DOI: 10.1111/tmi.13658

RESEARCH ARTICLE

Pattern of abnormalities amongst chest X-rays of adults undergoing computer-assisted digital chest X-ray screening for tuberculosis in Peri-Urban Blantyre, Malawi: a cross-sectional study

Hussein H. Twabi[1,2] | **Robina Semphere**[2] | **Madalo Mukoka**[2] | **Lingstone Chiume**[1] | **Rebecca Nzawa**[1] | **Helena R. A. Feasey**[1,3] | **Trancizeo Lipenga**[2] | **Peter MacPherson**[1,3,4] | **Elizabeth L. Corbett**[1,3] | **Marriott Nliwasa**[2]

[1]Malawi–Liverpool–Wellcome Trust Clinical Research Programme, Blantyre, Malawi

[2]College of Medicine, Helse Nord TB Initiative, University of Malawi, Blantyre, Malawi

[3]London School of Hygiene and Tropical Medicine, London, UK

[4]Liverpool School of Tropical Medicine, Liverpool, UK

Correspondence
Hussein Twabi, Helse Nord Tuberculosis Initiative, Department of Pathology, College of Medicine, Private Bag 360, Chichiri, Blantyre 3, Malawi.
Email: husseintwabi@hotmail.com

Funding information
This work is supported by the SCALE trial core funding through the Wellcome Trust. Wellcome is a politically and financially independent global charitable foundation. The views expressed in this publication are those of the authors and not the funder, Wellcome Trust.

Abstract

Background: The prevalence of diseases other than tuberculosis (TB) detected during chest X-ray screening is poorly described in sub-Saharan Africa. Computer-assisted digital chest X-ray technology is available for TB screening and has the potential to be a screening tool for non-communicable diseases as well. Low- and middle-income countries are in a transition period where the burden of non-communicable diseases is increasing, but health systems are mainly focused on addressing infectious diseases.

Methods: Participants were adults undergoing computer-assisted chest X-ray screening for tuberculosis in a community-wide tuberculosis prevalence survey in Blantyre, Malawi. Adults with abnormal radiographs by field radiographer interpretation were evaluated by a physician in a community-based clinic. X-ray classifications were compared to classifications of a random sample of normal chest X-rays by radiographer interpretation. Radiographic features were classified using WHO Integrated Management for Adult Illnesses (IMAI) guidelines. All radiographs taken at the screening tent were analysed by the Qure.ai qXR v2.0 software.

Results: 5% (648/13,490) of adults who underwent chest radiography were identified to have an abnormal chest X-ray by the radiographer. 387 (59.7%) of the participants attended the X-ray clinic, and another 387 randomly sampled normal X-rays were available for comparison. Participants who were referred to the community clinic had a significantly higher HIV prevalence than those who had been identified to have a normal CXR by the field radiographer (90 [23.3%] vs. 43 [11.1%] p-value < 0.001). The commonest radiographic finding was cardiomegaly (20.7%, 95% CI 18.0–23.7). One in five (81/387) chest X-rays were misclassified by the radiographer. The overall mean Qure.ai qXR v2.0 score for all reviewed X-rays was 0.23 (SD 0.20). There was a high concordance of cardiomegaly classification between the physician and the computer-assisted software (109/118, 92.4%).

Sustainable Development Goals: Good Health and well-being

Conclusion: There is a high burden of cardiomegaly on a chest X-ray at a community level, much of which is in patients with diabetes, heart disease and high blood pressure. Cardiomegaly on chest X-ray may be a potential tool for screening for cardiovascular NCDs at the primary care level as well as in the community.

KEYWORDS
digital health, epidemiology, radiography, screening, tuberculosis

INTRODUCTION

As of 2019, tuberculosis (TB) was the single leading infectious cause of mortality in the world [1]. Globally, there were about 132 (118–146) new TB cases per 100,000 population in 2018 [1]. A considerable number of TB cases go undiagnosed [2], driving the need for alternative measures to actively identify new cases of TB in communities in the hopes of meeting the targets for the End-TB Strategy [1,3].

There is a growing interest in the automated analysis of chest X-rays (CXR) as a sensitive and inexpensive means of screening populations for tuberculosis [4]. Computer-assisted digital chest X-ray (CADXR) displays high sensitivity for the identification of features of TB but is not well calibrated for identifying non-TB X-ray abnormalities [5]. Additionally, non-TB X-ray abnormalities have not been well characterised in the sub-Saharan African setting [4].

The pattern of diseases in low- and middle-income countries is shifting from predominantly communicable diseases to the emergence of non-communicable diseases (NCDs) [6-8]. Yet, the focus still remains on mainly combatting infectious diseases, leaving an unmet need for interventions focused on NCDs [9]. NCDs account for nearly 70% of deaths worldwide, with an estimated 75% of these deaths occurring in low- and middle-income countries [10]. There is, however, a paucity of data on the true burden of non-communicable diseases in low-income countries [11].

