RESEARCH PROTOCOL

EVALUATING THE PERFORMANCE OF COMPUTER AIDED DETECTION (CAD) SOFTWARE IMPLEMENTATION IN TRIAGING CHEST X-RAY IMAGES IN TB SCREENING PROGRAMME IN UKRAINE

Version 2.1 from March 20, 2024

Acronyms

AI	Artificial Intelligence
CAD	Computer Aided Detection
CXR	Chest X-ray
HCF	Health Care Facility
MOH	Ministry of Health of Ukraine
NGO	Non-governmental Organization
PHC	Public Health Center of the Ministry of Health of Ukraine
Se	Sensitivity
Sp	Specificity
TB	Tuberculosis
TP	True positive
TN	True negative
WHO	World Health Organization

1.1. Background

Combating tuberculosis is a matter of the country's national security. This challenge has become especially critical in the context of russia's military aggression against Ukraine. Constant stress, unsatisfactory living conditions, and poor nutrition in the settings of hostilities or occupation can lead to exacerbation of various diseases, including tuberculosis.

A crucial component of combating tuberculosis is timely detection and diagnosis of this disease and was included as a core part of the WHO END TB strategy. The WHO guidelines note that screening in high-burden settings should be conducted using the most sensitive and specific screening algorithm possible; in this regard, X-ray examination of the chest cavity organs is highly sensitive, compared to other methods, such as symptom screening [1].

The Public Health Center of the Ministry of Health of Ukraine (PHC) is working intensively to implement innovative methods and technologies for TB diagnosis in Ukraine, which allows to reduce the burden on physicians under the conditions of personnel shortage and increase the quality of diagnostics.

One of these methods is the use of artificial intelligence (AI) technologies for medical diagnostics; AI-powered deep learning neural networks are increasingly being used to analyze medical images, such as chest x-rays (CXR). Such technologies provide an opportunity to vastly increase image reading capacity in a variety of contexts. including to identify TB-related abnormalities from CXRs (refs). Possessing the ability to process huge amounts of data simultaneously, they can quickly point out differences between records of healthy people and those who are sick. Therefore, their use is especially expedient in the conditions of scarce human resources when access to qualified personnel may be limited [1].

Due to the war on the territory of Ukraine, the health care system operates under conditions of a humanitarian crisis and the population has limited access to health care. There is an outflow of personnel from health care facilities leaving the country. Logistical problems and damaged infrastructure additionally contribute to the decline in TB detection rates. In this context, up-to-date technologies that allow physicians to be more efficient in their work can become a real solution to the problem.

Innovative technologies can help increase the rate of TB detection and diagnosis, which in turn can save human lives and reduce further spread of the disease, bringing the country closer to the ambitious goal of ending tuberculosis by 2035.

1.2. Country context

TB is an infection that is the leading cause of a disease and one of the main causes of death worldwide. Before the coronavirus (COVID-19) pandemic, tuberculosis killed more people worldwide than any other pathogen. The COVID-19 pandemic disrupted the years of progress in reducing the global burden of TB, resulting in a significant drop in detecting new TB cases in 2020 – 5.8 million vs. 7.1 million in 2019 [2]. Chest radiography (CXR) plays a key role in the detection of pulmonary tuberculosis (TB) as a screening tool, as outlined above [1].

TB has been a serious health challenge in Ukraine since the 1990s. However, according to WHO estimated data, the incidence of TB in Ukraine has significantly decreased over the previous 15 years: over 127 cases per 100,000 people in 2004-2005 to up to 73 cases

per 100,000 people in 2020 (decreased by 43%). Within the same period, TB mortality (according to the WHO estimated data) (excluding TB/HIV co-infection) decreased by 64% (25 cases per 100,000 people to 9 cases per 100,000 people).

Despite the positive global epidemiological trend, Ukraine belongs to the group of 18 high-priority countries of the WHO European Region due to the high TB burden [3]. According to the latest 2020 WHO estimated data, Ukraine ranks fifth among 53 countries in the WHO European Region in terms of TB incidence (new cases and recurrence) with the rate of 57.7.

According to routine surveillance data, 18,241 cases of active TB, including recurring cases, were reported in Ukraine in 2021. The incidence rate is 44.0 per 100,000 people, which is 2.2% higher than in 2021. Most experts explain this by the recovery of the medical system after the pandemic of COVID-19 caused by SARS-CoV-2 coronavirus.

Over the previous six years, the incidence rate has decreased by 40% (70.5 in 2015 to 37.5 per 100,000 people in 2021), and there has been a decreased incidence rate of approximately 4% annually during 2013-2019, and by 29.8% in 2020.

Ukraine was recognized as “best practice in Eastern Europe” in its TB control efforts by Hans Henri P. Kluge, WHO Regional Director for Europe. This was due to TB incidence falling by almost half over the past 15 years, because of the investment in modern diagnostic technologies to rapidly identify TB infection, and effective treatment regimens for multidrug-resistant tuberculosis.

Destruction of health care facilities, supply chain breakdown for medicines and medical supplies, and mass displacement because of the war threatens to overturn the progress which the country has made in TB detection and treatment. Destruction of health infrastructure limits access to tuberculosis and public health services, including provision of essential TB services. This results in significant delays in TB diagnosis, initiation of preventive treatment, and treatment of active tuberculosis.

