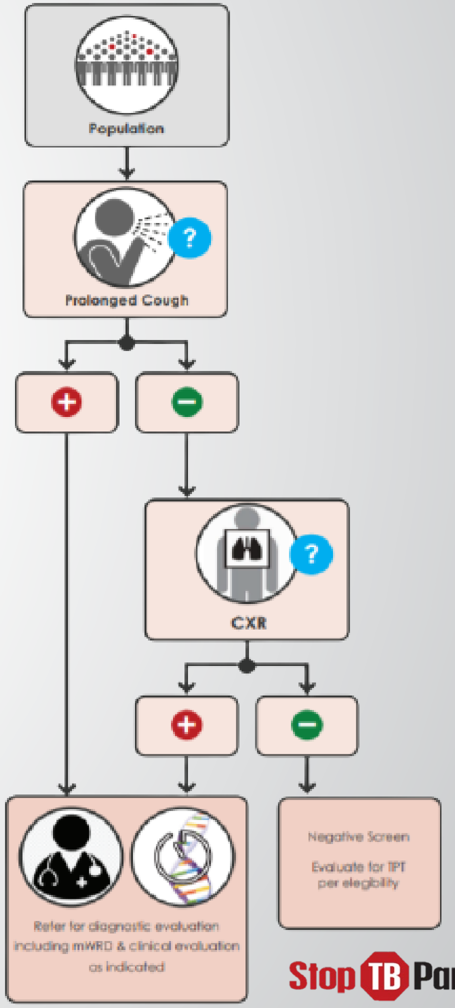
Parallel screening algorithm with CXR



Sequential positive serial screening algorithm



Sequential negative serial screening algorithm



Source: WHO Operational Handbook on Tuberculosis: Systematic Screening for Tuberculosis Disease

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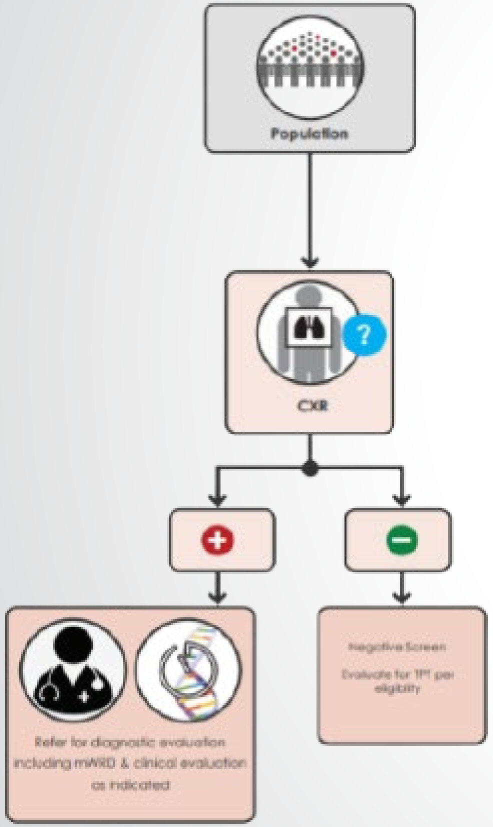
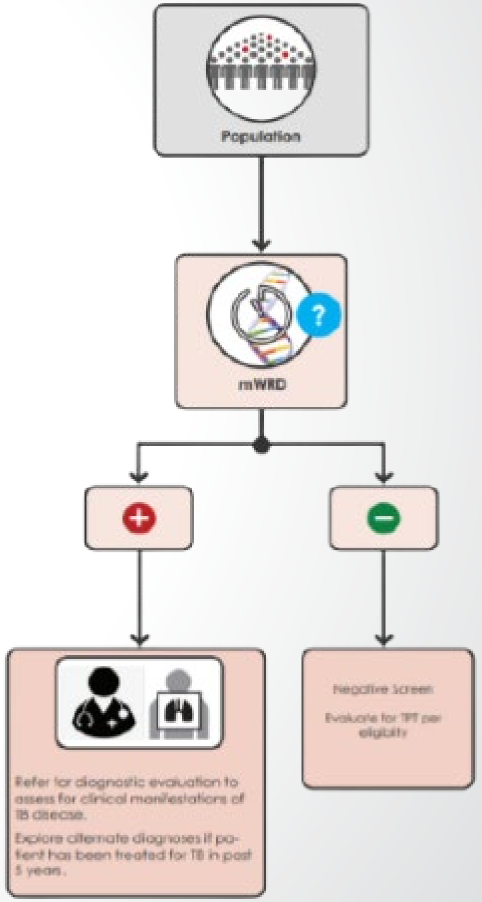
General Population (aged 15+) and High-risk Groups (not HIV+)

Initial screen: CXR	Initial screen: mWRD

Single screening algorithm



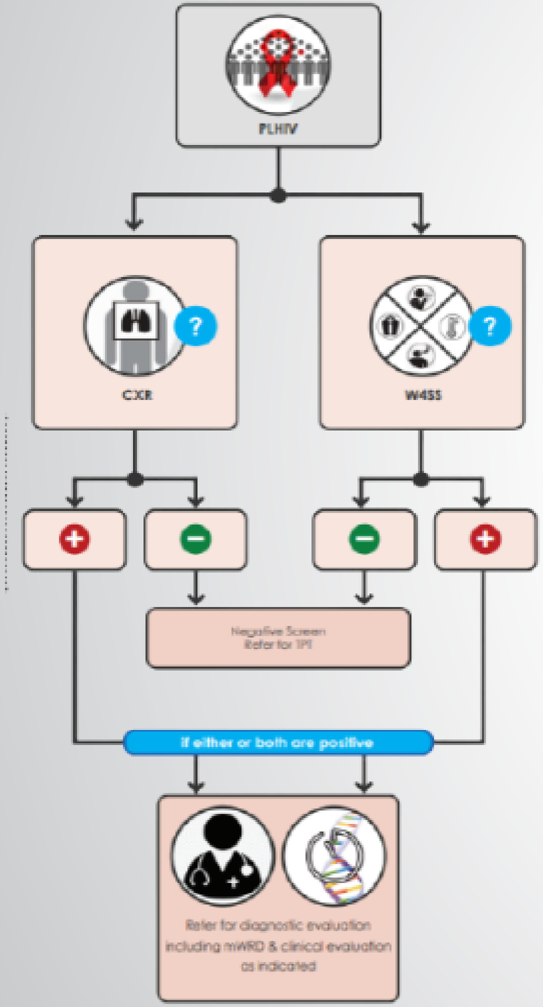
Single screening algorithm



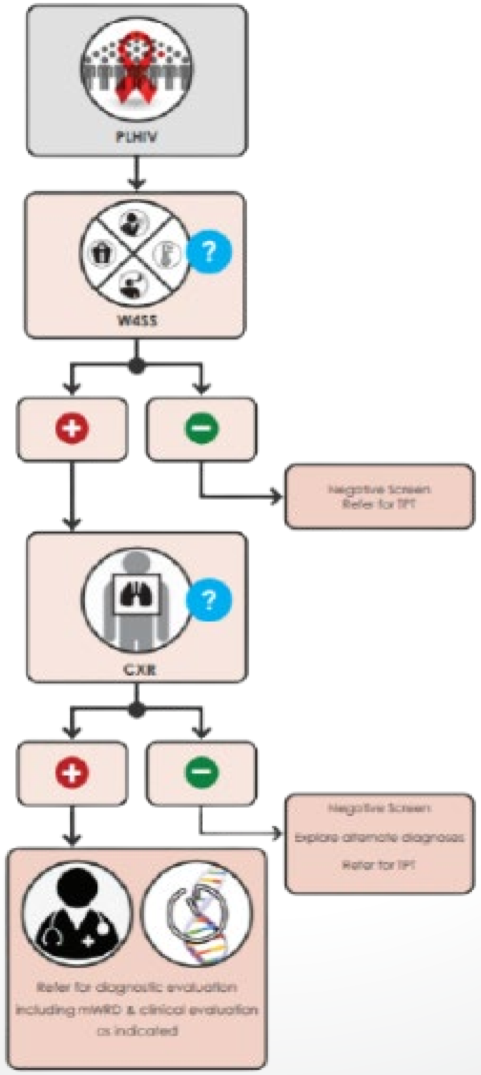
Source: WHO Operational Handbook on Tuberculosis: Systematic Screening for Tuberculosis Disease

Screening Algorithms for Adults and Adolescents Living with HIV involving X-ray

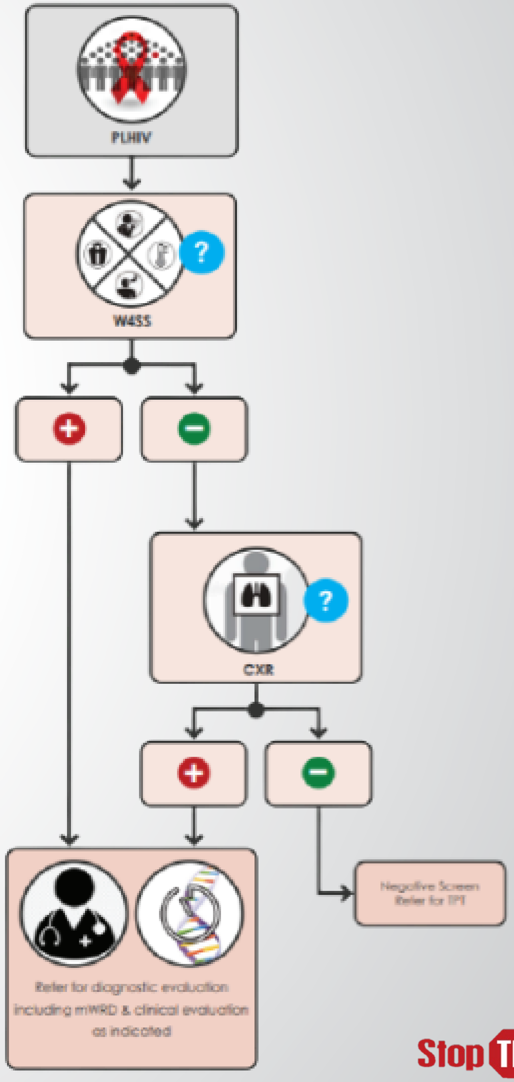
Parallel screening with W4SS and CXR



Sequential positive screening with W4SS and CXR



Sequential negative screening with W4SS and CXR



Source: WHO Operational Handbook on Tuberculosis: Systematic Screening for Tuberculosis Disease

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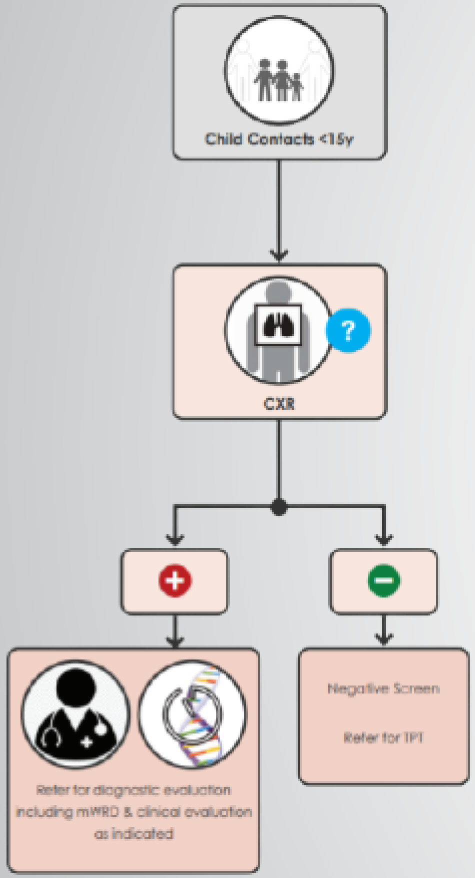
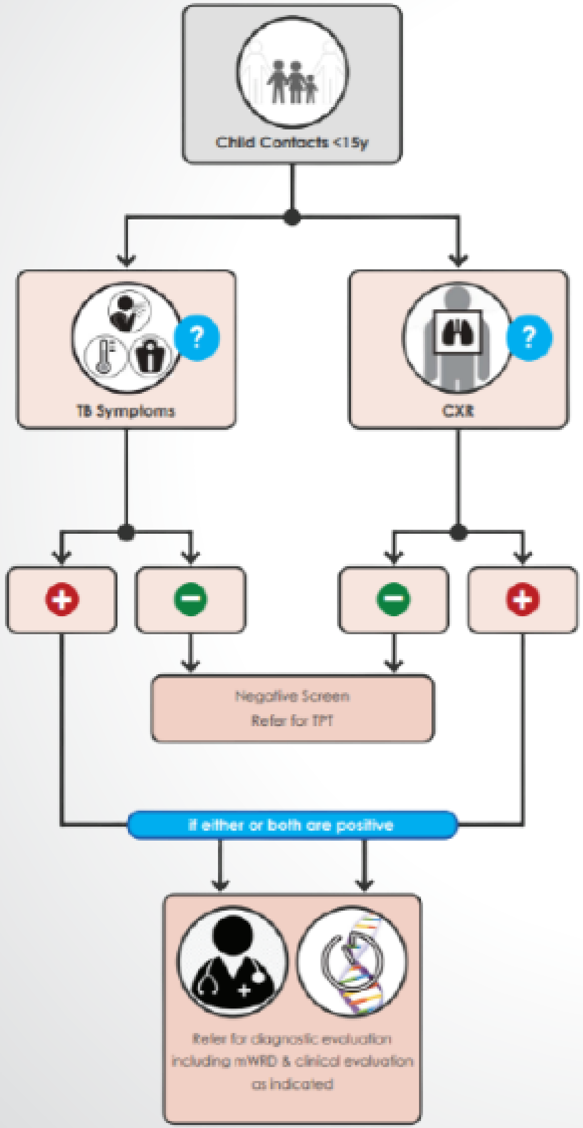
Screening Algorithms for Children involving X-ray

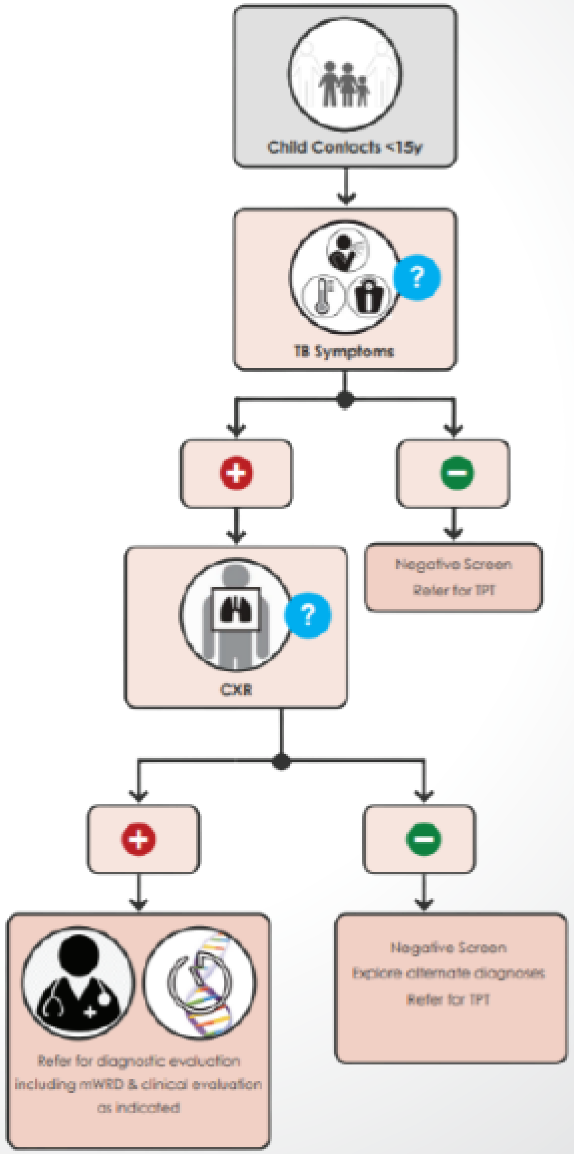
Single screening with CXR



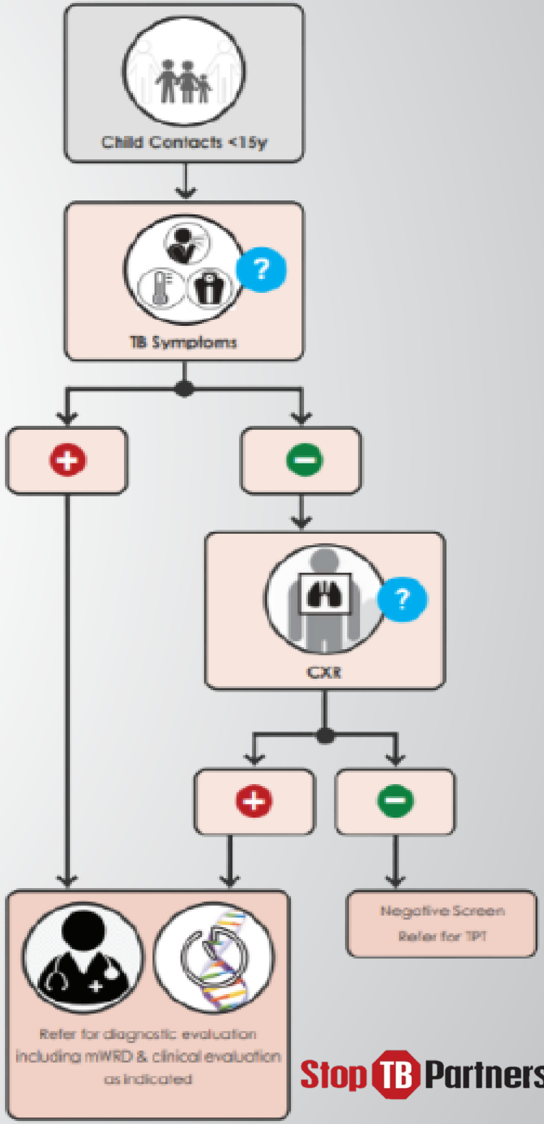
Parallel screening with symptom and CXR



Sequential positive screening with symptoms and CXR



Sequential negative screening with symptoms and CXR



Source: WHO Operational Handbook on Tuberculosis: Systematic Screening for Tuberculosis Disease

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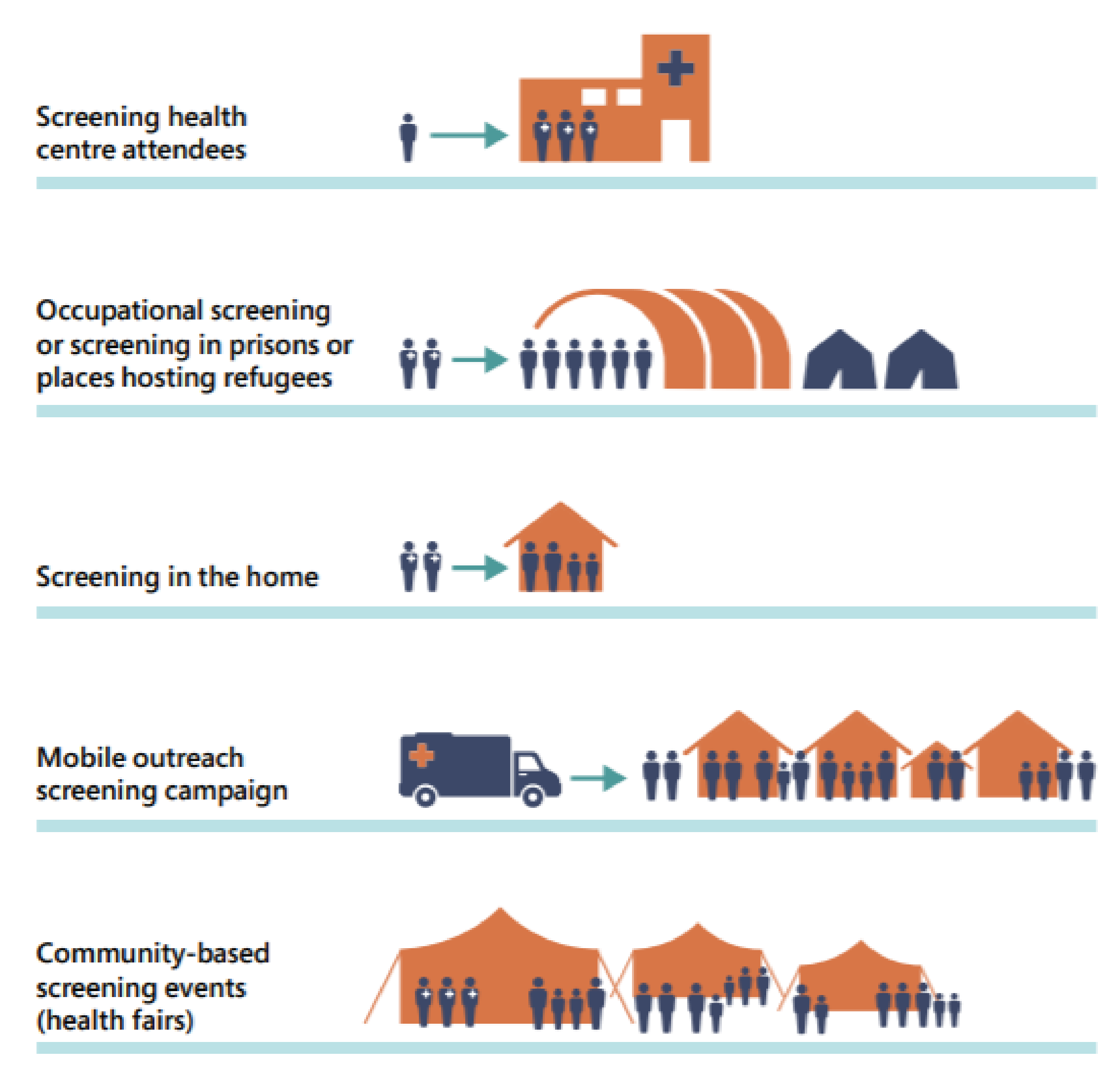
Different Screening Program Models

There are a number of established screening program models. Which model is used should be tailored to the **target population,** with **consideration for the available resources**.