Table 1: Incidence of active tuberculosis, including relapses, among the entire population of Ukraine for the first quarter of 2022 compared to the same period of 2021

No	Administrative territories	Total				± from 2021 to 2022, %
		Absolute numbers, N		Per 100 thousand population		
		2021	2022	2021	2022	
1	The Autonomous Republic of Crimea	-	-	-	-	-
2	Vinnytsia	111	135	7,2	8,9	+23,6
3	Volyn	167	129	16,2	12,6	-22,2
4	Dnipropetrovsk	491	1054	15,5	33,6	+200,0
5	Donetsk*	240	149	12,7	7,9	-37,8
6	Zhytomyr	142	135	11,7	11,3	-3,4
7	Zakarpattia	165	270	13,2	21,6	+160,0
8	Zaporizhzhia	188	140	11,1	8,4	-24,3

9	Ivano-Frankivsk	106	102	7,8	7,5	-3,8
10	Kyiv	251	206	14,1	11,6	-17,7
11	Kirovohrad	129	160	13,9	17,5	+25,9
12	Luhansk*	74	45	10,9	6,7	-38,5
13	Lviv	340	339	13,6	13,7	+0,7
14	Mykolaiv	150	100	13,4	9,0	-32,8
15	Odesa	516	488	21,8	20,7	-5,0
16	Poltava	106	123	7,7	9,0	+16,9
17	Rivne	130	139	11,3	12,1	+7,1
18	Sumy	103	98	9,7	9,3	-4,1
19	Ternopil	54	83	5,2	8,1	+150,0
20	Kharkiv	248	135	9,4	5,2	-44,7
21	Kherson	136	119	13,2	11,7	-11,4
22	Khmelnytskyi	97	100	7,8	8,1	+3,8
23	Cherkasy	113	119	9,5	10,1	+6,3
24	Chernivtsi	51	53	5,7	5,9	+3,5
25	Chernihiv	116	116	11,8	12,0	+1,7
26	Kyiv city	180	159	6,2	5,4	-12,9
27	Sevastopol city	-	-	-	-	-
Ukraine		**4404**	**4696**	**10,6**	**11,3**	+6,6

* government-controlled areas of these regions

Radiological examination of the chest cavity (chest X-ray or CXR) is used as a screening tool for the detection of tuberculosis (TB), both among individuals at the highest risk of developing TB, including medical risk groups and communities with high TB prevalence, and for persons with distinctive complaints/symptoms that may indicate tuberculosis or individuals with a positive questionnaire result (active and passive tuberculosis detection respectively).

TB detection includes the following actions of health care professionals: formation of risk groups for the development of TB in order to organize timely detection of TB and/or diagnosis and treatment of latent tuberculosis infection (prophylactic TB treatment); systematic identification of persons with symptoms suggestive of TB in a pre-defined target group using CXRs, rapid tests or other screening procedures for TB detection (systematic screening or active TB detection). Active detection of TB is initiated by a medical worker of a healthcare facility (hereinafter – HCF) by forming field mobile groups with the use of a mobile fluoroscope; selection of patients who may have TB disease when they turn for medical help to HCFs for any reasons for further examination for the purpose of TB detection (passive TB detection). In the field of public health, systematic TB screening contributes to the improvement of the TB epidemiological situation by increasing the detection rate of active TB cases, reducing the prevalence of TB, decreasing the transmission of infection, and preventing new cases and relapses of the disease.

Chest radiography (CXR) plays a key role in the screening and triage of pulmonary tuberculosis (TB) and can guide the effective use of diagnostic testing to improve case detection and cost-efficiency (ref). Reasons that CXR is recommended as a TB screening tool include:

- Highly sensitive – can detect disease early, prior to onset of symptoms
- Can improve the efficiency of screening algorithms as a secondary screen
- Can improve the sensitivity of routine screening among people living with HIV
- Can help rule out TB prior to initiating TPT.

Computer-aided detection (CAD) products use artificial intelligence (AI) to analyze CXR images for the presence of abnormalities suggestive of pulmonary TB, producing an abnormality score that can be used to determine the need for follow-on diagnostic testing for TB relative to a selected threshold. CAD technology can improve the feasibility and performance of CXR for screening and triage for TB disease and may benefit TB programs by enhancing the capacity for TB screening. Such technology can replace or augment human expert interpretation of plain CXR when screening for TB and can avoid inter-reader variability and reduce delays in reading radiographs when skilled personnel are scarce.

At present, a computer-aided detection (CAD) system for diagnosing tuberculosis has not been introduced in Ukraine. However, the National TB Program, the Public Health Center, the Ministry of Health of Ukraine, are interested in introducing innovative technologies in order to improve the rates of TB detection. Therefore, Ukraine is planning to introduce CAD throughout the country, following a pilot in the regions of Lviv and Sumy oblast. To support this implementation, Public Health Center, as the main grant recipient, has been allocated a budget within the current Global Fund grant application for procurement and technical assistance to implement CAD in 2022.

2. Study objectives

Overarching goal: to determine the optimal models for CAD implementation in pilot regions of Ukraine.

Specific aims:

1. To assess current workload for radiologists in Lviv and Sumy oblasts (number of patients assessed per day) and identify gaps in TB screening;
2. To assess attitudes towards and acceptability of AI solutions among radiologists and HCF administrators in Lviv and Sumy oblast, and determine potential models for CAD implementation (e.g., mass screening or triage, replacement or combination);
3. To determine appropriate CAD thresholds for priority subpopulations and implementation models and potential benefits (in terms of predictive value) of combination approaches;
4. To estimate costs of prospective models of CAD implementation and compare to existing options.

2.1. Aim 1 (assessment of workload): Healthcare facilities survey

A facility-level questionnaire will be used to collect data on the specific characteristics of facilities to analyze workload for radiologists in Lviv and Sumy oblasts and potential institutional gaps in TB screening.

The questionnaire will include questions related to:

a) performance of pulmonary TB screening: number of radiologists per facility; number of hours the radiologists work per day / week; number of assessments per day / week by radiologist; time a radiologist needs to read, interpret and generate the report per 1 assessment/ image; populations not sufficiently screened; other.
b) technical infrastructure of the facility: availability of internet bandwidth (online vs offline mode of work); availability of reliable power supplies; availability of printers for printing out images.

The research team will contact the heads of the study sites with a request to fill out the questionnaire. The questionnaire will be filled out using the self-completion method. After the site managers have completed the questionnaire, it will be sent to the research team by e-mail.

Sources of information for this component: statistical forms, facility survey, staff registries.

Data analysis. Descriptive statistics (including visualizations) will be utilized for the data analysis. Indicators will include: number of radiologists, workload (n or images per day, time to read one image), existing number of assessments, recommended/optimal number of assessments, populations not sufficiently screened).

Ethical considerations. Data collected will not be identifiable to any individuals. Obtained data will be stored on the PHC secured server during 5 years after the completion of the study, and then destroyed.

2.2. Aim 2 (assessment of attitudes): Qualitative research

This component aims to assess attitudes and acceptability of CAD among clinicians, including radiologists and phthysiatrists, and HCF administrators and their views on the different potential models for CAD implementation (i.e., to augment or replace radiologists). It aims to identify the barriers and enablers to the roll-out of this technology. Specific topics it will cover include:

- health facility pathway of screening for pulmonary TB;
- perceptions of patients' pathway when screening for pulmonary TB;
- clinician and administrator attitudes towards CAD technology (in professional community), potential benefits and disadvantages;
- clinician views on potential scenarios of CAD implementation.

Study design. This component will use semi-structured in-depth interviews as a method of data collection, with each interview lasting to 60 minutes. Semi-structured interviews will be conducted with a range of participants including: radiologist, phthisiologists, healthcare facility administrative personnel and national experts, for example: NTP manager / MoH official / WHO official / legal support department (MoH or PHC), PATH. This range of participants will ensure that the views of decision makers and end-users of the equipment, both of whom influence the overall feasibility and acceptability of roll-out, are explored.

Interviews with radiologists, phthisiologists, healthcare facility administrative personnel are meant to describe their attitude and identify potential barriers and facilitators of the

intervention from the perspective of healthcare workers, while national experts will provide insight into decision-making and previous experiences rolling out CAD.

Interview topic lists will be developed to guide the interviews. To develop these interview guides before the fieldwork starts, the research team will first map all possible topics based on existing knowledge of pulmonary TB screening with an accent on a chest radiography and develop questions to explore the acceptability of using AI in TB detection.

In case potential respondents accept the invitation, they will be given a choice of convenient date and time for the interview in order not to disrupt their work and service provision.

Population and inclusion criteria

17 in-depth interviews will be conducted with healthcare workers and national experts. We will recruit individuals with at least 1-year experience in their current role. Purposive sampling will be used to select the respondents best placed to give information-rich and relevant accounts to fulfill the study's objectives. In-depth interviews will be conducted prior to CAD implementation in Ukraine to assess attitudes and acceptance.

Table 2: Sampling for the qualitative study

Population	Functions	Inclusion criteria	Lviv site	Sumy site	Total
Healthcare workers	Radiologist	In the position at the facility for > 1 year	2	2	**4**
	Phthisiologist	In the position at the facility for > 1 year	2	2	**4**
	Clinic's administrator	In the position in the facility for > 1 year	2	2	**4**
National experts	NTP manager / MoH official / WHO official / legal support department (MoH or PHC), PATH	Work experience in the position for > 1 year	4		
Total			6	6	**16**

Recruitment: qualitative research

Prior to initiating data collection, the study team will conduct a meeting with the research sites, during which the study team will brief the Medical Director on the study purpose, study procedures, and intended roles of personnel in conjunction with the study. The Medical Director will inform the medical personnel about the study and his/her support for study activities before recruitment of health workers. The Medical Director will emphasize the voluntary nature of participation.

Medical personnel: study team will work with the Medical Director at each study site to identify a list of radiologists, phthysiatrists and clinic administrators, involved into the screening for pulmonary TB. During a staff meeting, the Medical Director will share a brief overview of the

study covering talking points identified in attached documents on recruitment procedures. A study coordinator will be present during the staff meeting to answer questions and will share a participant information sheet with further information about the study and an email address to enrol in the study and/or seek further information. Study personnel will ensure that participants meet the eligibility criteria of being staff members acting in their position for at least one year.

Key Stakeholders: the national study team will map stakeholders experienced or involved in the implementation of CAD. It is expected that to be representatives of the Ministry of Health, members National Tuberculosis Program, members of partnering organizations / donors.