- Offering screening where the target population lives or works may be particularly important in target populations that face barriers to accessing health care.
  - But this may require **more resources,** like a mobile van and radiography system.
- Depending on resources and need, programs may be **continuous** or **event-based.**



Barriers to accessing health care services may also apply to diagnostic and treatment services.

- How screen positive people will access these services should also be planned for.

Algorithm Considerations for Risk Groups

Miners

High risk of transmission

Highly sensitive algorithms

CXR preferred

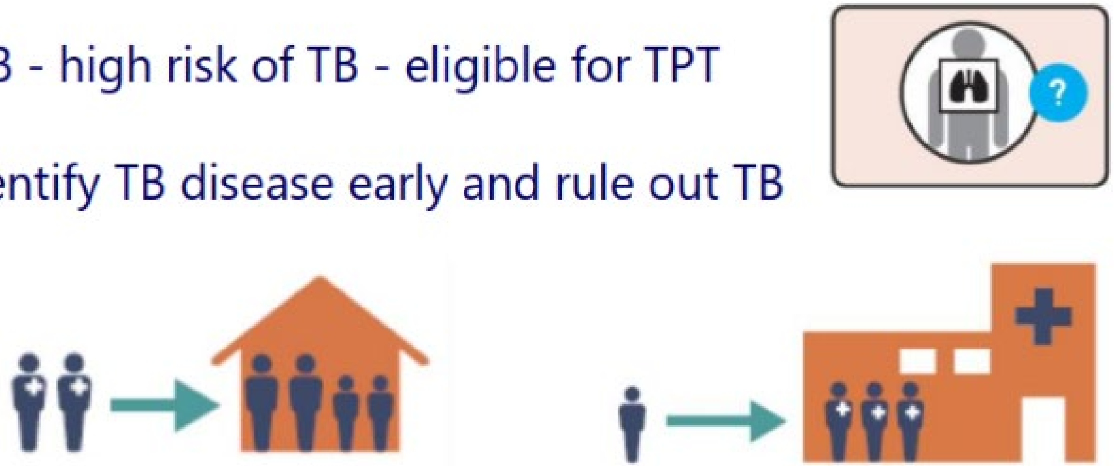
Contacts

High prevalence of TB - high risk of TB - eligible for TPT

Goal of screening: identify TB disease early and rule out TB

High sensitivity

CXR preferred



Algorithm Considerations for Risk Groups

Prisons

High risk of transmission

Highly sensitive algorithms

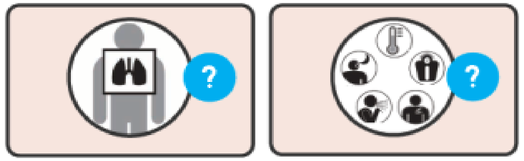
CXR preferred

People with clinical risk factors

Setting with TB prevalence > 100 / 100 000

TB screening in people seeking healthcare or who are in medical care

CXR screening for increased sensitivity



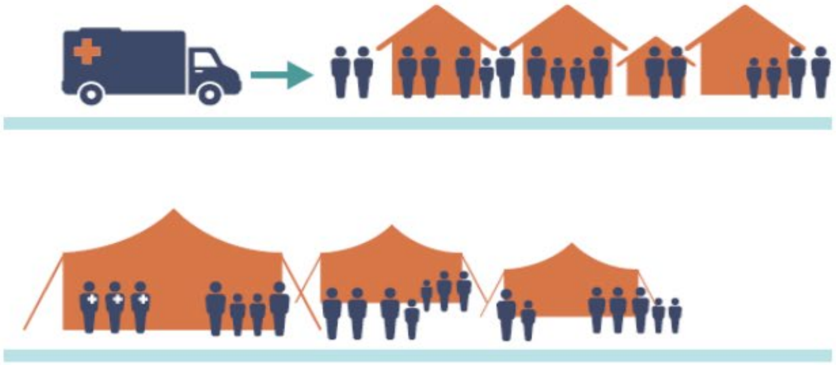
Symptom screening for triage and infection control

Algorithm Considerations for Risk Groups

General population & high risk communities

If TB prevalence is ≥ 0.5%

Depending on required sensitivity, resources and feasibility of implementations



Country TB Context

TB data/prevalence

- Number of cases (TB and MDR-TB) TB incidence
- Number of TB deaths
- Treatment coverage and undiagnosed TB cases
- HIV burden and TB co-infection
- Pediatric TB

Country TB Context

National priorities

National priorities per the TB strategic plan

Country TB Context

Overview of the diagnostic network screening and diagnostic algorithms and target populations to screen and how under the iNTP project

Plenary Session

Key challenges in screening and diagnosing TB disease in the country

Insert challenge

Insert challenge

Insert challenge

Insert challenge

Summary

Summary

- Systematic screening plays a key role in the global TB response, especially for identifying the “missing cases” of TB.
- A screening intervention should be tailored to the barriers and needs of the target population.
- There are four WHO-recommended screening tools for TB in general population (aged 15+) and high-risk groups (not HIV+). These can be used alone, in parallel, or in sequence in screening algorithms.
- Different screening tools and algorithms are recommended for screening people living with HIV and children for TB.

Knowledge Check—Question 1

Which populations does WHO **strongly** recommend to screen for TB? (Select all that apply.)

A. People living with HIV
B. People with malnourishment, diabetes, history of TB, chronic lung disease, and other conditions
C. Miners exposed to silica dust
D. The general population in high-burden countries
E. Contacts of people diagnosed with TB
F. Migrants
G. Prisoners

Knowledge Check—Question 2

What tools does WHO recommend be used to screen children (<15 years of age) who are contacts of someone diagnosed with TB? (Choose one.)

A. Symptom screening only

B. Symptom screening and chest X-ray

C. Chest X-ray only

D. Symptom screening, chest X-ray, molecular WHO-recommended diagnostic tests

Knowledge Check—Question 3

What is a benefit of using CAD to screen for TB? (Select all that apply.)

A. Provides results in <1 minute

B. Can be used in the absence of trained human readers

C. Can be used to achieve cost savings

D. Reduced inter- and intra-reader variability

E. Can be used in children <15 years of age

Knowledge Check—Question 4

What are some of the disadvantages of using X-ray to screen for TB? (Select all that apply.)

A. Trained human readers not available in many settings

B. Poor sensitivity

C. High inter- and intra-reader variability

D. Requires exposure to radiation

Thank you

New Tools for TB Screening: Introduction to Computer-Aided Detection (CAD) and Ultra-Portable X-Ray

MODULE 2

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Acknowledgements

These training modules were developed as a collaboration between the United States Agency for International Development (USAID) and its Infectious Disease Detection and Surveillance project (IDDS) and the Stop TB Partnership, as part of the *introducing New Tools Project* (iNTP). The content is based on the Stop TB/USAID/GLI *Practical Guide to Implementation of Computer Aided Detection (CAD) Technology with Ultraportable X-Ray Devices to Screen and Triage TB.*

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Introduction

This module explores new tools for TB screening: delving into detail on the use of computer-aided detection (CAD) and introducing ultra-portable X-ray (UP-XR) systems. The module also describes how the two systems may be integrated and their individual and combined utility for TB screening and triage.

Course Outline

- → Overview of CAD as a screening tool for TB
- → Understanding, interpreting, and using CAD output
- → Using CAD in TB screening programs
- → CAD products in the GDF catalog
- → Overview of different X-ray technologies and introduction to ultra-portable
- → Ultra-portable X-ray systems in the GDF catalog
- Summary

Learning Objectives

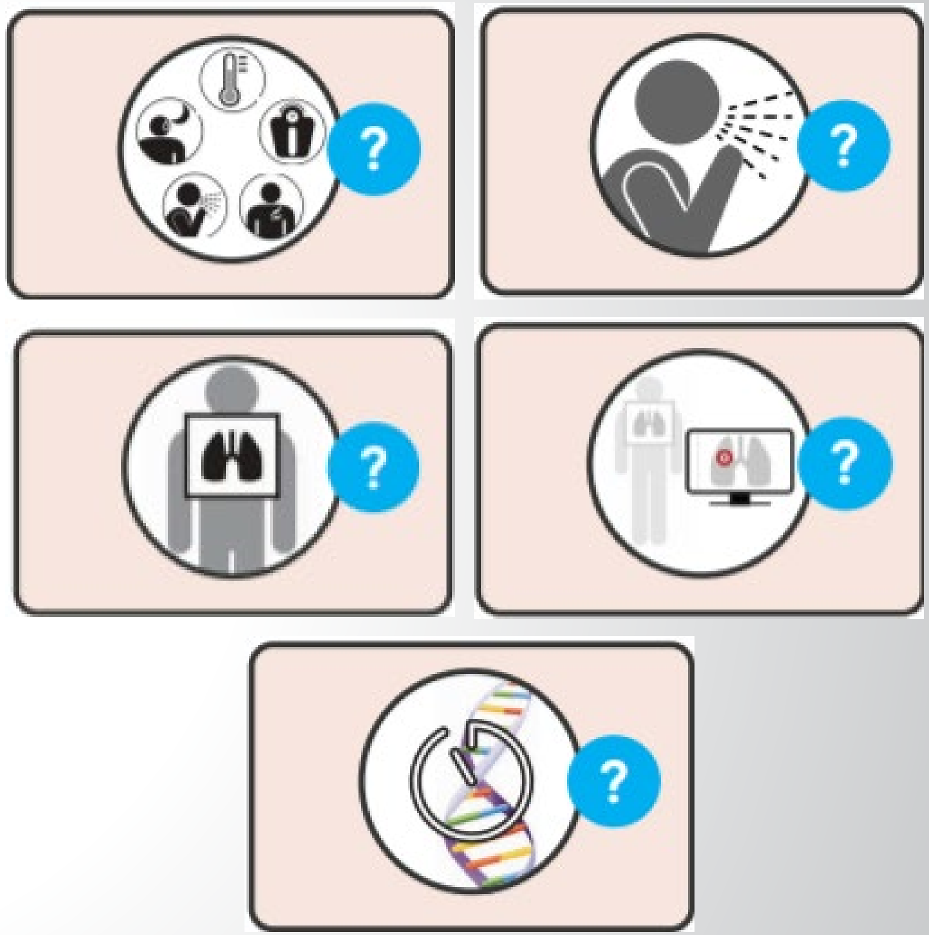
By the end of this module, participants should be able to:

- Describe what CAD technology is and how it can be applied in TB screening.
- Know the key features of the CAD products available from the GDF catalog.
- Understand what is meant by "ultra-portable X-ray" and the advantages and disadvantages of using it.
- Detail the components and pricing of the ultra-portable X-ray systems available in the GDF catalog.
- Understand the different ways CAD and ultra-portable X-ray can be integrated for use in TB screening and triage.

Reminder: WHO Guidelines on Systematic Screening

In general populations without HIV aged 15 years and older in which TB screening is recommended:

- Systematic screening for TB disease may be conducted using a **symptom screen**, **chest X-ray with computer-aided detection (CAD) software,** or **molecular WHO-recommended rapid diagnostic tests,** alone or in combination.
- **CAD software** may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease.



Computer-Aided Detection (CAD) Software for Screening and Triage of TB

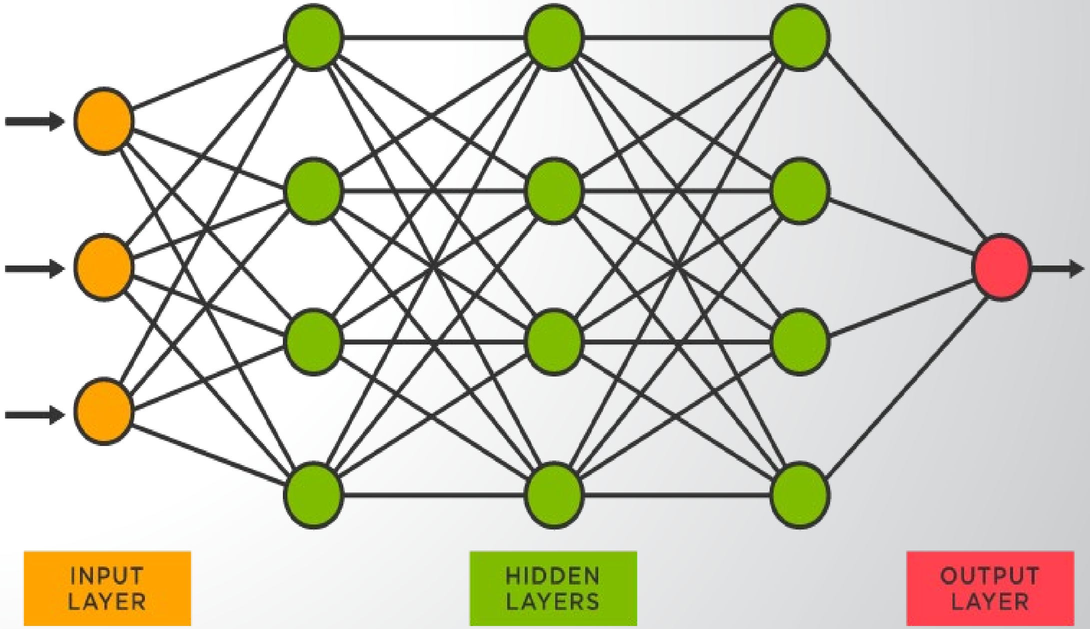
Overview of CAD as a Tool to Screen and Triage TB

Computer-aided detection (CAD) improves the detection of TB by circumventing inefficiencies in the interpretation of chest X-ray (CXR) images, automating and standardizing X-ray interpretation, and supplementing existing human health workers.

CAD uses a type of artificial intelligence known as **deep learning neural networks** to read chest x-rays and identify signs of TB. Deep learning neural networks take inspiration from the human brain to allow machines to learn to perform specific tasks.

In March 2021, WHO recommended the use of CAD as an alternative to human readers to interpret CXR for screening and triage of TB in individuals aged 15 or over.

CAD is **not** recommended nor validated for use as a **diagnostic** tool.



CAD Output

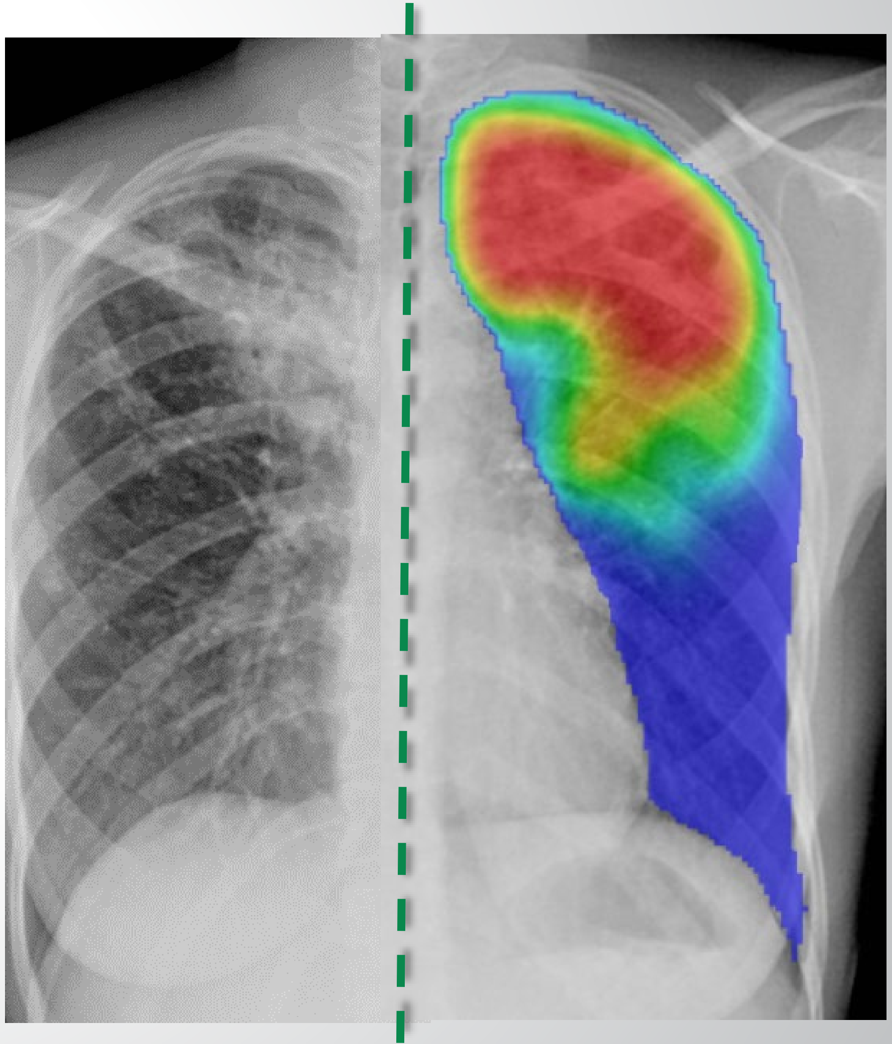
CAD receives digital X-ray or digitized analogue X-ray films and uses artificial intelligence to analyze them for signs of TB. This process can be done with or without an Internet connection.

In general, for **each** X-ray received, CAD provides:

- An **abnormality score** (between 0–1, or 0–100). High abnormality score = higher likelihood of TB.
- A **heatmap** showing where abnormalities are detected by CAD.
- Some CAD products provide a **binary classification** ("TB-related abnormalities present" or "TB-related abnormalities absent").

These can be summarized in a **customizable report** format.

CAD products increasingly also offer a number of **add-on features** such as **data dashboards.**



How to Understand the CAD Output

Abnormality score

Abnormality scores are a **continuous output (between 0–1 or 0–100)** and represent the **likelihood** of TB being present in a particular X-ray.

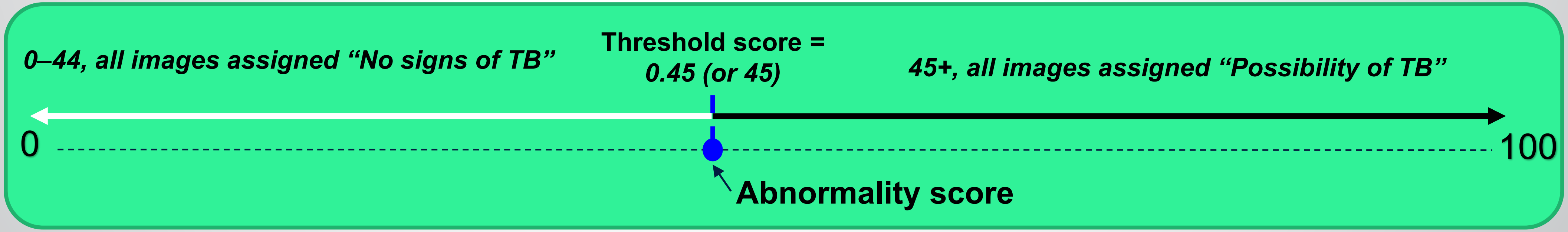
However, abnormality scores are **not** probability and are not standardized across CAD software, so:

- An image with a score of 0.4 is **not** twice as likely to contain TB as an image with a score of 0.2
- A score of 0.5 from CAD product A does **not** mean the same as a score of 0.5 from CAD product B.

Binary classification

Selecting a **threshold score** translates this continuous output into a **binary classification: "Possibility of TB" // "No signs of TB."** All X-ray images higher than the threshold are assigned the "Possibility of TB" classification.

Binary classification



Detecting Non-TB Abnormalities by CAD

- Increasingly, more and more CAD products can function far more like a human radiologist than the simple TB-detecting tools from which they have evolved.
- Some TB-CAD software products can classify common CXR abnormalities, such as calcification, cardiomegaly, mass, nodule, and pleural effusion, as well as bone and heart abnormalities.
- However, there is a lack of independent evaluation data on the performance of CAD for differential diagnosis and how accurately it localizes abnormalities.

CAD Landscape Analysis

A recent landscape report identified **28 CAD** developers and **12 TB-specific** products already on the market. At least **7 of these have CE-marks.**

Common characteristics include:

- Mostly suitable for people >15 years old
- Read postero-anterior DICOM images
  - Antero-posterior images and other image formats (JPEG, PNG) also widely accepted
- Summarize results in a radiologist-style report
- Can be deployed online (cloud) and offline
- Integration with PACS and other clinical information systems
- Ability to be deployed with most mainstream X-ray systems

ai4hlth.org is a regularly updated online marketplace of CAD products for TB. 2021 update coming soon.

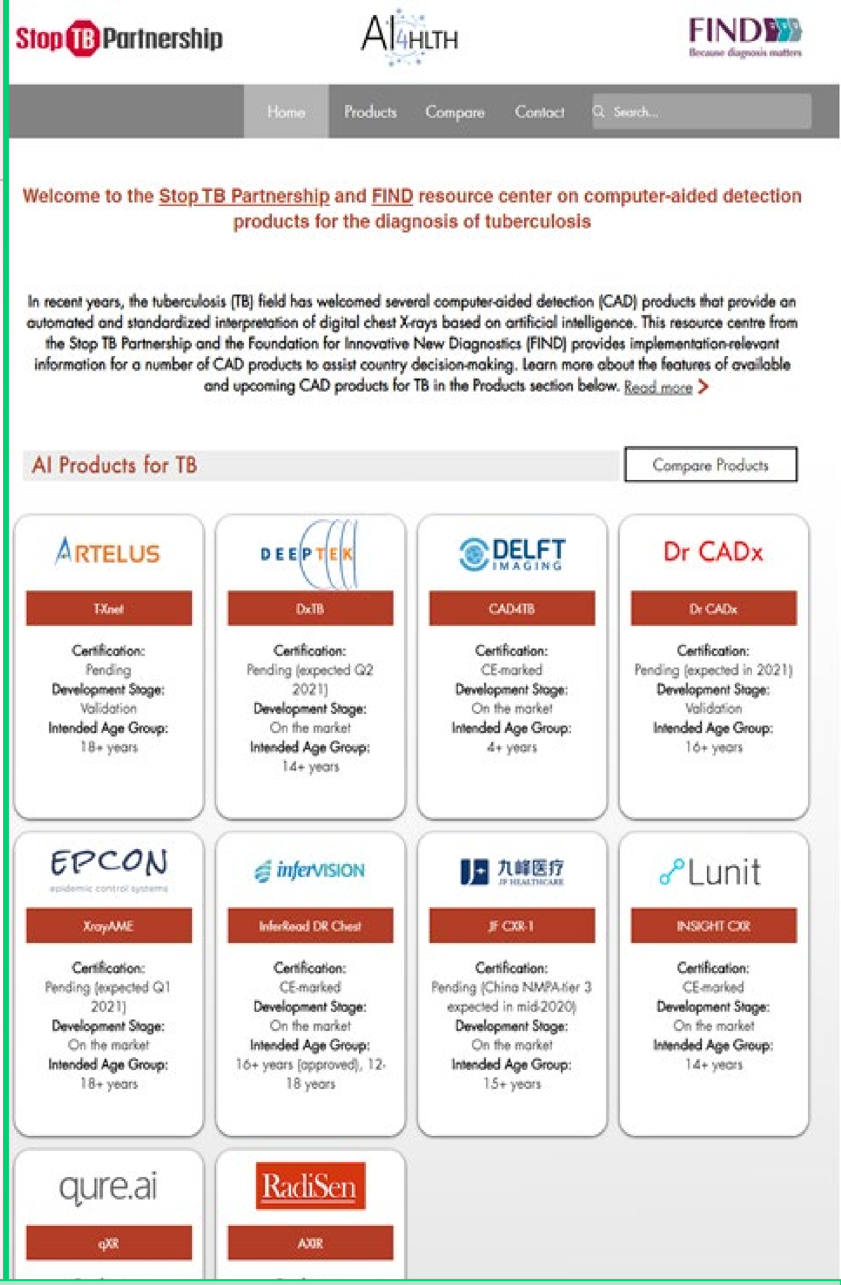
CAD Landscape Analysis

A recent landscape report identified **28 CAD** developers and **12 TB-specific** products already on the market. At least **7 of these have CE-marks**.

Products vary in that some:

- ➔ Can tailor their performance using local data (continuous learning)
- ➔ Require additional training using local data before deployment
- ➔ Can identify non-TB abnormalities

(However, there is a lack of independent evaluation data on the performance of CAD for differential diagnosis and how accurately it localizes abnormalities).



ai4hlth.org is a regularly updated online marketplace of CAD products for TB. 2021 update coming soon.

Validation of CAD for Interpreting Digital X-ray

In 2020, the WHO Guidelines Development Group independently evaluated three independent evaluations of three different CAD software for detecting bacteriologically confirmed TB in a range of populations and settings.

The results show the variability of both human readers and CAD software programs across different settings and populations.

Type of case/reader	Sensitivity	Specificity
WHO target product profile	**> 0.90**	**> 0.70**
Screening use case		
CAD software	0.90–0.92	0.23–0.66
CXR with human reader	0.82–0.93	0.14–0.63
Triage use case		
CAD software	0.90–0.91	0.25–0.79
CXR with human reader	0.89–0.96	0.36–0.63

Conclusion: There is **substantial overlap** in the sensitivity and specificity of human readers and CAD software, suggesting that there is **little difference** between the two.

Further:

- In many settings, health providers **without training in radiology** are tasked with interpreting chest X-rays.
- These readers may not be as highly skilled as the "gold-standard" readers used for comparison in the evaluations.
- So, CAD may perform even more favorably in comparison.

Source: WHO Consolidated Guidelines on Tuberculosis

Validation of CAD for Interpreting Digital X-ray

Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms

Zhi Zhen Qin, Shahriar Ahmed, Mohammad Shahnewaz Sarker, Kishor Paul, Ahammad Shafiq Sikder Adel, Tasneem Naheyan, Rachael Barrett, Sayera Banu*, Jacob Creswell*

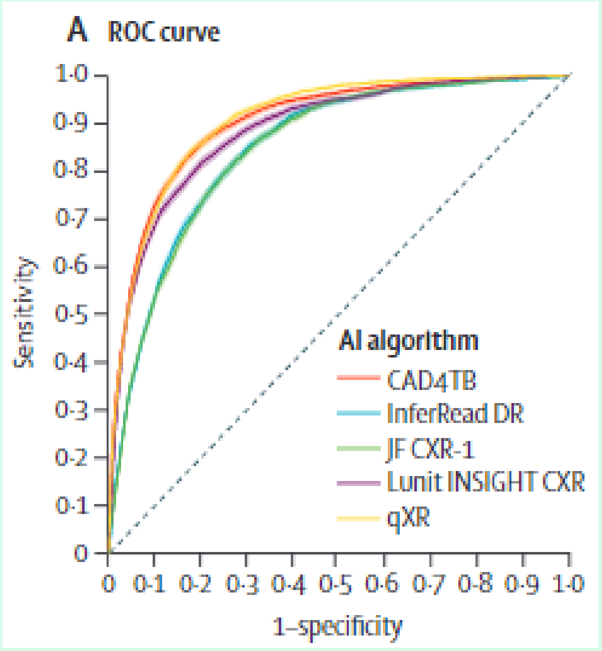
In the **latest head-to-head comparison** of the overall performance of the newest version of five commercial CAD software products, **all CAD products:**

- Significantly outperformed local radiologists
- Were able to halve the number of Xpert tests required, while maintaining high sensitivity (>90%)
- Performed worse in older age groups and those with a history of TB

Comparing different CAD products

The performance of different CAD products can be compared by constructing a **Receiver Operating Characteristic (ROC) curve** and calculating the **area under the curve (AUC)**.

CAD performance ranking from high to low:



CAD product	AUC
qXR	90.81%
CAD4TB	90.34%
Lunit INSIGHT CXR	88.61%
InferRead DR Chest	84.90%
JF CXR-1	84.89%

Shortcomings in CAD Literature

New versions of CAD software become available rapidly and require evaluation as the underlying AI model is likely different in newer versions compared to older versions.

CAD's ability to detect **non-TB abnormalities** has not been validated, even though products' ability to do this is often marketed.

Many studies are based on the area under the receiver operating characteristic curve. **More precise and implementation-relevant measures** should be explored.

The performance of CAD in **children, risk groups,** and **TB key populations** needs more examination.

Many studies in CAD literature are **conducted with the involvement of the manufacturer** and focus on one product (CAD4TB) in particular.

Where to Place CAD in the TB Screen Algorithm

CAD can be used **with** trained human readers as a decision support tool or **in place of** trained human readers.

Alongside human readers

CAD can also work **with** human readers:

- Helping radiologists to optimize their workflow
- Alerting human readers to abnormal images requiring prioritization
- Providing reporting assistance
- Providing quality control
- Performing pre-reading assistance

In place of human readers

WHO recommends CAD to **replace** human readers in two broad situations in individuals aged 15 and older:

Screening: CAD can be a valuable tool for screening asymptomatic individuals without significant risk factors (e.g., active case finding).

Triage: CAD can be useful in identifying TB in individuals with TB symptoms, risk markers, or other positive test results (e.g., in health care facilities).

The CAD software used must be to the same standard as those evaluated by the WHO Guidelines Development Group.

In either situation, there is insufficient evidence to support the use of CAD with CXR alone for TB diagnosis.

Where to Place CAD in the TB Screen Algorithm

There are a number of **advantages** to either technique.

Alongside human readers

The entire output of CAD, or parts of the output, may be used to inform triage decisions by trained human readers alongside clinical information.

Advantages:

- CAD can be used to supplement decision-making, potentially improving on human reader performance.
- While human readers' judgement can be used:
  - Where a CAD reading is not conclusive/near the threshold score
  - In populations where CAD is not approved (e.g., in children <15 years)
  - Alongside CAD for reading X-rays that show a non-TB abnormality

In place of human readers

The CAD output may be used by trained non-radiologist personnel to decide the triage outcome. A threshold score is set, and everyone assigned a CAD score higher than this receives confirmatory diagnostic testing.

Advantages:

- Increased access to chest X-ray where there is a scarcity of trained human readers or no human readers
- May be used to rapidly triage people by non-radiological personnel in high throughput settings
- CAD does not become exhausted when reading large quantities of images
- No intra- and inter-reader variability

CAD Products in the GDF Catalogue

CAD4TB

Latest version: Version 7
Certification: CE marked, class IIb

DELFT IMAGING

Input

- Postero-anterior (PA) digital chest X-rays
- Can be used to read images from any kind of chest X-ray machine
- Chest X-ray image format: DICOM, PNG, JPEG
- Using an app (SNAP4CAD), analog X-ray images can be used as well

Output

For each X-ray read, CAD4TB provides:

- Abnormality score for TB
- Binary classification "TB" or "Not TB"
    - Customizable default threshold score: 60
- Heat map

For the screening program, CAD4TB provides a full report with screening results. Advanced management dashboard to monitor screening progress also available.

Deployment

Online, offline, hybrid (offline use with online synchronization)

PACS: CAD4TB is a mini PACS system that can store up to 30,000 x-ray images.

If the user has their own PACS system, CAD4TB output (score, report and heat map) can be send to the PACS system.

https://sam4tb.cad4tb.care/project/archive/series/

thirona Browser

Administrator

24 series

Search

Patient ID	Name	Birthdate	Sex	Study Date	Study Time	Institution	CAD4TB 7	CAD4TB Report
010100000002	D. Anonymous		F	2010-12-13	155852		2	No TB
010100000006	O. Anonymous		F	2011-01-25	150733		2	No TB
010200000012	W. Anonymous			2012-03-30	173248		5	No TB
010100000005	L. Anonymous		F	2016-07-10	081923		6	No TB
010200000005	H. Anonymous		F	2010-04-14	080226		8	No TB
010200000010	U. Anonymous		M	2006-09-01	151210		11	No TB
010200000002	C. Anonymous		M	2010-10-17	095222		14	No TB
010200000013	X. Anonymous		F	2014-08-04	151129		21	No TB
010100000007	P. Anonymous		M	2014-11-04	130938		23	No TB
010100000004	K. Anonymous		F	2004-07-04	094515		26	No TB
010300000001	F. Anonymous		M	2012-03-07	142412		26	No TB
010100000003	J. Anonymous		M	2012-12-23	102350		33	No TB
010200000009	T. Anonymous		F	2009-05-20	113118		51	No TB
010200000011	V. Anonymous		M	2008-09-26	143901		53	No TB
010200000006	I. Anonymous		M	2016-05-22	174020		67	Possible TB
010100000008	R. Anonymous		F	2004-07-26	121754		71	Possible TB
010200000001	B. Anonymous		F	2016-07-21	135043		73	Possible TB
020100000001	Q. Anonymous		M	2011-09-26	140704		75	Possible TB
010200000007	M. Anonymous		M	2016-07-15	171259		75	Possible TB
010200000008	N. Anonymous		M	2009-05-05	140958		76	Possible TB
010100000009	S. Anonymous		M	2015-06-11	125748		84	Possible TB
010100000001	A. Anonymous		M	2006-11-16	164408		90	Possible TB
010200000004	G. Anonymous		M	2009-03-06	151306		94	Possible TB
003	E. Anonymous		M	2012-08-20	094931		96	Possible TB

Online

View Series

CAD4TB viewer window showing heatmap and score, no TB

CAD4TB viewer window showing heatmap and score, possible TB

CAD4TB symptom and GXP report

Patient Information

PatientID	010100000001
Name	A. Anonymous
Gender	Male
Date of birth	1971-10-12

010100000001

Patient Symptom Information

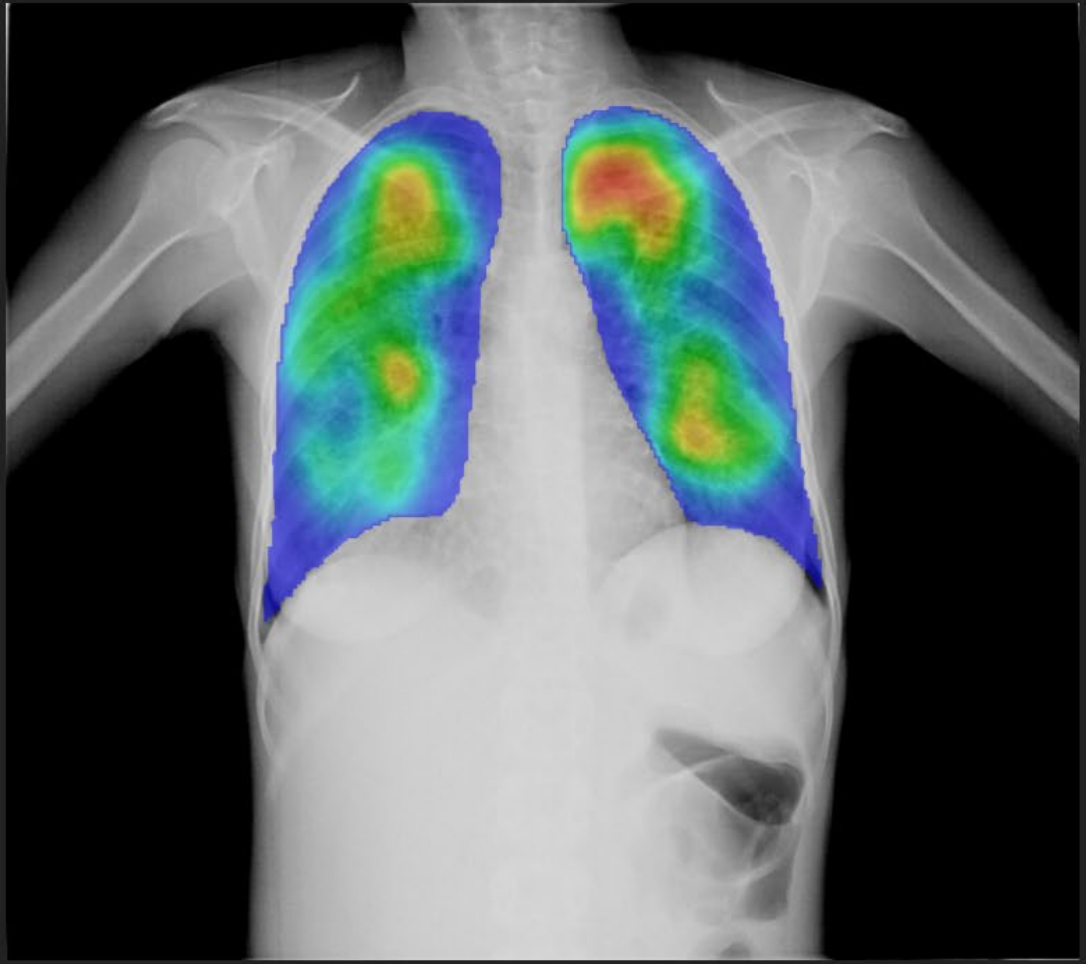
Cough:	Yes (3 days)
Fever:	Yes (7 days)
Shortness of breath	No
Household TB:	No

Patient lab results

GeneXpert:	MTB Detected
RIF resistance:	Not detected

CAD4TB Assessment

CAD4TB 7	90
CAD4TB Report	Possible TB



Online

CAD4TB insights module showing gender, age and score distribution

Stop TB Partnership

CAD4TB V7 Package and Price

One CAD4TB software perpetual license with 12-month support and maintenance ● Five viewing licenses ● Options for data and images hosting and storage on local server, local cloud, or supplier's server, up to client's preference. Hosting and storage up to 300 images per license and per day offered by Delft on its servers (using Amazon Web Services). ● Option to automatically de-identify and (pseudo) anonymize patient's DICOM data ● One year of support and maintenance included, starting on the day of successful installation and user acceptance	$12,750
One CAD4TB box + 10" tablet ● IntelNUC , i-5 Quad core, 8 GB RAM, 256 GB SSD ● Storage capacity approx. 20,000 images ● No power autonomy: should be connected to a power source ● Supplied with a rugged USB disk (1TB) for an offline backup facility ● One-year warranty included, starting on the day of successful installation and user acceptance ● Total period of warranty of one CAD4TB box cannot exceed four years from the day of initial successful user acceptance	$2,750

A **volume-based pricing discount** when procuring multiple CAD4TB perpetual licenses

Number of CAD4TB perpetual licenses purchased	Price (per license) in USD
1–9	12,750.00
10–19	11,475.00
20–49	10,837.50
50+	10,200.00

CAD4TB V7 Package and Price

Installation and training ● Software operating environment and server configuration ● Installation (software and hardware) and software calibration study in the setting of intended use based on WHO protocol and toolkit	$1,150
One-year extension of support and maintenance ● Free software patches, upgrades, and update ● Remote support for issue resolution of reported problem within one working day from the date of reporting ● Corrective maintenance as required, hardware to be replaced, shipment to site, disposal of faulty hardware, cost of replacement work, personnel transport, and arrangements ● One-day remote session of theoretical and practical training of up to 10 operators on software administration and use delivered in English or French ● Provision of hard and digital copies of training materials and access to Delft eLearning online platform for each trainee ● Should be procured at the time of procuring one CAD4TB software perpetual license or one CAD4TB box or while the initial warranty period of item to be covered is still running. It extends the initial warranty period of one CAD4TB system (license and box) for 12 months.	$5,100
Three-year extension of support and maintenance	$11,475

InferRead DR Chest

Latest version: Version 1
Certification: CE marked class IIa

InferVision

Input

- Postero-anterior (PA), antero-posterior (AP) digital chest X-rays
- Can be used to read images from any kind of chest X-ray machine
- Chest X-ray image format: DICOM, PNG, JPEG

Output

For each X-ray read, InferRead DR Chest provides:

- Heat map
- Dichotomous output for TB
- Abnormality score for TB
- Dichotomous output for non-TB abnormalities
- Abnormality score for non-TB abnormalities

These are summarized in a structured report.