The National Tuberculosis Program will issue and distribute among potential key informants a letter describing the goal, objectives of the research; the need to count on her/his participation as a key informant in order to obtain information; the benefits and risks that may derive of her/his participation; the safety, privacy and confidentiality measures in place; Voluntary nature of participation in the interviews; name, email and phone number of the study coordinator. If ready to take part in the interviews key informants will be asked to voluntarily contact Study Coordinator and agree on convenient time of the interview. The respondent will be allowed to select a convenient date and time for their interview to avoid potential disruptions to their work. The interviews will be conducted in a face-to-face manner by trained study staff, in a private location within the study site, other location identified by participant or remotely via Zoom or other VoIP applications (Skype, WhatsApp, Zoom etc.) according to the respondent's preference. The interview will last for about one hour. Turning on the video during the call will be optional. With participant consent, the study team will record notes and audio recordings during individual interviews within this study. Basic socio-demographic information will be collected about the participants, e.g. age, gender, position, years of experience in position. This will be for the purpose of transcribing the interviews into an MS Word format, after which the audio will be deleted.

Data analysis: qualitative research

The in-depth interviews will be digitally recorded and then transcribed verbatim.

For the qualitative data, thematic analysis following the approach outlined by Braun and Clarke (2006), will be undertaken to generate themes on the acceptability and use of the CAD among respondents. As per the first step, manual transcription and repeated readings of the transcripts among the research team will allow for data familiarization. A sample of transcripts will then be reviewed and coded independently by members of the research team to generate initial codes, identifying meaningful patterns in the data from ideas, views, opinions, perceptions, and beliefs of respondents. Codes will be both deductive based on the conceptual framework, topic guide and objectives, and inductive based on what comes up through the interviews. The research team will then meet to discuss identified codes and patterns and resolving any points of disagreement and finalize themes. Microsoft Word and Excel software will be used for qualitative data analysis.

Analysis of the qualitative data will mainly be descriptive.

Ethical considerations: qualitative research

Informed consent will be sought from each participant verbally before commencing the interviews. A participant information sheet will be provided to each potential participant, outlining the purpose of the study, how data will be handled, and confidentiality procedures. When any potential respondent is contacted, the informed consent and all the following will be explained to her/him: the goals and objectives of the research; the need to count on her/his participation in order to obtain meaningful information to meet the research goals; the benefits and risks that may derive of her/his participation; the safety, privacy and confidentiality measures; voluntary nature of participation in the interviews. Participants will be given the option to cut short the interview or withdraw from the process at any time without giving a reason, at no cost to them.

Information obtained via the individual interviews will be audio-recorded. This will be for the purpose of transcribing the interview to a MS Word file, after which the audio will be deleted. The transcripts will be de-personalized and coded (region, city, gender: 1 for male, 2 for female, function/position in the healthcare facility), with any identifying information retracted to ensure confidentiality. Only the research group members will have access to this information. All supporting notes and qualitative information describing, and interpreting text and other material will be stored as Word files.

No compensation is foreseen for national experts and healthcare workers.

2.3. Aim 3: CAD calibration

CAD calibration objective

The main goal of the calibration study is to determine the local calibration of CAD software thresholds and other parameters for pulmonary TB detection in Lviv oblast of Ukraine.

The purpose of the CAD calibration component is to use the existing repository of CXR images (see below “Data collection and management”) to determine the most appropriate thresholds for the selected CAD product in the local context and use case, to facilitate future implementation of CAD at the community level.

CAD calibration design

Retrospective, cross-sectional study using the existing repository of CXR images.

This study will adopt a retrospective cross-sectional design conducted under standard programmatic settings among individuals presenting for TB screening / participating in community-based active case finding activities. Existing data will be used to calculate sensitivity, specificity, false positive rate, false negative rate, positive predictive value, negative predictive value, area under the receiver operating curve (AUROC) (Table 3).

Table 3: Key outcome definitions

Outcome	Definition
Sensitivity (Se)	The proportion of TB cases correctly identified as positive (TP), calculated as the number of correctly diagnosed TB cases divided by the total number of true TB cases
Specificity (Sp)	The proportion of non-TB cases correctly classified as negative (TN), calculated as the number of correctly diagnosed non-TB cases divided by the total number of true non-TB cases
False positive (FP)	The number of non-TB cases incorrectly classified as a TB case
False negative (FN)	The number of TB cases incorrectly classified as a non-TB case
True positive (TP)	The number of TB cases correctly classified as a TB case
True negative (TN)	The number of non-TB cases correctly classified as a non-TB case
Positive predictive value (PPV)	PPV represents the probability that a positive test result represents a true positive, calculated as the number of correctly diagnosed TB cases divided by the total number of TB positive diagnoses
Negative predictive value (NPV)	NPV is used to describe the performance of a test and represents the probability that a negative test result represents a true negative, calculated as the number of correctly diagnosed non-TB cases divided by the total number of TB negative diagnoses

TB diagnosis reference standard for CAD calibration

In the available data set, bacteriological (nucleic acid amplification test for rapid TB diagnosis, which is based on sputum study (GeneXpert)) results are available only for CXR images graded by a specialist as "possible TB case". For this subsample of images, bacteriological results will be used as a reference standard. For the images that were graded by the specialists as ‘no TB signs’, two analytic approaches will be used. First, all these images will be treated as true TB negatives. Second, we will query the TB treatment registry to identify individuals who were diagnosed with TB later. These cases will be treated as false negatives, and those who will not be found in the registry as true negatives.

Outcomes of interest

The outcomes of interest are related to the diagnostic performance of CAD compared to selected reference standards (see above). The predicative probabilities of TB detection by CAD at various thresholds will be used to estimate cost and programmatic implications, in particular the number of TB cases missed or misdiagnosed and additional costs of follow up testing incurred or saved at different thresholds. This will be used to select the most appropriate threshold to meet programmatic aims.

Data sources

Existing repository of digital images from Lviv site of Ukraine, CAD scoring results (to be done externally by a partner institution), bacteriological results from TB registry (only available for X-ray positive), TB treatment registry (TB Manager).

For reference: for the first half of 2022, the study site in Lviv has about 3156 images of chest X-ray examinations, of which the number of X-rays with a probable diagnosis of pulmonary tuberculosis is 1140, of which the number of bacteriologically positive images is 57.

Data collection and management

3156 TB screening results of individuals aged 10 and older with received CXR image with specialist reading result, the results of existing bacteriological tests (in case of specialist TB-positive CXR result) and other patient information (including age, sex, and risk factors) will be collected by site in Lviv of Ukraine.

According to the specialist reading result all patients will be divided into 2 groups and will be coded by the study team according to the conclusion of the specialist (radiologist): 0 = non-TB case, and 1 = TB case.

According to TB confirmation by bacteriological testing all patients will be divided into 2 groups and will be coded by the study team: 0 = non-TB case, and 1 = TB case.

All available patients' data, including CXR images and results of bacteriological tests (if available), will be de-personalized and assigned a unique numeric identifier by site and subsequently sent to the study team.

De-personalized CXR images in DICOM format will be uploaded to the secured WHO server and then will be downloaded and analyzed using the CAD4TB vendor software, Delft Imaging. If possible, additional CAD software will also be used for calibration. Each of the CXR images will be assigned a CAD-score from 0 to 100 according to the probability of TB-positive CXR. Analysis results with CAD-scores will be sent back to the study team in the CSV file.

CAD-scores will be entered into a standardized CSV spreadsheet and uploaded to the online CAD for TB detection calibration tool (https://worldhealthorg.shinyapps.io/CAD4TB_validity) developed by WHO to facilitate the analysis of data needed for CAD calibration studies. This data along with additional information (including age, sex and TB-positive risk factors) obtained from site will be used to perform data analysis.

Table 4 describes the main variables that will be used for data analysis.

Table 4: Data collection variables for CAD calibration study

Variable name	Description	Data type	Codes/ranges
Patient ID	Unique number used to identify participants	Numeric	Approx. 9000 codes
CAD_score	Numerical output score produced by a CAD reading	Numeric	0 – 100
TB_conf	Outcome of TB confirmation by bacteriological testing	Numeric	0 = non-TB case 1 = TB case
TB_spec	Outcome of TB confirmation by specialist	Numeric	0 = non-TB case 1 = TB case
Age_gp*	Classification of patient aged >15 years and over based on age groups	Numeric	0= Aged between 15 and 55 years 1 = Aged 55 and above
Previous_tb*	Indicates previous diagnosis of TB	Numeric	0 = no 1 = yes 2 = unknown/not disclosed
HIV *	Indicates HIV positivity in patient	Numeric	0 = no 1 = yes 2 = unknown/not disclosed
DM *	Indicates diabetes mellitus in patient	Numeric	0 = no 1 = yes 2 = unknown/not disclosed
Smoke *	Indicates smoking status of patient at time of contact	Numeric	0 = Never smoke (i.e., patient does not smoke and has no history of smoking) 1 = Current smoker (i.e., patient currently smokes) 2 = Past smoker (i.e., patient has history of smoking but does not currently smoke)

* optional indicator

Data analysis

Will be conducted using the online CAD for TB detection calibration tool. The analysis will be based on a dichotomous classification of each participant as binary interpretation of CAD score (abnormal/normal) at various CAD thresholds (Figure 1) in order to assess the diagnostic performance of CAD (see above) against a TB or non-TB case. Thresholds of suppliers' software will be used to determine abnormal CXRs after the CAD-solution will be chosen.

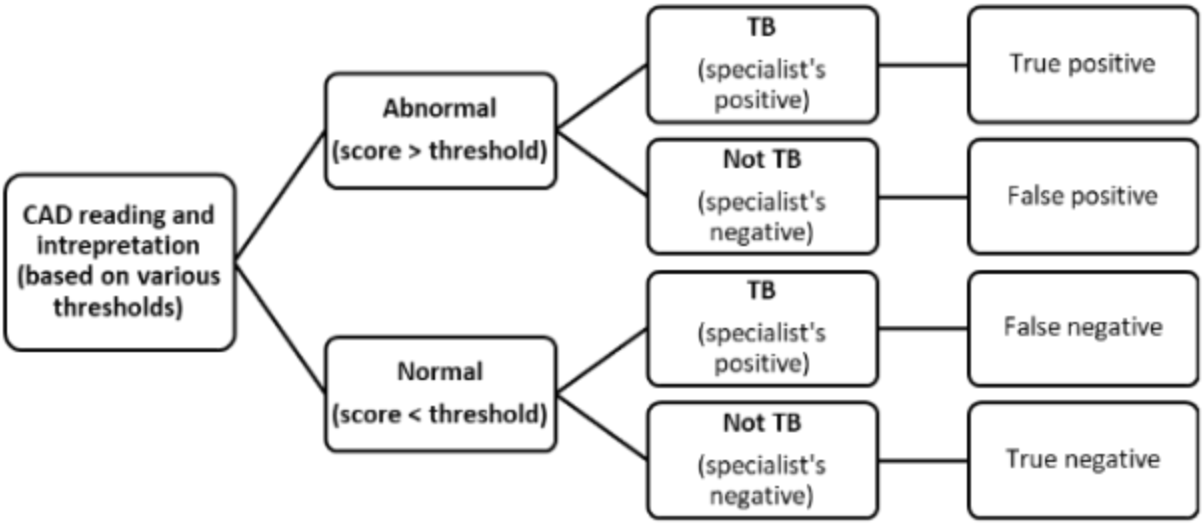

Figure 1: Comparison of CAD reading with specialist reading results

Protection of patient's data and confidentiality

No personally-identifying information will be collected during the study. De-identified patient data will be recorded against unique patient identifiers, which will be linked back to a separate, master list. All data collection electronic records will be securely protected by a password-protected file on a secure computer on site and will be accessible only to authorized people involved in the study.