Deployment

Online, offline, hybrid (offline use with online synchronization)

INTRODUCING ULTRA-PORTABLE X-RAY

Types of X-ray Technology

Digital radiography (DR)

Digital generator and detector package

- Latest development in X-ray technology
- **Image receptor:** Solid state detector
- **Image processing** is automatic using provided software
- Output is digital (DICOM, JPEG)
- **Integration** with PACS possible due to digital image format
- **Reading by CAD** is automatic
- **High image quality** and better radiation dose efficiency
- **Portable DR** systems available
- **Rapid image** generation time

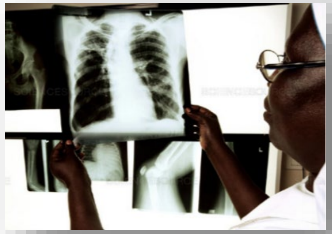
Retrofit and computed radiography (CR)

Existing analog generator and digital detector or CR reader

- Combination of analog X-ray equipment and a new digital detector or a reusable phosphor plate with digitizer/CR reader
- **Image receptor:** New digital detector (retrofit) or digitizer/CR reader (CR)
- **Image processing** can be automatic using software (retrofit) or need digitization using CR reader (CR)
- **Output** is digital (DICOM,JPEG)
- **Integration** with PACS possible due to digital image format
- **Reading by CAD** possible after digitization
- **Lower** radiation dose efficiency than DR systems

Analog radiography

Analog generator and manual image processing



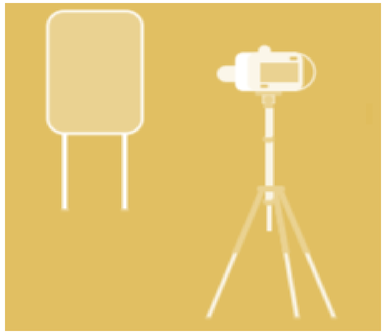
- Traditional method of X-ray imaging
- **Image receptor**: Analog film
- **Image processing**: Wet processing required to generate final image
- Because of requirement of wet processing and **need of trained human** reader to interpret film, **difficult to use in the field**
- **Output** is the X-ray film
- **Integration** with PACS not possible
- **Reading by CAD** only possible after digitization
- **Lower** throughput possible due to complex image processing
- **Poor** radiation dose efficiency

Introducing Ultra-portable X-ray (UP-XR)

Types of radiographic systems:

Stationary:
High workload, stable electricity, general radiology, delivers high image quality

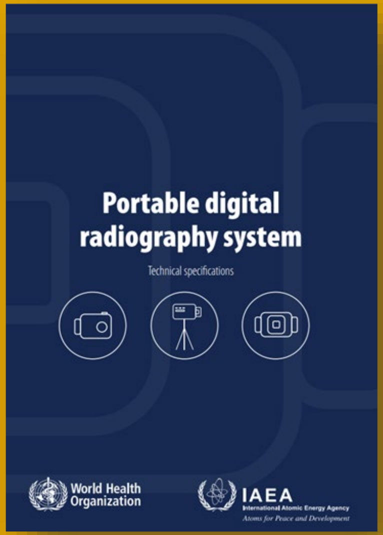
Mobile:
Moderate workload, intermittent power supply, can be moved/rolled around, high image quality



Ultra-portable:
Low to moderate workload, battery powered, acceptable image quality, low radiation, field friendly

Advances in X-ray technology have resulted in increasingly portable “ultra-portable” digital X-ray systems.

WHO-IAEA working group jointly developed minimum technical requirements for X-ray digital portable systems (published in August 2021).



Recommended to support decision-making regarding the selection, incorporation, allocation and use of portable X-ray systems.

Intended for health care providers, managers of imaging departments, procurement and regulatory agencies, policymakers, and planning officers in ministries of health.

Stop TB Partnership

Introducing Ultra-portable X-ray (UP-XR)

Advantages of UP-XR:

- De-centralize X-ray screening and expand access
- Built in battery operated
- Low weight—reduced physical strain on staff carrying or setting up the system
- Reduced radiation exposure
- Image quality reportedly comparable to stationary X-ray

Disadvantages of UP-XR:

- Limited battery life when operating devices without connection to electrical mains
- Low to medium throughput
- More portable detector and generator stands may be more manual to operate

DELFT LIGHT

Core System

- CE-marked for Medical Device Systems and Procedure Packs
- The **generator, detector, and console** all have **built-in Li-ion** batteries, allowing use in the field without electricity for limited periods of time.
- The **generator** is provided with a **handswitch** to allow the remote operation of the system from a distance of 3 meters.
- The aluminum **generator stand** is capable of 360-degree rotation and can be dismantled for transport in its own bag (also supplied).
- The **detector panel hanger** (VersariX) can be used to hang the detector from improvised mounts (walls or doors) and can be adjusted vertically (40 cm–200 cm range).
- The **console** has image processing and manipulation software installed and also provides the link to CAD4TB.

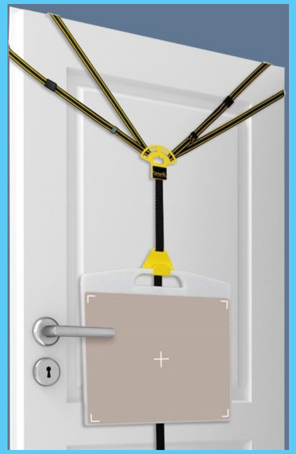
The **core system** consists of an **X-ray generator TR 90/20 (manufactured by Mikasa), X-ray detector CXDI 702-C with accompanying application software (Canon NE) and HP laptop**, and accompanying software package.

Detector

Generator

Console

Generator stand



Detector panel hanger

Accessories

- **Backpack,** which is able to transport all Delft Light components except the generator stand (which comes with its own bag)

Radiation protection equipment
- Including 1 **protective lead apron,** 10 **shock detection stickers,** and 5 water-resistant, durable and portable **radiation warning signs**, mentioning radiation hazard and pregnancy

Supplementary and external power sources
- **Replacement detector batteries (x2) and chargers** are provided with the system. The charger recharges two batteries simultaneously.

- **Solar panel and power bank** to recharge all electrical components in screening situations without access to electricity

Alongside the **core system,** accessory equipment is provided to ensure the smooth and safe operation of the system in the field, including;

Backpack

Radiation protection equipment

Radiation hazard signs

Lead apron

Shock stickers

Supplementary and external power sources

MobiSun solar panel with built-in power bank

Exchangeable generator and detector batteries with battery charger

Delft Light Full Kit—Pricing

From the GDF catalog, the price of the Delft Light full kit is **$66,750.**

Volume-based discount is available:

# Kits	Price (per item)
01 – 04	$66,750.00
05 – 10	$66,057.50
11 – 19	$65,365.00
20 – 49	$64,672.50
50 +	$63,980.00

If purchasing this item together with one CAD4TB software perpetual license, one CAD4TB box is provided **free of charge,** and the support and maintenance on the CAD4TB software perpetual license is **valid for 15 months instead of 12 months.**

The **full kit** of Delft Light includes:

Component	Weight (kg)
X-ray generator	7.0
X-ray generator Stand	8.0
X-ray detector (incl. batteries)	3.8
X-ray detector stand	0.4
Console laptop/workstation	1.5
Lead apron	3.0
Battery chargers	1.0
Solar panel/power bank	6.0
Carrying case (empty)	2.5
Total	**33.2**

One-year warranty is included with purchase. Installation, training and warranty **extensions** are available at **added cost.**

Delft Light Full Kit—Pricing

Warranty

One-year warranty is included (including batteries) starting on the day of successful installation and user acceptance or 15 months from the date of invoice.

Warranty includes:

- **One remote session** for preventive maintenance, including the provision of a maintenance report
- **Software patches, upgrades, and updates**
- **Delft Imaging Helpdesk** 24/7 availability for service calls, ensuring an issue resolution within five working days maximum from the date of issue reporting
- **Replacement/repair** of faulty components (**excluding batteries**), including associated transport costs

Installation and training

- One session of theoretical and practical training of up to two operators on safety, use, transportation, and maintenance per instrument
- Provision of hard and digital copies of training materials and access to Delft eLearning online platform for each trainee
- Installation performed at the same time as training

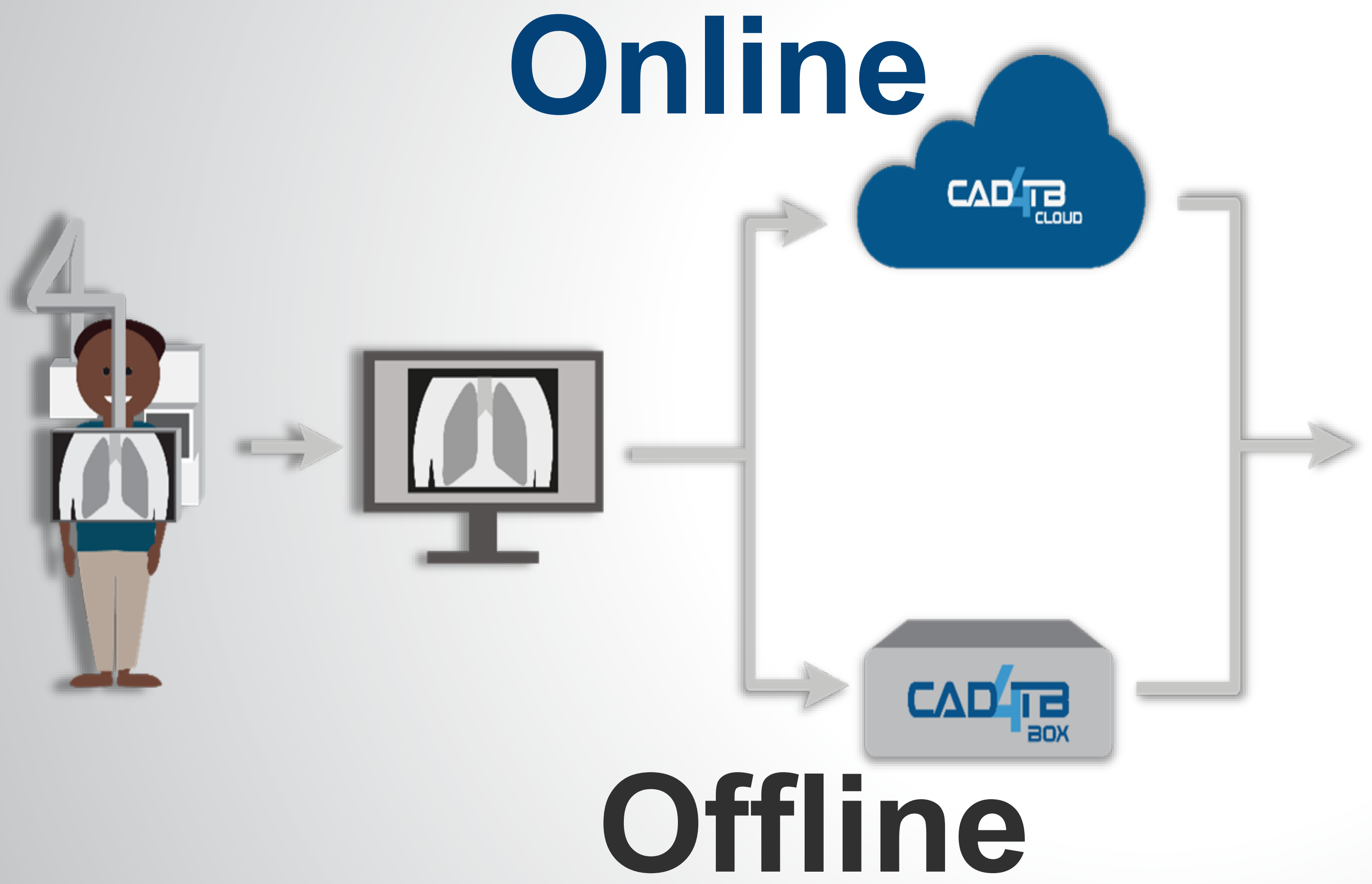
Warranty extension

- One-year extension: $4,460
- Three-year extension: $27,834

Warranty extension should be procured when purchasing the Delft Light full kit or while the initial warranty period is still running.

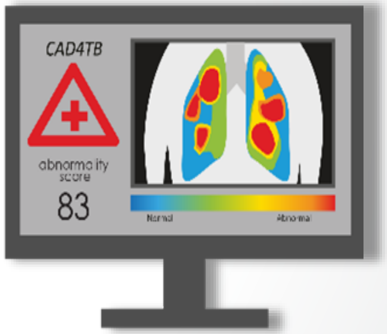
Connection with CAD4TB

How Delft Light connects to CAD4TB depends on whether the system is used online or offline.



CAD4TB cloud

- Images are stored online.
- Data are analyzed through a secured data server.



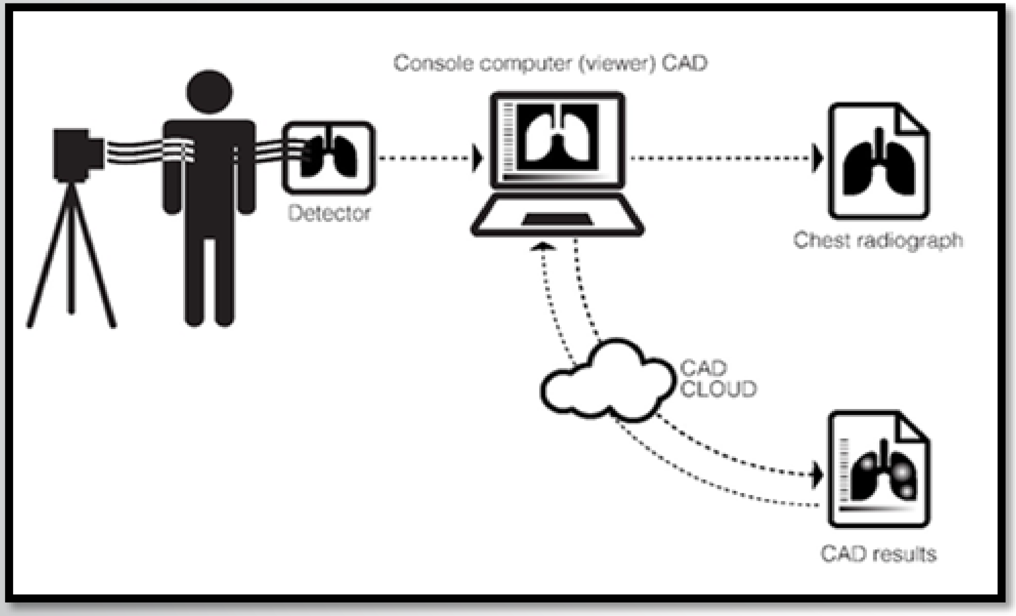
CAD4TB box

- Images are stored locally.
- Images are synchronized with CAD4TB cloud when Internet is available.

Connection with CAD4TB

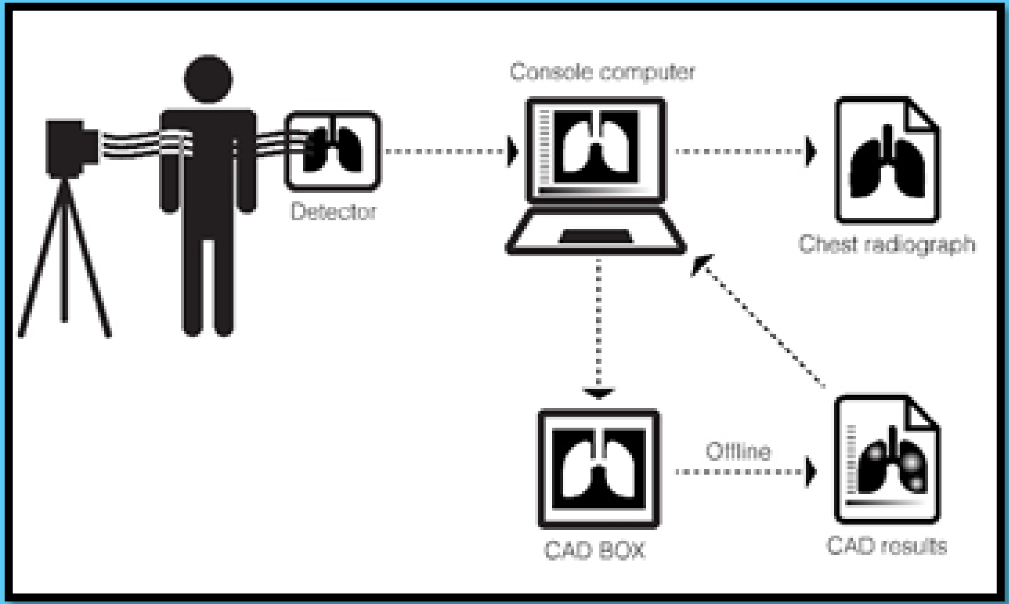
Online

- The Delft Light console receives CXR images from the detector and is used to upload them to the CAD cloud containing the artificial intelligence.
- Results from CAD4TB are shown on the CAD4TB web platform, accessed from Internet browsers.



Offline

- The CADTB box (pictured) containing the artificial intelligence is connected to the console laptop and analyzes the CXRs it receives from the laptop.
- Results from CAD4TB are shown on the console laptop.



Hybrid

Hybrid setup uses the offline equipment configuration but with pre-configured synchronization of data to a server when the Internet connection is restored after periods of operating offline.

Both CAD and UP-XR offer an opportunity to increase the reach of TB screening programs:

- **CAD** by replacing or supplementing constrained trained human reader resources
- **UP-XR** by being portable enough to transport to hard-to-reach communities, such as those not in easy reach of road networks

Furthermore, at lower levels of a health system, the use of the two technologies alongside other emerging portable confirmatory diagnostic tools (such as the battery-powered Truenat TB assay) will decentralize screening and detection of TB, and, with appropriate planning and funding, will vastly increase public access to sensitive screening and diagnostic tools.

Summary

- CAD software is an interpretation tool that uses artificial intelligence to detect TB on chest X-rays.
- CAD software has accuracy comparable to, or even better than, human readers.
- WHO recommends CAD to be used with human readers or in place of human readers when screening the general population (>15 years old).
- UP-XR is recognized by WHO as a subtype of the portable digital X-ray.
- UP-XR systems are field friendly. They can be operated on battery alone, emit less radiation, and produce images comparable to stationary machines.
- When procured, UP-XR systems come with a complete core system and set of accessories.
- UP-XR and CAD are integrated in different ways, depending on whether use is online, offline, or a hybrid of the two.
- Together, UP-XR and CAD are an opportunity to decentralize TB screening and care.

Knowledge Check—Question 1

Two chest X-rays are taken from individuals by CAD. One is assigned a score of 80 and the other a score of 60.

Does this mean the second person is 25 percent less likely to have TB than the first?

ANSWER

No, because the CAD output is not linearly related to the probability of having TB. There is no relationship between the two scores.

Knowledge Check—Question 2

Can CAD results alone be used to diagnose TB?

ANSWER

No, CAD is not validated to diagnose TB and is not recommended by WHO to do so. Anyone with a high score on CAD should receive confirmatory diagnostic testing, for example, using Xpert or Truenat.

Knowledge Check—Question 3

What does CAD output usually include?
(Select all that apply)

- ❑ Numerical abnormality score
- ❑ Classification “Active TB,” “Healed TB”
- ❑ Heatmap

Knowledge Check—Question 4

There are four types of X-ray technology.

Can you name them?

ANSWER

Digital (DR), computed (CR), retrofit, analog

Knowledge Check—Question 5

What are some of the benefits of using ultra-portable X-ray? (Select all that apply)

- ❑ Ability to screen high-risk groups in areas difficult to reach by road
- ❑ Higher throughput compared to stationary
- ❑ Reduced radiation exposure
- ❑ Reduced physical strain on staff operating the machine

Thank you

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Stop TB Partnership

PROGRAM PLANNING AND IMPLEMENTATION CONSIDERATIONS

MODULE 3

Stop TB Partnership

Stop TB Partnership

Acknowledgements

These training modules were developed as a collaboration between the United States Agency for International Development (USAID) and its Infectious Disease Detection and Surveillance project (IDDS) and the Stop TB Partnership, as part of the *introducing New Tools Project* (iNTP). The content is based on the Stop TB/USAID/GLI *Practical Guide to Implementation of Computer Aided Detection (CAD) Technology with Ultraportable X-Ray Devices to Screen and Triage TB.*

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INTRODUCTION

This module offers a menu of the key programmatic and procedural considerations steps to consider when designing and implementing a project to deploy ultra-portable X-ray systems with CAD software to screen and triage for TB.

Outline

- → Stakeholder framework and situational assessment
- → Site selection and preparation
- → General screening workflow
- → Key implementation considerations
- → What to expect from suppliers
- → Challenges and lessons learned from early users of CAD and UP-XR
- Summary

Learning Objectives

By the end of this module, participants should be able to:

- Engage key stakeholders from early stages of a CAD and UP-XR program.
- Perform a tailored situational assessment for a CAD and UP-XR program.
- Identify suitable sites and prepare for CAD and UP-XR field activities.
- Understand the human resource requirements of CAD and UP-XR programs.
- Understand the general screening workflow involving CAD and UP-XR programs.
- Be aware of key implementation considerations for CAD and UP-XR.
- Be aware of some challenges and lessons learned from pilot projects.

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PROGRAM PLANNING AND SITE SELECTION AND PREPARATION

Stakeholder Framework

Implementer and NTP/MoH should consider engaging the other important stakeholders for the implementation of ultra-portable X-ray systems with CAD software, such as:

National radiography, radiology, and medical associations or equivalent

Could be **opposing** the operation, so it is important to engage and sensitize them to ensure support for projects. Engagement should include radiographers, radiologists, chest specialists, and relevant clinical officers specialized in lung health.

National center for personal data

To address any regulatory concerns around the collection, storage, and processing of patient data, particularly by CAD.

National radiation/atomic energy regulatory authority or equivalent

To confirm whether the ultra-portable X-ray systems can be imported (from a radiological safety standpoint). Design radiation safety protection measures for patient and operator.

ICT companies/Internet providers

To ensure that a suitable Internet connection is provided for running CAD software and for data synchronization if using CAD online or hybrid.

Civil society and TB-affected community organizations

For active case finding activities and advocacy for sustainable funding of the intervention.

Medicines and medical devices agency or equivalent

To confirm whether the ultra-portable X-ray and CAD software are classified as a medical device in the country. If necessary, complete national registration.

Donors and international partners

Provide funding for system procurement and investigations as well as technical assistance on various aspects in the implementation.

Situational Assessment

As an initial step, a country situation analysis should be conducted to select possible sites for implementation to identify how CAD and UP-XR can **slot into** and **reinforce** the existing health system.

A situational assessment should cover the following:

1. Existing public health interventions
2. The available literature on CAD and X-ray screening
3. National and district regulations and policy
4. Existing health system integration and capacity
5. Existing ICT infrastructure

Reviewing the existing situation should make it possible to:

→ **Select possible implementation sites.**

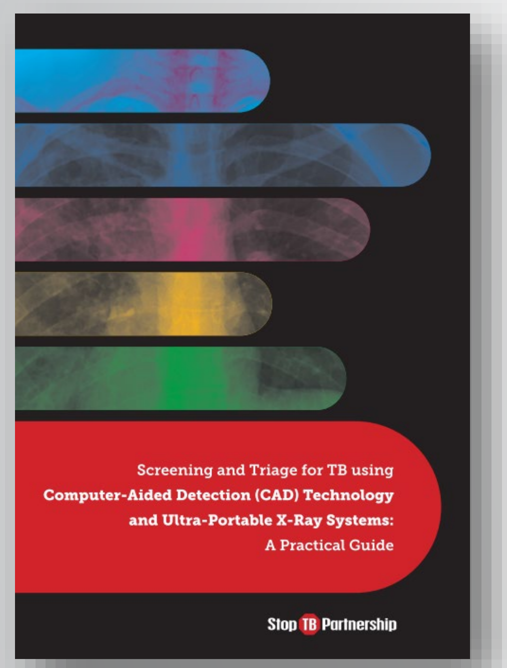
→ **Establish relationships with nearby facilities for:**

1. Referral of people for confirmatory testing (such as community to facility, primary health care to facility, or diagnostic site to Basic Management Unit)
2. Storing backup X-ray images and CAD software reading outcomes

→ **Establish the roles and responsibilities of the NTP, local distributors, and implementing partners.**

→ **Develop a costed operational plan for implementation.**

Site Selection and Preparation



Following completion of all implementation steps and prior to beginning X-ray screening, the site and staff should be evaluated for readiness.

The site should be evaluated for:

- ❑ Planning and HR
- ❑ Equipment, service, and maintenance
- ❑ Screening facility readiness
- ❑ Relevant procedures for patient registration, results reporting, and CAD maintenance
- ❑ Digital data and diagnostics connectivity
- ❑ Monitoring and evaluation
- ❑ Recording and reporting of results
- ❑ Capacity to train and assess competency of staff

A checklist for assessing site readiness can be found in Annex 7 of the Stop TB Partnership's Practical Guide.

Highlighted Considerations for Site Selection and Preparation

1. Patient management

- How will a presumptive patient be registered?
- Do the X-ray and CAD results need to be printed for referral?
- Where will presumptive patients with an abnormal X-ray be referred for confirmation testing?
- Will sputum samples be collected onsite and transported to Xpert labs?
- What is the expected daily throughput of the site?
  Note: Ultra-portable X-ray systems are not ideal for sites anticipating high throughput (e.g., 300 scans per day).

2. Equipment requirement

- Are there sufficient sockets available for battery re-charging of essential devices: CXR detector, generator, PACS laptop?
- Is there an available electricity source to power the CAD4TB box and the router?
- Is there a place to hang the detector with the Versarix holder?
- Is there secured storage for the Delft Light backpack?
- Does the X-ray unit ensure an optimal environment:
  - Working: operating: 0–60 degrees Celsius, 5–95% RH (no condensation)
  - Storage: 0–60 degrees Celsius, 10–90% RH

3. Radiation safety and regulation

- Is Delft Light allowed to be used in open spaces/non-specialized facilities without lead wall shielding?
- Is there adequate space to perform X-ray exposure in compliance with relevant national regulatory requirements?
- What is the patient flow, where do patients enter/exit the room /radiographer area?
- Radiographer area: What is a safe distance for the radiographer? additional lead shielding available? What is the maximum distance between the X-ray generator and detector?

Human Resources

1. Identify and hire **X-ray technicians or radiographers** to operate X-ray systems, and **community health care workers** to conduct screening activities.
   Note: If CAD is used for screening and triage purposes, **radiologists might not be required** to be onsite, according to WHO recommendation.

2. Identify existing **biomedical and IT staff** (or hire new staff) to support the configuration, installation, maintenance, and support of ultra-portable X-ray systems and CAD software.
   Note: CAD projects may necessitate capacity building in this area.

3. Ensure sufficient **staff to transport** ultra-portable X-ray systems and necessary accessories, if necessary. A **minimum of two people** will be required.

4. For threshold selection (see Module 4), consultants with **operational research and statistics background** may be necessary.

5. Engage a **legal expert** to advise on how to best protect the patient information while allowing for necessary data flow.

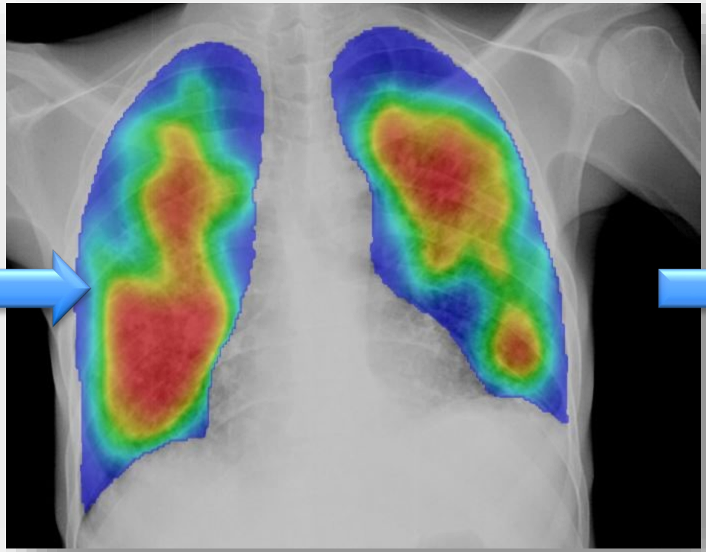
General Screening Workflow

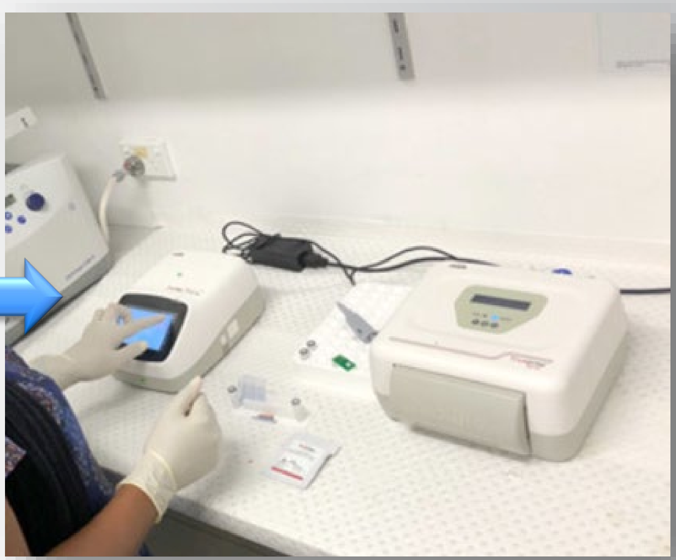
1. Outreach and promoting X-ray and CAD screening projects and identify presumptive patients who require X-ray examination as per national TB screening and diagnostic algorithm

2. Presumptive patient screening and registration

3. Presumptive patient preparation and X-ray exposure

General Workflow





4. After the exposure, the detector receives the images and immediately transfers the X-ray image to the console PC using Bluetooth (or wired connection). The console laptop automatically processes and generates the X-ray image.

X-ray images may also be viewed on the tablet accompanying the CAD4TB box.

5. The X-ray is then automatically read by CAD4TB and generates results.

   CAD4TB results can be displayed on the console PC (online) or accompanying tablet (offline).

6. Post-screening referral and diagnostic and care provided, along with monitoring and evaluation (Module 5).

IMPLEMENTATION CONSIDERATIONS

Electricity and Power

Because of the limited battery capacity and charging options, ultra-portable X-ray may not be suitable for high throughput settings without power in the field.

The entire Delft Light system has **built-in batteries** so it can be operated in screening settings without access to electrical mains.

The charging requirements of the system are:

Generator battery	Capable of approximately 200 exposures. Recharging takes approximately 4 hours. **Note:** The battery must be **removed from the tube for charging** and inserted into the generator charger. This means that the X-ray generator **cannot be charged and operated** at the same time.
Detector battery	Capable of approximately 100 exposures per set of 2 batteries. A second set of batteries means up to 200 exposures are possible. Recharging takes approximately 2.5 hours. 
CAD4TB box	The CAD4TB box requires an AC connection to operate. It is **not** capable of storing its own power.

Electricity and Power

If implementers plan to deploy the systems for high throughput in an off-grid setting, external power sources are critical to ensure continued operation.

MobiSun solar panel and power bank

All system components (generator, detector, workstation, and CAD4TB box) can be recharged from a portable, water-resistant MobiSun solar panel with built-in power bank in settings without access to electrical mains.

- The solar panel power bank takes **16 hours to fully charge in direct sunlight.**
- There were some difficulties experienced by early users using the solar panel due to the difficulties and deficiencies of charging by sunlight.
- Alternatively, the solar panel's power bank can be charged from the electrical grid in **approximately 2.5 hours.**
- Solar charging cannot occur while the system is in operation.

Note: 12 second gap is required between exposures.

Portability and Setup

The full kit contains several components in addition to the X-ray generator and detector. The overall weight of a complete set can still be **too much for a single person** to carry.

The Delft Light comes with two bags for carrying the system:

- **Backpack** for the generator, detector, detector stand, console, CAD box, and accessories
- **Carrying case** for the generator stand

Photo credit: KNCV Nigeria

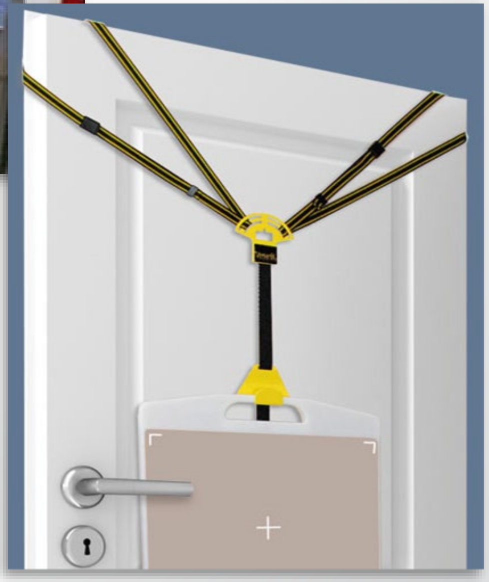
Delft Light component	Weight (kg)
X-ray generator	7.0
X-ray generator stand	8.0
X-ray detector (incl. batteries)	3.8
X-ray detector stand	0.4
Console laptop/workstation	1.5
Lead apron	3.0
Battery chargers	1.0
Solar panel/power bank	6.0
Carrying case (empty)	2.5
Delft Light total	**33.2**
CAD4TB Box	1
System total	**34.2**

Portability and Setup

For portability, a Versarix holder is provided instead of a detector stand, and this must be hung onto improvised mounts at the field location, such as doors or trees.

Daily set-up can take approximately **30–35 minutes** after identifying a suitable field site, with one person setting up the detector and stand and the radiographer preparing the generator.

A further 35–40 minutes may be required to tidy up and clean the equipment after a screening session.



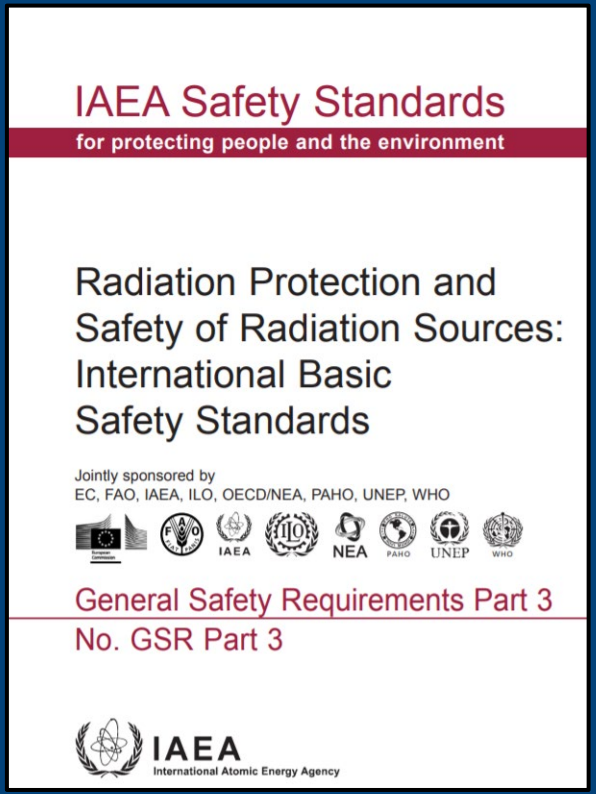
Radiation Safety

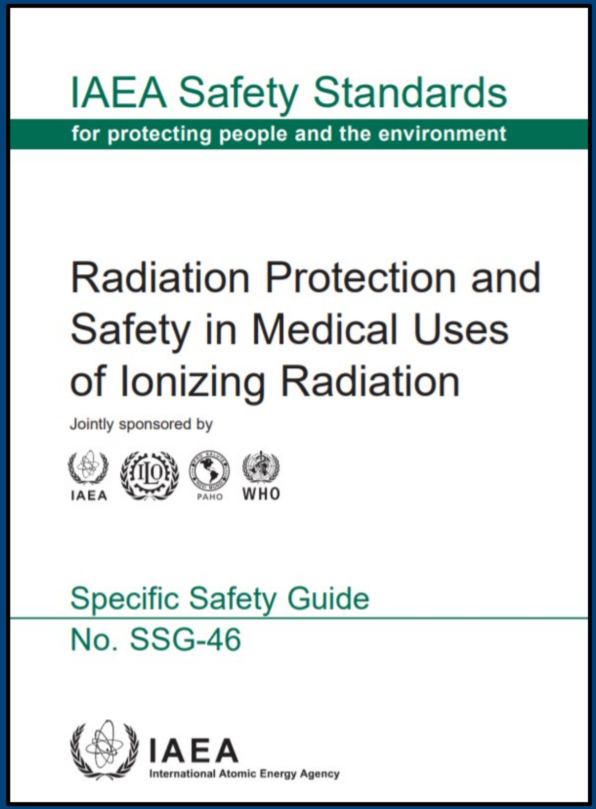
Radiography involves exposure to ionizing radiation. Although the risk remains low when the levels of radiation are controlled, precautions are needed to ensure the safety of health care workers and patients.