All identifiers will be deleted at the level of the Lviv site; a de-identified database with unique numeric identifiers will be transferred to the study team. Study team will use a unique numeric identifiers only.

All study team members involved with collecting, handling, and analyzing patients' data will be trained on procedures to protect data confidentiality and will read and sign a "Confidentiality Form" (Annex 3). Only members of the project team who have completed the data training and signed the "Confidentiality Form" will have access to data.

2.4. Aim 4: CAD implementation cost assessment

The aim of this component is to define the cost of a single reading with CAD.

We will calculate the cost per 1 reading and a cost per 1 pulmonary TB case detected.

As the cost may vary in different sites and settings, for our calculation we will use the information available for the Lviv study site (for more details of site description and population, please, see "Study area" chapter).

The objective of the analysis will be to understand what kind of additional cost will using of CAD alongside reading of CXR assessed by radiologist, as well as identify any cost savings / efficiencies.

We expect that introducing CAD into routine pulmonary TB detection will be accompanied by increases in training costs, equipment cost, maintenance and cost per each assessed by CAD CXR.

The cost of screening using a CAD will be assessed based on the next elements:

1. *The cost of purchasing and upgrading CAD equipment:* will be provided by the NTP program based on the available arrangement made prior to setting up CAD in Lviv site.
2. *The maintenance cost of the equipment:* the maintenance cost of the equipment will depend on the type of annual maintenance contract. The information will be provided by the site based on available contracts.
3. *The cost of CAD software usage:* the cost will be calculated dividing the cost of average expected number of cases read per year multiplied by the cost of 1 CXR analysis.
4. *The cost of training the personnel will be calculated based on the:*
    - amount of days of training;
    - fee and travel expenses to the mentor;
    - possible cost of retraining;
    - fee for uploading training images to CAD.

The cost will be calculated dividing the cost of training a of a radiologist by the average expected number of cases read each year.

The cost per 1 CAD reading will be calculated as the sum of purchasing and upgrading equipment, maintenance cost, cost of software usage and cost of training the personnel divided by the average expected number of cases read each year.

The cost per 1 detected pulmonary TB case by CAD will be calculated as the sum of purchasing and upgrading equipment, maintenance cost, cost of software usage and cost of training the personnel divided by the average expected number of bacteriologically confirmed cases of pulmonary TB per year.

Data sources: program (grant) budget for CAD procurement, training, technical support, etc., program budgets for staff, facility costs.

Indicators for comparison: cost per image assessed, cost per case detected.

3. Study area

Lviv oblast

Lviv oblast is one of the leaders in the fight against tuberculosis in Ukraine. For many years, innovations and new approaches have been developed by the example of the Lviv region for further implementation of systemic solutions and policies at the level of the national program to combat tuberculosis. Currently, Lviv oblast is the region that has sheltered the largest number of internally displaced persons and individuals who require radiological examination as a risk group for the development of TB.

Components 1, 2 and 3 will be conducted in the Lviv region.

Lviv oblast: Site description

Equipment

- There are 2 digital X-ray machines in the X-ray department. Pictures are archived in the devices. The software and hardware complex of the X-ray information system (RIS) is expected to be installed.
- Available Internet speed at the facility is 200 mb/s.

Facility context

- For the first half of 2022, there are about 3156 images of chest X-ray examinations;
- The number of chest X-rays with a probable diagnosis of pulmonary TB is 1140;
- The number of bacteriologically positive images for the first half of 2022 is 57;
- The facility has 54 phthysiatrists;
- The facility has 7 radiologists;
- The number of working hours of a phthysiatrist per day/week – 8 hours/40 hours;
- The number of working hours of a radiologist per day/week – 6 hours/30 hours;
- The number of images read by a phthysiatrist – 25 per day/125 per week;
- The number of images read by a radiologist – 20 per day/100 per week;
- Time required for a phthysiatrist and radiologist to read, interpret and create a report for 1 image is for 15 minutes.

Sumy oblast

In Sumy oblast, heavy fighting was observed for a long time and most of the territories were occupied, which caused a severe humanitarian crisis: During the fighting, residents of settlements were forced to stay in shelters, a significant number of which were overcrowded and poorly ventilated. Leaving the war zones, particularly at the beginning of the invasion, was associated with being inside station buildings, buses, trains and temporary shelters, which were also overcrowded and poorly ventilated. A significant number of patients with tuberculosis were not able to continue treatment due to difficulties in visiting a health care facility, changing their place of stay or restrictions in the work of the TB service. Interruption of treatment in these patients could lead to progression of the disease and they became a source of the TB pathogen for other people. The infrastructure in the region has been destroyed, many specialists have migrated. The issue of rapid and high-quality diagnosis of TB has become urgent in oblast, thus the utilization of artificial intelligence algorithms will be helpful for that.

In addition, oblast has sufficient organizational potential and focus on improving the quality of medical services.

Components 1 and 2 will be conducted in the Sumy region.