Local and international radiation safety regulations should be followed, especially when deployed in non-specialized facilities in the field.

The global benchmarks for radiation safety worldwide:

- Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards
- Radiation Protection and Safety in Medical Uses of Ionizing Radiation—Specific Safety Guide SSG-46





Radiation Safety

Best practices for safe operation include, but are not limited to:

- ★ Choosing a screening site far from residential areas, barricading places with an exposure risk, and ensuring that no one can enter the radiographic assessment zone
- ★ Ensuring the X-ray technician/radiographer operates the machine safely, using the handswitch, and wearing appropriate safety equipment/with shielding
- ★ Directing patient flow at screening sites to minimize exposure to radiation, with consideration to entry/exit route to screening room/ area and beam direction
- ★ Setting up the generator and detector so the minimum safe distance is adhered to
- ★ Ensuring that no more radiation than necessary is used to obtain images of adequate quality

Digital Data—Server and Storage

When using CAD in high throughput settings, large quantities of data are generated. Thought should be given to how that data will be stored securely.

Server

Options to consider include:

- Server type: physical or cloud server?
- Server location: in-country or not?
- Server purchase: from the CAD supplier or not?
    - Using the supplier-recommended cloud could result in lower costs, ease of access for server updates, as well as better physical and logistical security measures

Advantages: automatic back-up, accessible from different locations, scalable storage capacity

Disadvantages: costs and need for server admin (depending on choices of server), potentially less control over data security, and need for more robust legal protection

Physical Back-Ups

Options to consider include:

- External hard drives
- CD disks
- Pen drives/USBs

Advantages: can be inexpensive, more control over data security, back-up can occur without Internet connection

Disadvantages: manual, difficult to manage large volumes of data, possibility of damage/loss/corruption of storage device

Digital Data—Data Privacy and Security

Patient medical data are collected, stored, and transferred during CAD projects.
It is important that these data are kept **private** and **secure.**

Data privacy
is the right to restrict the use, access, disclosure, and dissemination of information.

Data security
comprises technological and non-technological mechanisms that limit the use, access, disclosure, and dissemination of information.

Restricting the use of digital data to a limited set of purposes necessary when using CAD technologies is essential for data privacy and security.

Patient data can be protected using technological and non-technological (legal) measures.

➔ For CAD companies in the GDF catalogue, the principal agreement stipulates that CAD companies can **only** use implementers' data to provide CAD services (i.e., to read CXR images and provide outputs).

Digital Data—Data Privacy and Security

Non-technological (legal) measures

As the legal data owner, there are two primary measures that can be used to ensure that the project's patient data are kept private and secure by CAD suppliers.

The Stop TB Partnership has produced templates of both agreements and accompanying instructions designed to maximize the data protection, privacy, and security of the patient data.

- **Data processing agreements (DPAs)** govern the legal rights and obligations of parties involved in the transfer, storage, and processing of personal data. Stop TB has created a DPA template to protect CAD implementers' data that manufacturers in the GDF catalogue are **required** to sign.
    - Access the template here and the instructions here.

- **Non-disclosure agreements (NDAs)** legally bind individuals and organizations to secrecy and confidentiality regarding shared information. Stop TB has created an NDA template to maximize data confidentiality.
    - Access the template here and the instructions here.

Both templates should be adapted in line with local legislation and regulation by a legal expert.

Digital Data—Data Privacy and Security

Technological measures (data de-identification)

Personally identifiable information (e.g., patient name) can be removed from CXRs before sharing them with CAD suppliers for processing and analysis.

The two primary methods to de-identify patient data in a DICOM file are:

Anonymization

- Removing identifying information like name, age, gender from header elements in a DICOM file, or replacing with random data.
- If the project links CAD output with other databases, a unique patient identifier system should be used.
- **Provides greater data privacy but does not allow for re-identification.**

Pseudonymization

- Modifying personal data so that they can no longer be attributed to a specific individual without the use of additional information (kept separately).
- The age/gender/name in the DICOM file is replaced with artificial identifiers.
- **Provides less data privacy than anonymization but allows for patient re-identification by authorized personnel.**

De-identification scripts should be set up with assistance of an IT specialist and CAD supplier engineer.

Further Considerations

Internet requirement: When using CAD products online or in hybrid mode, a **strong and stable Internet connection** is required for online mode because X-ray files are large (approx. 10–30 MB). If the intended use is in areas without reliable Internet access, it is important to purchase a CAD product that can analyze CXR images and generate results offline.

Privacy: Prospective sites should be assessed for suitability for mounting the detector in an area where **privacy** is available for anyone being screened who needs to remove any clothing with metallic components, or accessories, before taking a CXR.

What to Expect from Suppliers

- Onboarding training and installation, including system installation, theoretical and practical training on safety, use, transportation, and maintenance
- Monthly virtual support call
- Extended onsite/remote training with eLearning
- Threshold point calibration and troubleshooting
- Onboarding toolkit, including the IT, infrastructure, and human resource requirements for running CAD
- User manual capturing installation process, software update process, troubleshooting, and maintenance
- To be discussed in Delft's training

CHALLENGES AND LESSONS LEARNED FROM EARLY USERS OF CAD AND UP-XR

Challenges and Lessons learned

Interviews with six early implementers of CAD with UP X-ray identified through Stop TB's partner network revealed the following insights:

Reluctancy from radiologists and fear of being replaced by artificial intelligence can still exist → underscores the importance to engage and sensitize these medical professionals and associations. Artificial intelligence has many use cases when used WITH human readers.

HR capacity and training: Some countries had a lack of or inadequately qualified radiographer/radiology technicians and had to train additional community health workers and clinicians to operate the X-ray system.

Portability is a clear advantage, especially compared to previously used solutions which still need specialized vans/ trucks. Sometimes the UP-XR system was described as **not as portable as marketed** due to the number of components and their combined weight.

Assembly and ease of use
Overall, the system was described as **easy to assemble and use,** but it can take about 30–35 min. It also needs proper cleaning.

- *"It's easy to set up, its easy to consult, and there are less repeats."* —Radiographer

Image quality
Generally, image quality was described as **comparable to stationary machines** when taking images of most people.

- *"Before we started using the UP XR, we had another stationary one. I think the one that we're using has better quality images than the one we had before." —Clinician*

Challenges and Lessons learned

Threshold score selection is difficult: Most new users just start with manufacturer recommendations or adjust in response to false positives. Once they gain experience, they do operational research.

Potential problematic behavior change: The potential for the **interpretation of CAD output as diagnosis** was a concern:

- *"My worry is as it's rolled out, as the WHO has now approved, is that clinicians may interpret a CAD score as TB and I suspect that we already see that in some places." —Project Lead*

Referral and linkage to confirmatory testing: May need to print X-ray and CAD result, consider collecting sputum on the spot, and use of unique patient identifier for both x-ray and confirmatory test.

Server and storage: A key **by-product** of using the CAD cloud was that images stored on the cloud be consulted remotely by non-field-based staff.

- *"I also like with the CAD4TB anyone can help you read the X-ray wherever they are as long as they're on the cloud, so it's easy for consultations as well."*

Although it is easy to integrate the CAD system with the PACS system, it is difficult to integrate CAD results with **the existing national TB database (e.g., DHIS2) or a project-specific electronic medical record system (e.g., openMRS).**

Challenges and Lessons Learned

Equipment fault and CAD reading error:

- Detector to the console connection: Bluetooth resulted in delayed or failed image transfer. A wire connection would make this more efficient, but the length of the wire can be limiting.
- The connection between the console and CAD laptops can also be a weak point. Some projects experienced loss in connection prior and fixed it by restarting the laptops.
- X-ray generator battery failed → new product, having a good service and maintenance contract is important.
- The detector battery is durable, but the battery life of the console laptop may not last with use. → new product, more actively engage Delft's client service
- Solar panel charges slowly without direct sunlight or in winter → charge it with electricity grid or replace with another power bank.

Manufacturer service: All projects reported positive experiences with the supplier's IT support system, but access to this service may be limited for implementers who work in settings without Internet connection.

Summary

Summary

- When implementing CAD and UP-XR key considerations include:
  - Electricity and power
  - Portability and set-up
  - Radiation safety
  - Data management and privacy
  - Internet access
  - Availability of private spaces
- CAD suppliers provide installation, training, and technical help to support the smooth operation of CAD programs.
- Preparations for implementation include identifying key stakeholders, performing a situational assessment, and analyzing field site readiness and suitability.
- CAD and UP-XR projects require a blend of clinical, IT, scientific, and legal expertise.

Thank you

INTRODUCTION TO THRESHOLD SELECTION

MODULE 4

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Course Outline

- → Threshold score selection
- → How to select a threshold score suitable for the local context
- → How to analyze program data for threshold selection
- → Planning for screening

INTRODUCTION

This module introduces the key concepts of threshold score selection when using CAD and proposes several different strategies for how a threshold score should be selected that is suitable for the local context.

Learning Objectives

By the end of this module, participants should be able to:

- Understand what a threshold score is and how to set it.
- Know the effect of changing threshold on key screening targets.
- Describe why a threshold score needs to be chosen based on the local context.
- Understand some of the current strategies for adapting and optimizing a threshold in the local context.

THRESHOLD SCORE SELECTION

What is a “threshold score”?

It is a numerical value between 0 and 100 (the default threshold is 60).

It translates the continuous output of CAD (abnormality score) into a binary output (a classification).

The first classification: Any chest X-ray with a score **above** the threshold value is automatically classified as “**TB**” (or similar) by CAD.

The second classification: All X-rays with a score **lower** than the threshold value are automatically assigned **“No TB”** (or similar) by CAD.

All images classified as “TB” by CAD should receive further confirmatory diagnostic testing.

Where CAD classification alone informs the triage decision, the threshold score will determine key outcomes for an intervention, such as the number of confirmatory diagnostic tests needed.

Basic Concepts in Threshold Selection

When using CAD classification alone to determine triage decisions, a threshold score can be chosen **based on programmatic goals.**

Some important factors to consider when identifying programmatic goals include:

- Accuracy (Sensitivity, Specificity)
- Cost Efficiency
- Test Positive Rate
- Confirmation Test Capacity

Impact of Threshold Selection

There is a clear trade-off between key considerations for programs, so a threshold score needs to be adjusted in an informed way.

In general, a **low** threshold score results in:

- **High** sensitivity but **low** specificity
  - More X-rays will have scores above the threshold, but a smaller proportion of these will have TB based on a diagnostic test.
- Needing to test **more** people to find a positive case, and therefore needing more diagnostic tests
- Increasing likelihood of **over-diagnosis** of TB

In general, a **high** threshold score results in:

- **Low** sensitivity but **high** specificity
  - More X-rays will be below the threshold, but a larger proportion of those above the threshold will have TB based on a diagnostic test.
- Needing to test **fewer** people to find a positive case, and therefore needing fewer diagnostic tests
- Increasing likelihood of **under-diagnosis/ missed cases** of TB

Threshold Score Trade-offs in Action

CAD score of population

49 39 32 6 22 86 9 51 29 51 37 7 45 16 33

Person without TB

Person with TB

Population with "Possibility of TB" according to CAD

Situation A:
Saving on diagnostic tests
Threshold score is 75.

86

Situation B:
Optimizing sensitivity with resource constraint
Threshold score is 50.

51 51 86

Situation C:
No limit on testing resources
Threshold score is 35.

37 39 45 49 51 51 86

Sensitivity = 33%
Specificity = 100%
Number of confirmatory tests needed = 1
Number of missed/ undiagnosed cases = 2

Sensitivity = 67%
Specificity = 92%
Number of confirmatory tests needed = 3
Number of missed/ undiagnosed cases = 1

Sensitivity = 100%
Specificity = 67%
Number of confirmatory tests needed = 7
Number of missed/ undiagnosed cases = 0

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Factors that Influence CAD Performance

- Underlying TB prevalence
- Presentation of TB in individuals with
  - Prior TB history
  - Co-morbidities (HIV, diabetes)
- Prevalence and proportion of other lung diseases
  - Silicosis, COVID-19
- Prevalence of risk factors for TB in specific populations

Factors that Influence CAD Performance

CAD's performance is shown to vary in different demographics and use populations.

The performance of CAD in a given population is therefore **impossible to predict precisely,** because it will depend on a combination of factors.

Individual variations in CAD performance may also occur.

The best way to choose a threshold score that will lead to a desired programmatic outcome is to collect local operational data.

HOW TO SELECT A THRESHOLD SCORE SUITABLE FOR THE LOCAL CONTEXT

How to Choose a Threshold Score

Selecting an appropriate threshold score is often described as challenging.

It is not possible to select one threshold score that applies between all CAD products, different software versions of the same CAD product, and different use cases and achieves the same results.

- Every CAD product is developed differently—an X-ray assigned 30 (or 0.3) by one CAD is not equally likely to have TB as an X-ray assigned 30 from another.
- Every CAD product performs differently in different sub-populations (for example older ages, HIV+), depending on the data used to develop it.
- Different versions of the same product may even be developed differently and perform differently in different sub-populations.

How to Choose a Threshold Score

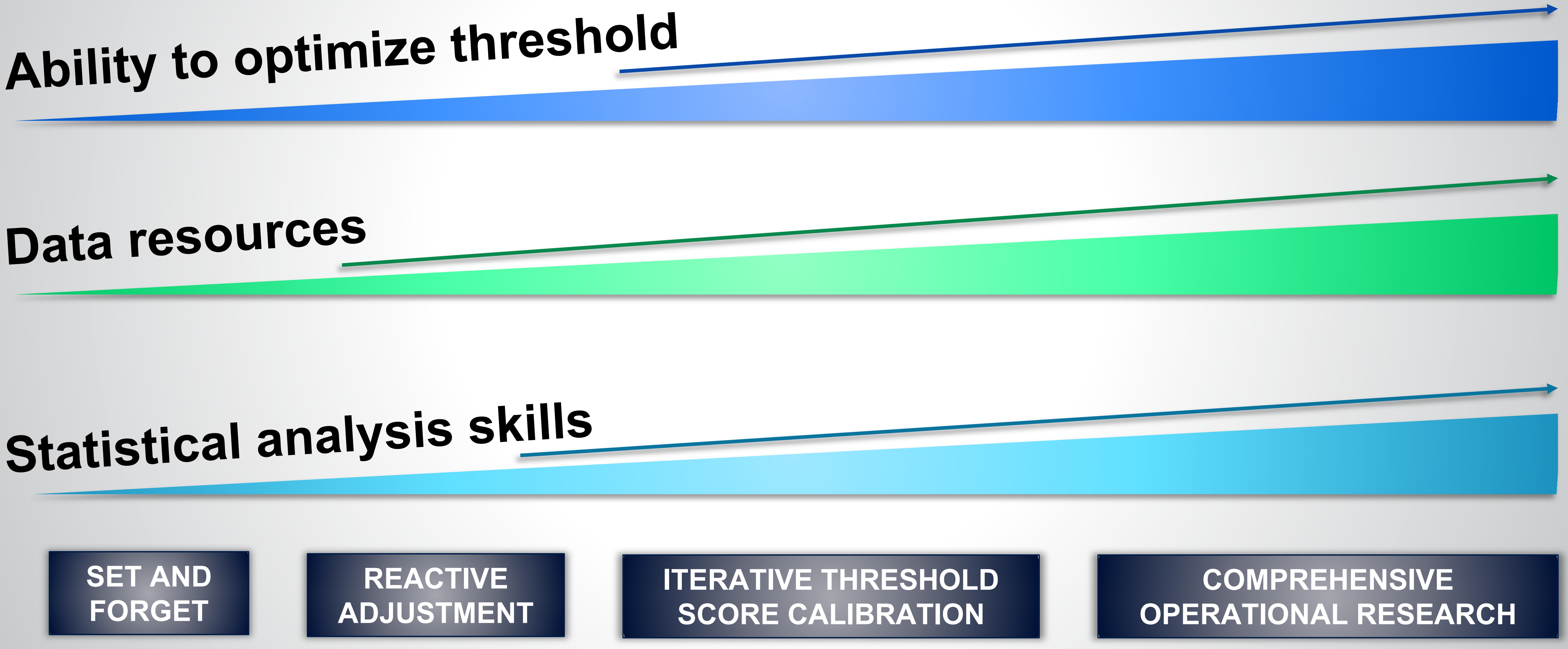
There are four main strategies for selecting a threshold score:

1. Set and forget
2. Reactive adjustment
3. Iterative threshold score calibration (ITSC)
4. Comprehensive CAD calibration study (“TDR” toolkit)

The most appropriate strategy to use depends on the availability of resources, such as:

- Staff with the correct skills
- Time available
- Data collected
- Availability of confirmation tests

Threshold Score Selection Strategy



Set and Forget

The selection of a threshold score is kept for the duration of the implementation.

Sources of initial threshold could include:

- Prior experience with CAD products (ideally, the same product)
- Research using CAD literature (ideally, the same product and similar population)
- Recommended or default score from the CAD supplier

This strategy rests on the (unlikely) assumption that CAD performance will be the same in the target population as in the population used in the source of the threshold selection (e.g., the study in the CAD literature on which a chosen threshold is based).

Ideally, thresholds selected in this way should be optimized (using the prior strategies).

“Set and Forget” may be a practical compromise if resources are not available.

Reactive Adjustment

- Adjustment of a threshold score already selected (e.g., the one recommended by the manufacturer) by small increments in reaction to the occurrence of undesirable outcomes
    - Undesirable outcomes: for example, CAD missing large numbers of people with TB, or a low positive confirmation test rate
- Performed **in parallel** to the implementation
- Similar to ITSC but **without concrete statistical methodology** and therefore potentially less accurate
- Requires **less statistical expertise** than following strategies

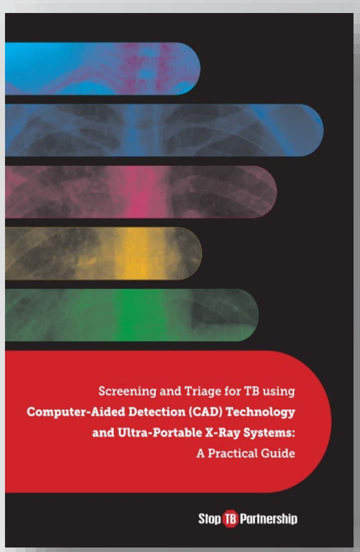
Data required:

- Participant demographic and clinical information
- Digital chest X-ray
- CAD score
- Confirmatory diagnostic test data (e.g., Xpert results)
- To adjust appropriately, people with a CAD score lower than the threshold score with other signs of TB will need to undergo confirmatory diagnostic tests.

Iterative Threshold Score Calibration (ITSC)

Strategy proposed by the Stop TB Partnership and Google.

- Requires setting an initial threshold score, then refining the initial score through ongoing rounds of data analysis until a target outcome is reached
- Can be performed **in parallel** to implementation
- If done correctly, selects a threshold score based on a targeted outcome (sensitivity, or confirmatory tests saved, for example)
- **Substantial statistical data analysis skills** required (may be necessary to engage an expert)



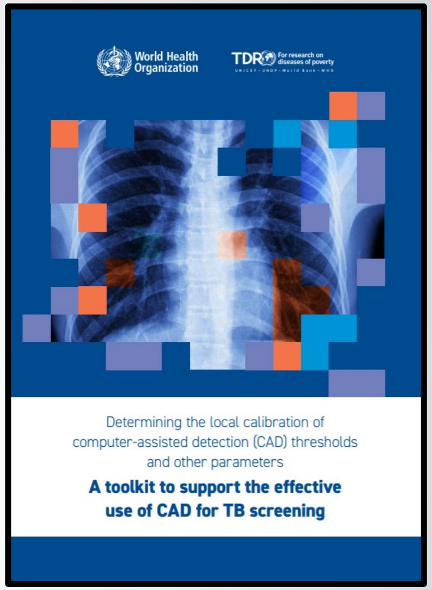
Data required:

- Participant demographic and clinical information
- Digital chest X-ray
- CAD score
- Confirmatory diagnostic test data (e.g., Xpert results) for all participants, or only for those with abnormality scores greater than the threshold

Comprehensive CAD Calibration Study

Strategy proposed by WHO and the Special Programme for Research and Training in Tropical Diseases (TDR)

- Involves conducting research in the population **in which CAD will be used**
- Can be **prospective** (before implementation) or **retrospective** (after implementation, to revise threshold score), depending on data resources
- If done correctly, selects a threshold score optimized for the population and use case
  - If TB prevalence in the population is low, large numbers of individuals may have to be screened to provide a sufficient sample.
- Also requires **substantial statistical analysis skills**



Data required:

- Participant demographic and clinical information
- Digital chest X-ray image
- CAD output score
- Confirmatory diagnostic test data for all participants (e.g., Xpert results)

Comprehensive CAD Calibration Study

Must be conducted in the same groups and regions where the tool will be used

Types of study:

- Cross-sectional
- Case-control

Do not forget any required ethical reviews!

Calibration study should not be used to make clinical decisions.

Comprehensive CAD Calibration Study

Cross-sectional study

Prospective study conducted with target groups and sites

Each eligible* participants will undergo:

- **Collection of key demographic and clinical patient information** (TDR toolkit has a data collection template)
- **Digital chest X-ray and reading** with CAD product
- **Collection of sputum samples** for testing with reference standard test (culture, WRD, etc.)

*** “Eligible participants” are ALL individuals in the selected use groups and sites.**

Sample Size Required for Cross-sectional Study and Level of Sensitivity (Based on 5 Percent Precision)

Cross-sectional Design	Sensitivity				
	50%	**60%**	**70%**	**80%**	**90%**
Number of **confirmed TB cases** required (assuming TB prevalence of 100%)	384	369	323	246	138
Number of **persons to screen** for reaching the expected number of TB cases, if the TB prevalence is **200**/100,000 persons	384 x 100,000 --------- = 192,000 200	369 x 100,000 --------- = 184,000 200	323 x 100,000 --------- = 161,500 200	246 x 100,000 --------- = 123,000 200	138 x 100,000 --------- = 69,000 200
Number of persons to screen for reaching the expected number of TB cases, if the TB prevalence is **500**/100,000 persons	384 x 100,000 --------- = 76,800 500	369 x 100,000 --------- = 73,800 500	323 x 100,000 --------- = 64,600 500	246 x 100,000 --------- = 49,200 500	138 x 100,000 --------- = 27,600 500

Comprehensive CAD Calibration Study

Case-control study

- Retrospective methodology conducted using data from the target groups and sites
- Individuals selected **separately and intentionally** on the basis of their **TB status** (cases or controls)
- Uses pre-existing patient data (outpatient department records, clinic records, prevalence surveys, and community screening) to conduct the calibration study
    - But must use data representative of the population intended to screen
- *May* be faster than a prospective study

Sample Size Required for Case–Control Study and Level of Sensitivity (Based on 5 Percent Precision)

Case-control design	Sensitivity				
	50%	**60%**	**70%**	**80%**	**90%**
Number of **confirmed TB cases** required (assuming TB prevalence of 100%)	384	369	323	246	138
Number of **confirmed non-TB cases** required (assuming the same precision and similar specificity as for the **cross-sectional** study)	384	369	323	246	138
Overall enrollment size required	**768**	**738**	**646**	**492**	**276**

Comprehensive CAD Calibration Study

Following the study (either cross-sectional or case-control), consider defining different CAD thresholds for sub-groups, such as:

- Patient age
- HIV status
- Prior TB history
- Local prevalence

Comprehensive CAD Calibration Study

Exercise: Compare study designs

Cross-sectional study	Case-control study
General conditions for selecting study design	
Sample size	
Benefits (advantages)	
Weaknesses (disadvantages)	
Requirements for study	

HOW TO ANALYZE PROGRAM DATA FOR THRESHOLD SELECTION OPTIMIZATION

Data Analysis for Threshold Optimization

The Decision Analysis Framework can be used to monitor the accuracy and programmatic implications of using CAD software and may be used to inform threshold optimization.

The Framework uses three indicators, each relating directly to a programmatic goal:

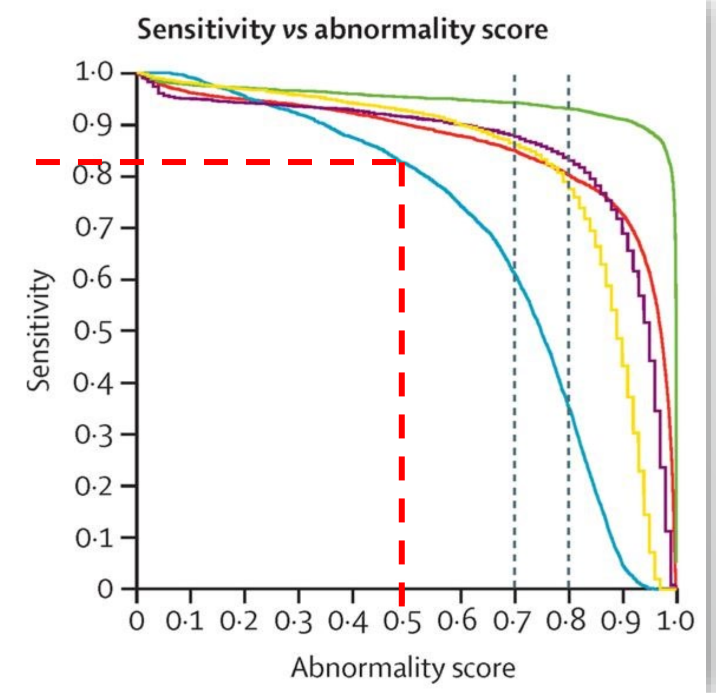
Indicator	**Definition**	**Related performance/ programmatic goal**
Sensitivity	True positive rate, ability of CAD to correctly identify people with TB in the population	High accuracy, maximizing TB cases detected
Number needed to test (NNT)	The number of people with a CAD score higher than the threshold who would need to be tested to find one person with TB	CAD's ability to triage
Proportion of confirmatory tests saved	The proportion of confirmatory tests that would be needed when using CAD as a triage tool, compared to the number without using CAD as a triage tool	CAD's cost-effectiveness

The effect of operating CAD at every threshold score in its range is modeled for the three indicators, and this is visualized as four key graphs.

Data Analysis for Threshold Optimization—Example

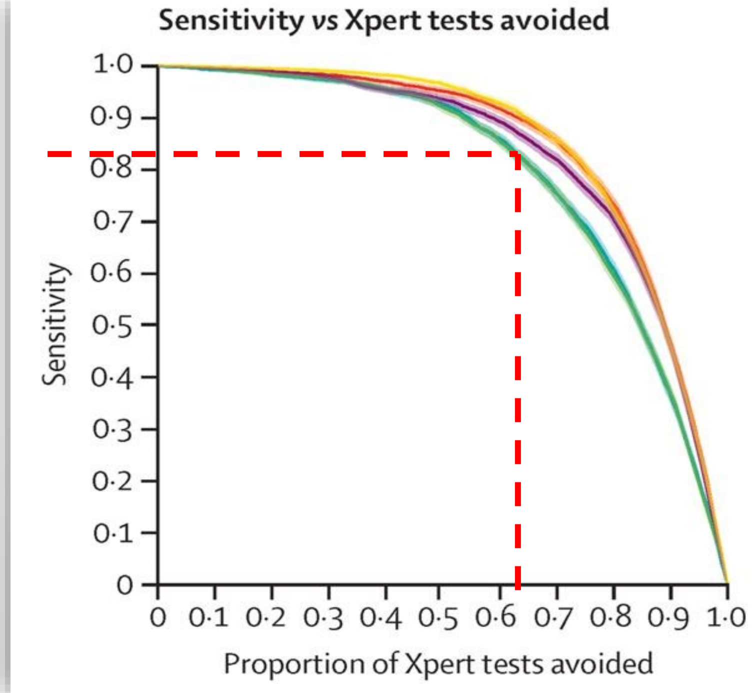
This example cites an application of the Framework to data from TB screening centers in Bangladesh. Different colored lines represent different CAD products.

It is possible to read the graphs for the effect of setting the threshold at different values.



A threshold score of 0.5 (or 50) for the **blue** product would result in sensitivity >80 percent (around 82 percent).

At this sensitivity for the **green** product, just over 0.6 (or 60 percent) of Xpert tests would be saved by using CAD as a triage tool.



Data Analysis for Threshold Optimization—Example

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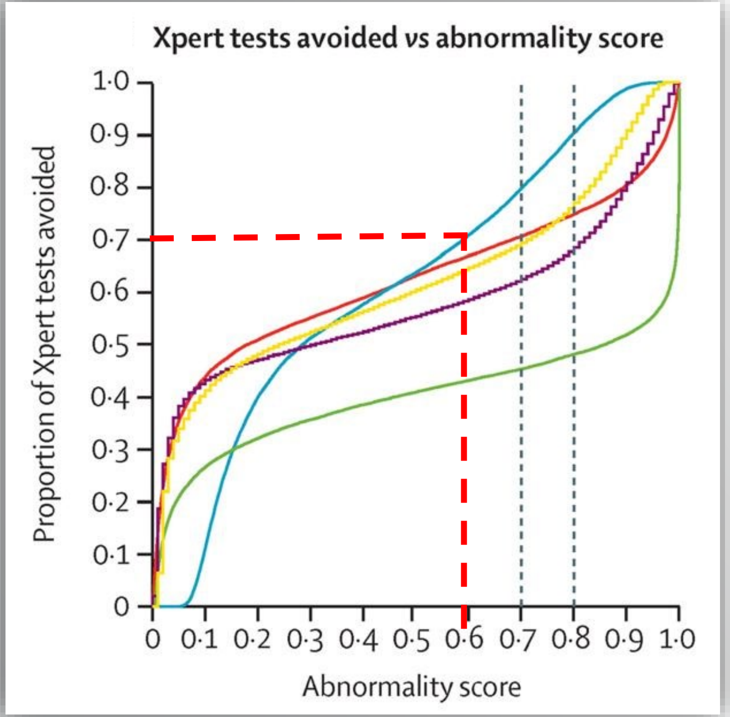
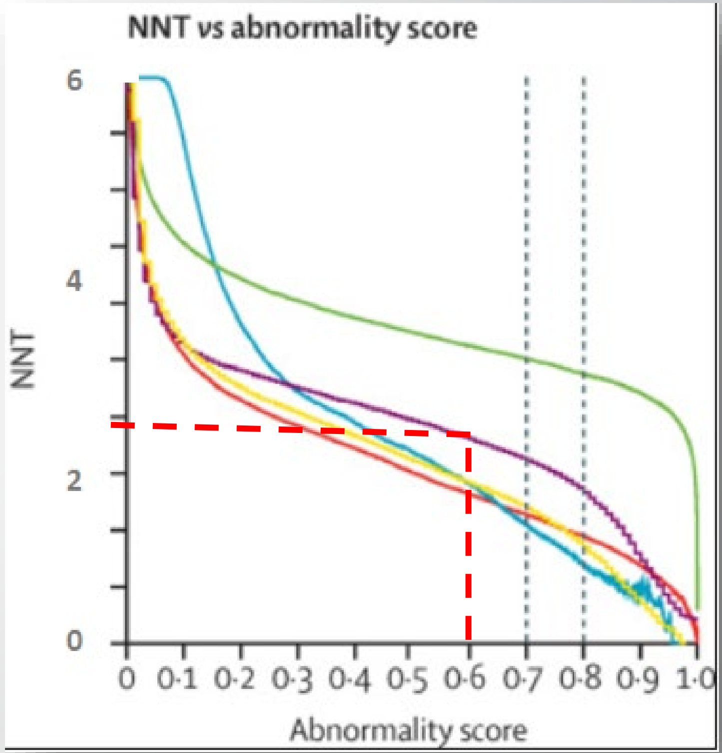


If wanting to save 70 percent of Xpert tests and using the **blue** product, the threshold score should be set at around 0.6.

If using a threshold of 0.6 with the **purple** product, the NNT would be around 2.6.



Exercise—Selecting Thresholds in line with Programmatic Goals

Use the graphs provided to determine what threshold to use for each of these products in the following scenarios:

1. An active case finding project with limited budget for confirmatory (Xpert) tests that would like to reduce Xpert testing by 60 percent
2. An immigration screening program that needs to achieve at least 95 percent sensitivity

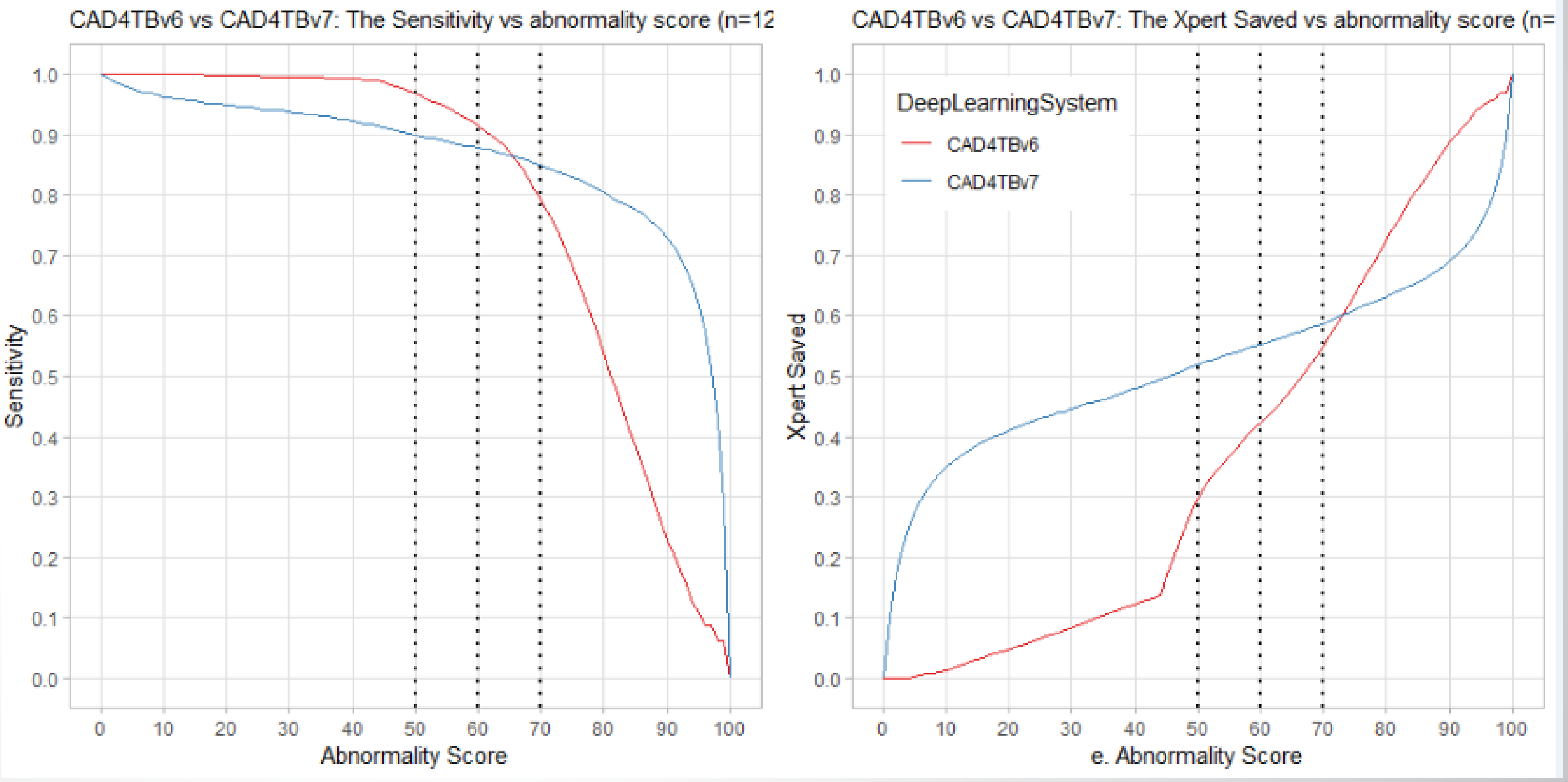
A program would like to operate at the WHO target sensitivity for a TB triage test (90 percent sensitivity). Use the graphs to tell:

1. What is the threshold score they should use?
2. What is the NNT?
3. What is the proportion/percentage of Xpert tests that would be saved?

Performance Change between Versions

Preliminary results from a study comparing version 6 and version 7 of CAD4TB shows that **version 7 significantly outperformed version 6** when compared to the Xpert reference standard.

	Abnormality score	Sensitivity	Xpert saved
V6	50	0.97	0.3
	60	0.92	0.43
	70	0.8	0.55
V7	50	0.9	0.52
	60	0.88	0.55
	70	0.85	0.59



PLANNING FOR SCREENING

Start How You Want to End

- Setting the threshold score will impact the cascade of care.
- If you increase the number of presumptive TB patients requiring follow-on testing, how will you meet the additional need?
- If you reduce the number of presumptive TB patients requiring follow-on testing, will you have additional testing capacity to deploy?

Start How You Want to End

- Are any infrastructural changes needed to accommodate additional testing needs?
- Does existing infrastructure limit the number of people we can test?

You Can Revisit the Threshold Score

- Over time, you may find the originally selected threshold score is no longer reflective of programmatic goals.
- Routine reviews of the CAD threshold score and the implications on sensitivity and specificity should be considered, especially as retrospective data (the case-control model) accumulates.

Summary

- A threshold score is a numerical output score used by CAD to classify chest X-ray images as “No signs of TB” or “Possibility of TB” based on how the abnormality score compares to the threshold.
- If using classification alone to triage patients, the threshold score determines key programmatic outcomes for a CAD screening intervention.
- Low threshold scores result in higher sensitivity and needing to test more people, so there is reduced cost savings and increased likelihood of over-diagnosis.
- A threshold score can be chosen to meet a programmatic goal, but research using locally collected data is required to do this accurately.
- There are four strategies for selecting a threshold score. Some of these strategies require large amounts of data and detailed statistical analysis.
- The Decision Analysis Framework suggests some key indicators that can be calculated to monitor a CAD intervention and may be used to optimize the threshold score.

Knowledge Check—Question 1

True or False

Although it is recommended, a universal threshold score has not yet been decided on for all CAD products.

Knowledge Check—Question 2

When might you adjust your threshold score?

(Select all that apply.)

- ❑ Moving from community screening to screening referrals in an outpatients department
- ❑ After a software update alters the CAD algorithm
- ❑ After performing operational research using data collected during the program
- ❑ After screening the general population, moving to screening only older individuals
- ❑ If you have a lower-than-expected yield of confirmed TB cases

Knowledge Check—Question 3

You are a program manager, and you realize that most of the cases classified as “Possibility of TB” by CAD are TB negative using confirmatory tests, so you have decided to adjust your threshold score.