Sumy oblast: Site description

Equipment

- The number of digital x-ray machines is 1. All pictures are digital, *.dcm format. All pictures contain personal data, so if the examinee had tuberculosis, the results of the bacteriological examination should be searched in the institution's register.
- X-ray radiographic unit “12f9 Ukraine” X-ray tube TOSHIBA E7239X.
- Computer characteristics: AMD A8-7600 processor, RAM-4GB, hard disk-1TB, OS-Windows7, X-ray software-Proskan 3.3.6.1.

- Internet speed 100 mb/s.

Facility context

- The number of general images at the institution is 51,000, including with various pathologies – 2,183;
- In 2022, for known reasons, the device did not work much, 2 suspected cases of tuberculosis + other pathology;
- The facility has 17 phthysiatrists;
- The facility has 2 radiologists;
- The number of working hours of a phthysiatrist per day/week – 7,42 hours/37,1 hours;
- The number of working hours of a radiologist per day/week – 6 hours/30 hours;
- The number of images read by a phthysiatrist – 7 per day/35 per week;
- The number of images read by a radiologist – 45 per day/225 per week;
- Time required for a phthysiatrist to read, interpret and create a report for 1 image is 15 minutes;
- Time required for a radiologist to read, interpret and create a report for 1 image is 9 minutes.

Database of a single HCF's device contains 51658 images which are stored on the work computer of a laboratory technician. More images are stored on the computer of a radiologist, but not the entire volume because the database needs to be cleaned from time to time due to the lack of space on the hard disk. The pictures are stored in a digital format, allowing easy access to them.

All pictures contain personal data, therefore, if an examined person had tuberculosis, the bacteriological examination can be found in the registry.

4. Ethics

The protocol was reviewed by the Ethics Commission of the State Institution "Public Health Center of the Ministry of Health of Ukraine".

Qualitative data and facility questionnaires will be collected by staff or consultants who have been trained in ethical evaluation and management and have experience in conducting research that requires harmonization of ethical principles. This will ensure the confidentiality and privacy of the human subject data that will be processed during this research.

All participants of qualitative study will undergo an informed consenting process. Oral informed consent will be obtained for all study participants. We will ask for oral consent because written consent would be the only record linking the subject and the research and the risk would be potential harm resulting from a breach of confidentiality. Participants will be given enough time to listen to the consent form during the interview. Participants will have the opportunity to ask questions. Participants will be asked to give their permission for audio recording the interviews and for their transcription.

No monetary compensation will be provided to the participants of the in-depth interviews.

Repositories of chest radiography images: we will not need to obtain consent from known, previously-diagnosed TB participants who are retrospectively identified through the study because (i) only routinely collected clinical data will be used, (ii) no additional data will be collected, (iii) all study datasets will be depersonalized, and (iv) the study presents no more than a minimal risks to human subjects.

5. Study team

Olena Nesterova – Principal Investigator, Head of Scientific Research Department PHC of Ukraine. ON will lead the protocol development. She will provide programmatic inputs in the protocol. She will contribute to the review of the methodology, key informant interview guides, reports, findings and recommendations.
o.nesterova@phc.org.ua

Yana Terleieva – Head of TB Management and Counteraction Department PHC of Ukraine. YT will consult the research team on the programmatic management of the TB screening in the country. She will contribute to the discussion of manuscripts, findings and recommendations.
i.terleieva@phc.org.ua

Kostyantyn Dumchev – Scientific Director of the Ukrainian Institute of the Public Health Policy. KD will provide methodological mentoring. He will contribute to the protocol, data analysis, report, findings and recommendations and development.
dumchev@uiphp.org.ua

Olha Gnatko – Chief Specialist of TB management and counteraction PHC of Ukraine. OG will provide the description of the country context and the need for CAD implementation in the country. She will contribute to the review of the methodology, key informant interview guides, reports, findings and recommendations.
o.gnatko@phc.org.ua

Myroslava Germanovych – Chief Scientific Research Specialist PHC of Ukraine. MG will lead the development of the qualitative research component of the protocol, including guides for healthcare workers and national experts. She will contribute to the development of the methodology. She will review and provide inputs into project reports, manuscripts, findings and recommendations.
m.germanovych@phc.org.ua

Mariia Moshura – Chief Scientific Research Specialist PHC of Ukraine. MM will lead the CAD calibration component of the research protocol. She will contribute to the development of

the protocol methodology. She will review and provide inputs into project reports, manuscripts, findings and recommendations.
m.moshura@phc.org.ua

Vladyslav Fedorchenko – Physician-and-Methodologist at the Scientific Research Department PHC of Ukraine. VF will contribute to the preparation of the protocol, engage in data analysis, participate in the formation of the report, conclusions, and recommendations.
v.fedorchenko@phc.org.ua

6. Workplan and timelines

Table 5: Timeline

Month	2022		2023									
	11	12	1	2	3	4	5	6	7	8	9	10
Preparatory phase												
Protocol finalization	X											
IRB approval	X											
Training on research procedures	X	X										
Data collection and analysis phase												
Component 1: facility survey				X	X							
Component 2: in-depth interviews									X	X		
Component 2: qualitative analysis										X	X	
Component 3: submission and CAD scoring of images									X	X		
Component 3: quantitative analysis										X	X	X
Component 4: data collection									X	X		
Component 4: cost analysis										X	X	
Analysis and dissemination												
Report and publication(s) writing										X	X	X
Dissemination meetings											X	X

References

1. World Health Organization, "Module 2: Screening WHO operational handbook on tuberculosis Systematic screening for tuberculosis disease.," 2021. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/340256/9789240022614-eng.pdf.
2. World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization; 2021. https://apps.who.int/iris/rest/bitstreams/1379788/retrieve.
3. WHO global lists of high burden countries for TB, multidrug/rifampicin-resistant TB (MDR/RR-TB) and TB/HIV, 2021–2025

Informed consent form for interviewer
Evaluating the performance of computer detection software implementation in triaging chest X-ray images in TB screening programme in Ukraine

Before the interview start, please ask the participant following questions:

1) Do you have questions that should be answered prior to the interview beginning?
2) Do you give the permission for recording of this interview?
3) Do you prefer having your camera off or on?
4) Is it ok to proceed with the interview?