Do you adjust your threshold score up or down?

Thank you

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Stop TB Partnership

Monitoring & Evaluation for CAD-Enabled Digital X-Ray as Part of TB Screening

MODULE 5

Stop TB Partnership

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These training modules were developed as a collaboration between the United States Agency for International Development (USAID) and its Infectious Disease Detection and Surveillance project (IDDS) and the Stop TB Partnership, as part of the *introducing New Tools Project* (iNTP). The content is based on the Stop TB/USAID/GLI *Practical Guide to Implementation of Computer Aided Detection (CAD) Technology with Ultraportable X-Ray Devices to Screen and Triage TB.*

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Stop TB Partnership

Introduction

This module will help national programs to track and monitor the impact of their usage of computer-assisted diagnosis and digital x-ray to screen for pulmonary tuberculosis

Course Outline

- → Connecting screening to confirmatory diagnostics
- → Monitoring & evaluation across the cascade of care
- → Indicators for a screening program
- → Putting it all together

Learning Objectives

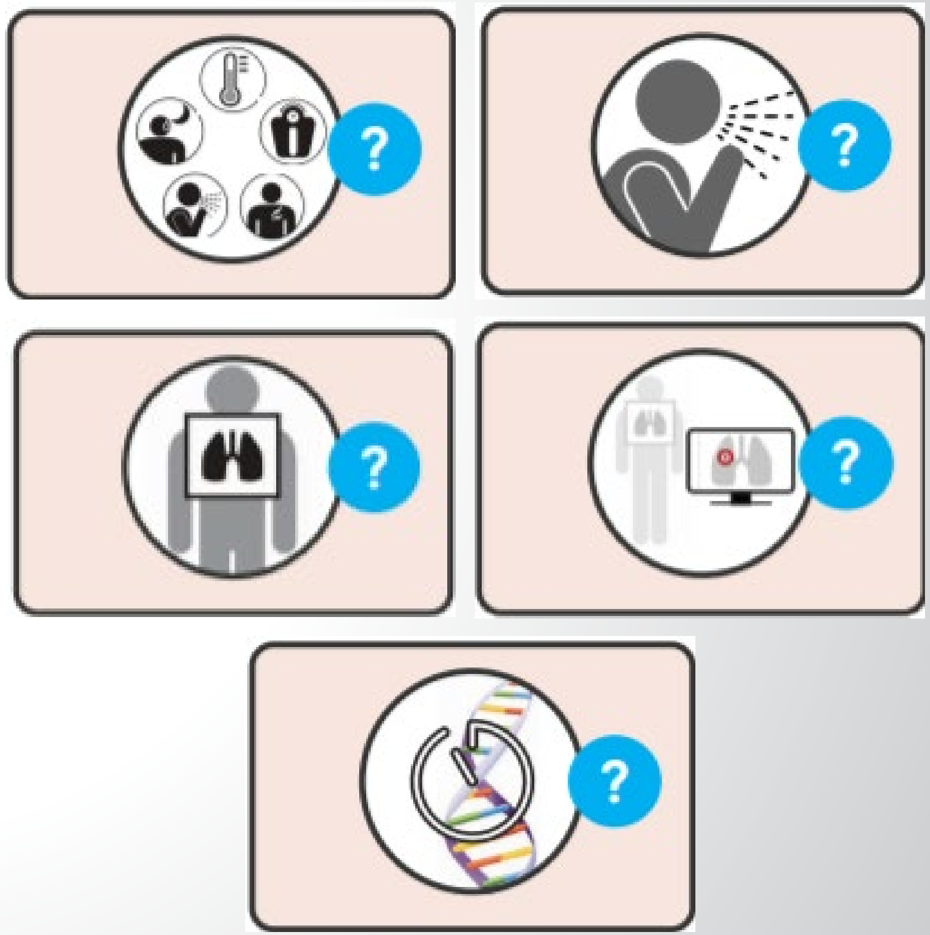
By the end of this module, participants should be able to:

- Describe how to integrate CAD-enabled X-ray into the diagnostic algorithm.
- Describe monitoring & evaluation requirement for a CAD-enabled X-ray system.
- Select indicators to use when establishing a screening program using CAD-enabled X-ray.
- Describe how they would do these in their own country.

Reminder: WHO guidelines on Systematic Screening

In general populations without HIV aged 15 years and older where TB screening is recommended…

- Systematic screening for TB disease may be conducted using a **symptom screen**, **chest X-ray with computer-aided detection (CAD) software**, or **molecular WHO-recommended rapid diagnostic tests**, alone or in combination.
- **CAD software** may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease



CONNECTING CAD-ENABLED X-RAY TO CONFIRMATORY DIAGNOSIS

Reminder: How is CAD-enabled X-ray being used?

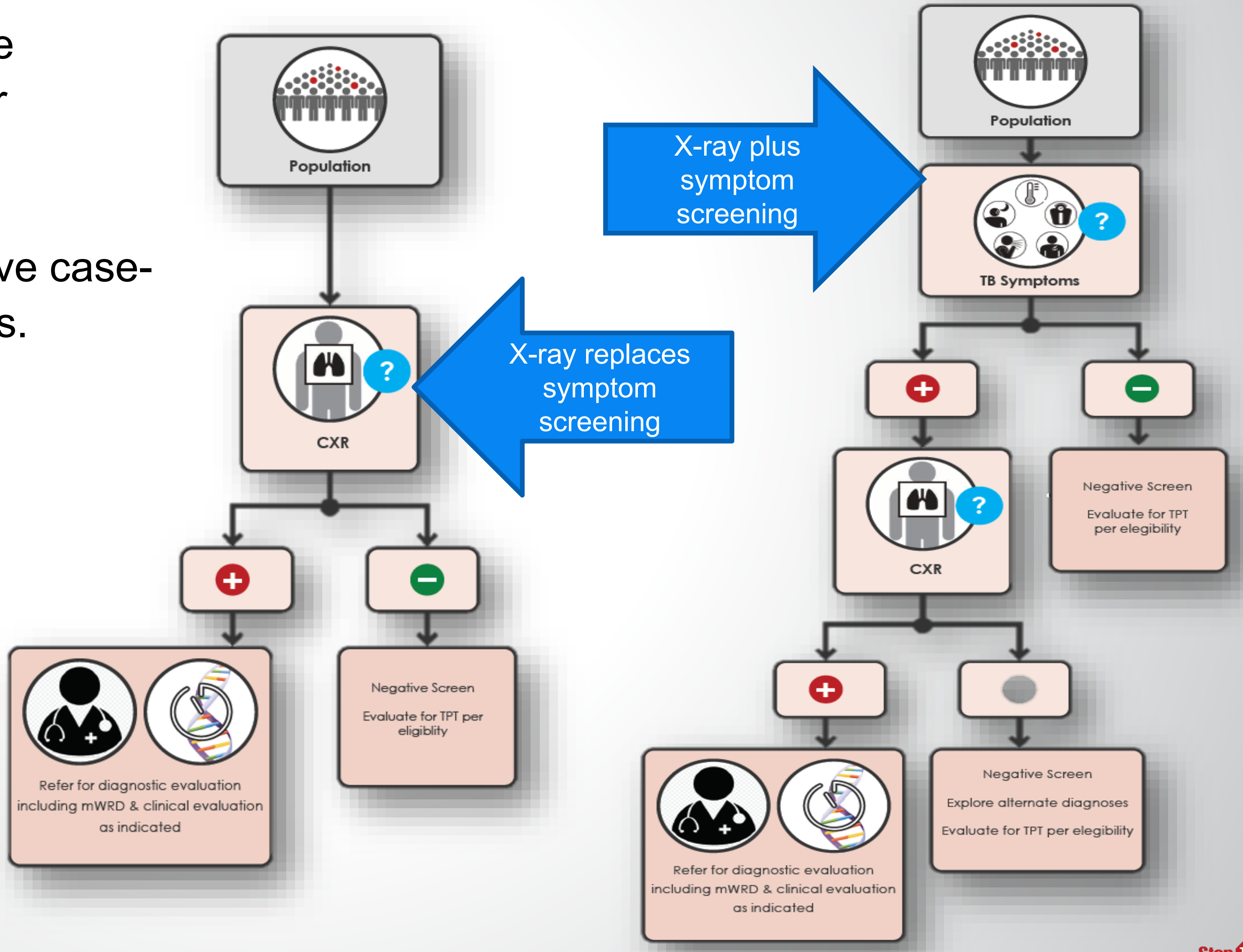
CAD-enabled X-ray screening needs to be integrated into the diagnostic algorithm for tuberculosis.

This integration may look different for active case-finding and passive case-finding strategies.

The outcome should be the same: X-ray results inform diagnostic decision-making

X-ray can also augment or replace symptom screening.

Consider: Does the expansion of X-ray as a screening tool change the working definition of “presumptive TB”?



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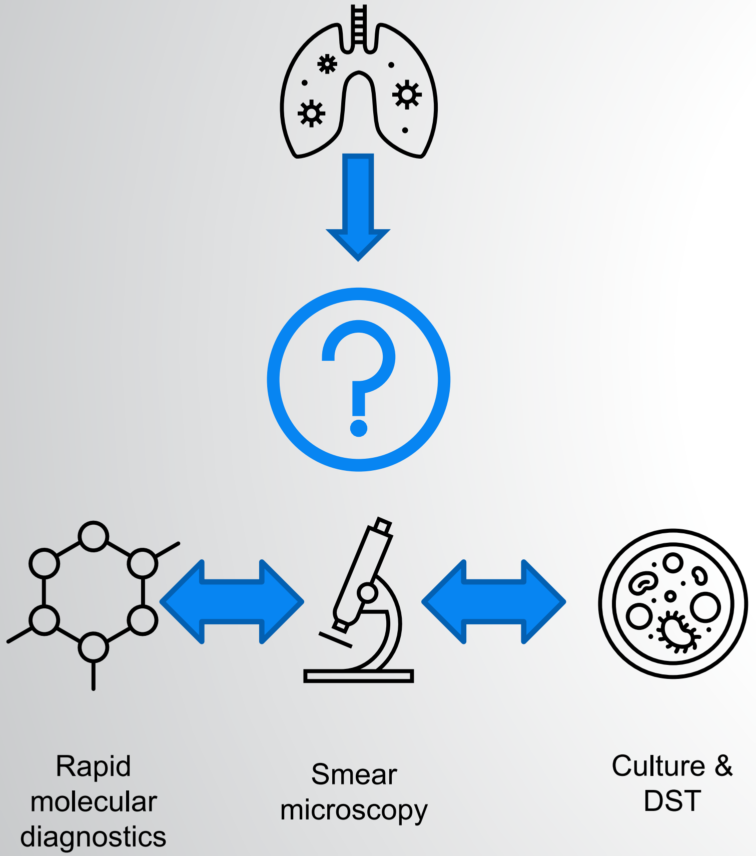
CAD-enabled X-ray results lead to confirmatory testing by the reference standard



- How to make the connection between screening and diagnosis?
  - Do patients have to go to nearby lab, or
  - Can specimens be collected at screening site & transported to labs?
- How are CXR & CAD results transmitted to patients / health provider?
  - Should the X-ray/CAD report be printed?
  - For all patients or only for those above the threshold score?
- How to link the X-ray data with diagnostic data?
  - How are patients registered for X-ray screening?
  - How are patients registered for lab diagnosis?
  - Are unique patient identifiers used for both system and are linked?

Who is responsible for this process?

SETTING UP AN M&E SYSTEM FOR CAD

What is needed for an M&E system for CAD?

A data register is needed to capture chest X-ray data and link to follow-up testing, notification and treatment enrollment.

A unique, national patient identifier is ideal for this link, but these are not always available.

Question:

What alternatives exist the absence of a unique patient indicator?

Linking to National M&E systems

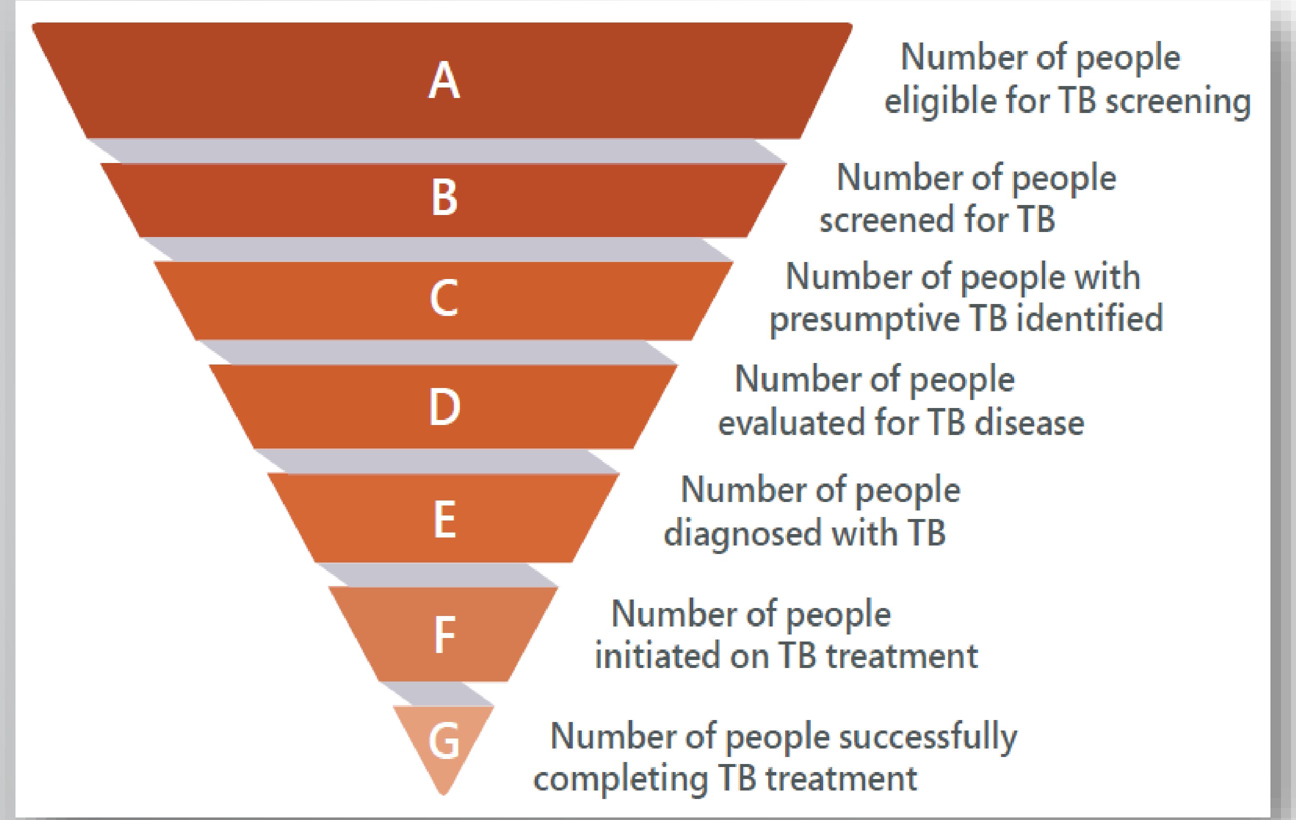
Chest X-ray data register must link to national notification systems, specimen referral systems, diagnostic testing, etc.

CAD software should be calibrated to send outputs directly to national M&E systems*

- Is software linked in real-time (through SMS, or internet) to system?
- If offline running is possible, how is data uploaded when connection is restored?

SELECTING INDICATORS FOR A CHEST X-RAY AND CAD SCREENING PROGRAM

Cascade of Care – Indicators



Consider the cascade of care for tuberculosis:

What are the standard indicators used in your context?

Calculations from the indicators for each screened group:

- ***Acceptability***: the proportion of people screened for TB among those eligible;
- ***Screened positive:*** the proportion of people screened by CAD with a score above the selected threshold score;
- ***Testing retention:*** the proportion of people tested or evaluated for TB with a confirmatory diagnostic test among patients presumed to have TB;
- ***NNS and number needed to treat:*** the proportion of people diagnosed with TB among those screened and tested;
- ***Linkage to care:*** the proportion initiating TB treatment among those diagnosed; and
- ***Treatment success:*** the proportion of people who successfully complete TB treatment among those who initiated treatment.

What indicators are already in use?

What indicators are captured in current electronic monitoring systems?

What indicators will you need to add?

Selecting indicators for a screening program

PROCESS ORIENTED

Enable you to evaluate the performance of the screening solution (e.g., CAD-enabled X-ray) during roll-out and maintenance

Adaptable over time (without losing integrity of information)

IMPACT ORIENTED

Evaluate the impact of the solution on case finding and other health outcomes, as well as program targets

Proposed indicators

for Monitoring the Performance of CAD Technology

1. Positivity rate of chest X-ray and CAD for TB diagnosis at implementation sites
2. Percentage of people screened positive for TB with X-ray and CAD that were referred for confirmatory testing
3. Positivity rate of confirmatory test for people screened positive for TB with X-ray and CAD
4. Percentage of people screened positive for TB with X-ray and CAD and received clinical diagnosis

TEAM EXERCISE:

PRACTICALITIES OF INTRODUCTION OF CAD-ENABLED X-RAY

Where to place CAD in the TB screen algorithm

CAD can be used **with** trained human readers as a decision support tool or **in place of** trained human readers.

Alongside human readers

CAD can work **with** human readers:

- → Helping radiologists to optimize their workflow
- → Alerting human readers to abnormal images requiring prioritization
- → Providing reporting assistance
- → Providing quality control
- → Performing pre-reading assistance

In place of human readers

The WHO recommends CAD to **replace** human readers in two broad situations in individuals aged 15 and above:

Screening: CAD can be a valuable tool for screening asymptomatic individuals without significant risk factors (e.g., active case finding).

Triage: CAD can be useful in identifying TB in individuals with TB symptoms, risk markers, or other positive test results (e.g., in healthcare facilities).

The CAD software used must be to the same standard as those evaluated in by the WHO Guidelines Development Group.

In either situation, there is insufficient evidence to support the use of CAD with CXR alone for TB diagnosis

Where to place CAD in the TB screen algorithm

There are a number of advantages to either technique

Alongside human readers

The entire output of CAD, or parts of the output, may be used to inform triage decisions by trained human readers alongside clinical information.

Advantages:

- CAD can be used to supplement decision making, potentially improving upon human reader performance.
- While human readers’ judgement can be used:
  - where a CAD reading is not conclusive/near the threshold score.
  - in populations where CAD is not approved, e.g., in children < 15 years.
  - alongside CAD for reading X-ray that show non-TB abnormality.

In place of human readers

The CAD output may be used by trained non-radiologist personnel to decide the triage outcome. A threshold score is set and everyone assigned a CAD score higher than this receives confirmatory diagnostic testing.

Advantages:

- Increased access to chest X-ray where there is a scarcity of trained human readers or no human readers.
- May be used to rapidly triage people by non-radiological personnel in high throughput settings.
- CAD does not become exhausted when reading large quantities of images.
- No intra- and inter-reader variability.

Review National Screening Algorithm

ASK YOURSELF…

1. What changes would be needed to adopt CAD-enabled X-ray?
2. How will you track CAD-enabled X-ray outputs and link them to confirmatory testing?
3. What screening threshold would you use?
4. What indicators will you use?
5. What adaptations to your current system would be needed to capture these indicators?

ASK YOURSELF...

A. Will CAD-enabled X-ray be used in active and / or passive case finding strategies

   1. Does the strategy impact the implementation?

B. How will you inform stakeholders about the opportunities from and availability of CAD-enabled X-ray?

C. What do clinicians need to trust the outputs?

CLOSURE

- Review exercise
- Team presentations
- Next steps
- Installation plans
- Monitoring
- Ongoing support

Thank you

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