Please, start the interview after the oral consent is received.

Statement from the person taking consent

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked have been answered correctly and to the best of my ability. I confirm that the participant has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Signature: _____ Date: _____

Informed consent form for respondent
Evaluating the performance of computer detection software implementation in triaging chest X-ray images in TB screening programme in Ukraine

Introduction

You are invited to participate in the research initiated by the SI "Public Health Center of the Ministry of Health of Ukraine". The following information describes the purpose of the study and what is expected of you as a participant, as well as the potential risks and benefits of participating in the study. You can ask questions before deciding to participate and at any time during the study itself.

We ask you to take part in the research as an expert familiar with the national context of pulmonary tuberculosis screening in general, and the path, drivers and barriers of chest radiography in particular.

The purpose of this form of consent is to provide you with the information you need to help you decide whether to participate in the study. Please, read the form carefully. You can ask questions about the purpose of the study, procedures, possible risks and benefits, your rights and anything related to the study that you do not understand. After answering all the questions, you can decide if you want to be part of this study. This procedure is called "informed consent". If you would like to keep a copy of this form for yourself, we will provide you with one.

Study procedures

You will be invited to take part in one in-depth interview. Overall, approximately 16 interviews will be conducted during the study. Radiologists, phthisiologists, healthcare facility administrative personnel and national experts is the profile of professionals asked to attend this interview. A professional interviewer will ask questions about your attitudes towards and acceptability of AI (artificial intelligence) solutions in TB screening and discuss potential models for CAD implementation in Ukraine.

The interview will last up to 60 minutes. With your permission, we will audio record the interview to remember what you said.

Risks and benefits

Risks: there are no foreseeable risks involved in participating in this study other than those encountered in daily life. There is a risk that you may feel uncomfortable talking about certain topics. However, we do not want this to happen. You will not have to answer any questions or discuss any topics if you are uncomfortable talking about them.

In cases of unforeseen circumstances related to hostilities (threat of missile strikes, enemy offensive, attacks on civilians and infrastructure, etc.), study personnel (interviewers) and respondents need to follow the instructions of the local military administration (such instructions are posted on the official website of governmental authorities). The most

common current threat is a missile attack, announced by air alerts; it is then necessary to proceed to the shelter of civil defense. Relevant pointers are placed everywhere in prominent places.

Benefits: there are no direct benefits for you personally associated with the study. Your participation is likely to help us learn more about how to improve TB screening in detection of pulmonary TB. You will be able to provide ideas that could help improve the quality of medical services in Ukraine.

Compensation

No compensation will be paid to you upon the end of the interview.

Confidentiality

Your participation in this interview is confidential, which means that the interviewer and researchers will not have access to your name or any other personal information. The recording of your interview will be identified with a number. An identification number will be assigned to the recording of your interview. Recordings of all interviews will be stored the password protected computers available for the research teams only. The recordings of the interviews with the healthcare workers will not be available for the management of the healthcare facility or any other staff.

Voluntary participation

Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. After you agree to participate in the study, you are still free to withdraw at any time and without giving a reason. You don't have to participate in this study.

If you are a healthcare worker invited to attend the interview your willingness or refusal to participate will not affect your role or position in the healthcare facility. The consent to participate in the study does not deprive you of any legal rights.

Contact information

If you have any questions about this study, you can contact the principal investigator Olena Nesterova by +380 44 576 41 13. If you would like to talk to someone else about the issues, comments, and questions you may have about the study, or discuss your rights as a research participant, you can contact the Ethics Commission of the SI "Public Health Center of the Ministry of Health of Ukraine" +380 44 334 57 86, e-mail: irb@phc.org.ua.

Signature of interviewer: _____ Date: _____

Confidentiality form

Evaluating the performance of computer detection software implementation in triaging chest X-ray images in TB screening programme in Ukraine

Full name	
Work place	
Role in the research	

The information obtained during this research is strictly confidential and has been provided by the research participants with the understanding that it will be kept strictly confidential. Mark each item and put your signature below it to certify that you agree to follow these rules

1. I understand that the information obtained during the research is confidential and has been provided by the research participants with the understanding that it will be kept confidential.	
2. I understand all data privacy aspects of this research and undertake to comply with them.	
3. I will not release the data to any researchers other than those working on the same project who have signed a copy of this form.	
4. I will not release datasets or information for any purpose other than that specified in the Research Protocol or to meet the requirements of applicable law.	
5. I will not share any part of the datasets with anyone who is not part of the research team.	
6. I undertake not to attempt to identify any research participants and will not attempt to re-identify the source of any information provided to me.	
7. I understand that I am required to ensure the safe storage of all data (paper forms and/or electronic databases) accessible to me.	

Date: _____