There is a rising prevalence of NCDs identified in health facilities [12], displaying a need for community-level attention to these diseases. Malawi has a high prevalence of HIV and TB [1]. Multiple studies affirm the association of these infectious diseases with certain NCDs, especially diabetes mellitus, hypertension and chronic obstructive pulmonary disease (COPD) [13-15]. These NCDs, though a result of multiple risk factors, have a higher risk of development in people living with HIV (PLHIV) than in the general population [9,16,17]. Near universal access to HIV antiretroviral therapy (ART) is leading to an increasing number of ageing adults living with HIV allowing for the emergence of chronic sequelae, such as cardiovascular diseases, chronic lung diseases and diabetes [18-20].

We report on the activities of an urban community clinic located within a TB prevalence survey using CADXR conducted in high-density settlements in Blantyre District, Malawi. The main aims of this study were to describe the abnormalities that reflect an abnormal chest X-ray during a community-wide prevalence survey for tuberculosis that included screening using chest radiography, as well as to compare the classification of X-rays by the radiographer, physician and the Qure.ai qXR v2.0 software. Additionally, we described the prevalence of communicable and non-communicable diseases in adult community members based on syndromic diagnoses by the physician.

METHODS

Design

This was a cross-sectional study of adults (≥ 18 years) identified during a TB prevalence survey for the SCALE Trial (Registration Number: ISRCTN11400592), which investigated the effect of community-wide active door-to-door screening for tuberculosis. The prevalence survey was conducted between 26 May 2019 and 31 March 2020 in 72 clusters.

Study population

The study was implemented in the geographically defined catchment population of 315 community health workers (CHW) in the high-density and peri-urban residential areas of Blantyre City. CHW catchment areas were grouped to form 72 clusters with a population of about 4400 adult residents each (approximately 320,000 adults total). CHW catchment areas and study population were defined by a city-wide enumeration survey conducted together with the Blantyre District Health Office (DHO) in 2015 [2].

Participants of the prevalence survey were adults (18 years and older) from randomly selected households from the defined CHW catchment areas. Participants had to provide informed consent, be willing to undergo radiological screening for TB, and intend to remain resident within Blantyre City for at least the subsequent eight weeks.

Study procedures

Resident adults (≥ 18 years) were recruited at their households. After the informed consenting process, participants were screened using symptom screening (cough, fever, night sweats or weight loss) and those with a cough were asked to submit spot sputum samples. All interviewed participants were then referred to a screening tent within the community, where they had digital chest radiography and

were offered HIV testing and counselling. HIV testing was offered using OraQuick HIV-1/2 and parallel finger-prick Alere (Abbott) Determine™ HIV-1/2. A positive HIV test result was confirmed using Trinity Biotech Uni-Gold™. All those with a chest X-ray classed as abnormal by onsite radiographers were asked to submit sputum. Sputum samples were sent to the laboratory for microscopy, Xpert MTB/Rif and culture.

Participants with abnormal chest radiographs after assessment by a radiographer were given a referral card and referred to a community-based tent clinic in the same cluster for further evaluation by a physician. Radiographers were radiology technicians with diploma-level training (two years) in radiology and study-specific training on radiological features of TB. The radiographers reviewed the radiographs for any identifiable abnormality (including features not suggestive of TB). All radiographs taken at the screening tent were analysed by Qure.ai qXR v2.0 software. The field radiographers referred patients to the tent clinic independent of the Qure.ai qXR v2.0 report.

The study clinic tent was mounted the week following the departure of the screening team from the community location. The tent clinic was held on one day for each of the 72 clusters in the prevalence survey. The clinic field worker contacted the participants using cellular phone contacts to remind them to attend the clinic. Participants attending the clinic were first evaluated by a nurse who recorded vital signs including blood pressure, resting heart rate, respiratory rate and oxygen saturation using a pulse oximeter.

The physician conducted a history and a focused physical examination. Paper-based forms were used to collect clinical data at the X-ray clinic and were stored in a locked cabinet. Variables that were collected included age, sex, smoking and alcohol history, TB history, HIV status, ART history (if HIV-positive), cough, fever, night sweats, weight loss, history of any chronic non-communicable diseases and any other symptoms.

The tent-based clinic was equipped with medications that allowed the management of simple infectious and non-infectious diseases, including amoxicillin, cotrimoxazole, doxycycline, metronidazole, paracetamol, ibuprofen, magnesium trisilicate, omeprazole, prednisolone, salbutamol inhalers, hydrocortisone 1% cream and clotrimazole 1% cream. All other diagnoses that required management were referred either to a primary care facility or to a tertiary centre.

Definitions

X-ray images of participants were reviewed on a laptop computer equipped with Microdicom DICOM Viewer (version 3.3.2). Physician classifications were done independently of Qure.ai qXR v2.0 reports. X-ray features were classified using the WHO Integrated Management of Adult Illnesses (IMAI) guidelines, designed for use in primary healthcare facilities, which include guidelines for classifying chest X-rays [21]. The classifications are as follows: 'normal', 'possible TB', 'old TB', 'pleural effusion', 'pneumonia', 'cardiomegaly' and 'chronic obstructive airways disease (COAD)'.

Qure.ai qXR v2.0 (http://qure.ai/qxr/) analyses the unobscured lung fields of a posteroanterior chest X-ray for the presence of abnormalities and outputs a TB score of between 0 and 1 [22]. Convolutional neural networks were trained to identify 10 individual CXR abnormalities, which include blunting of costophrenic angles, nodules, cardiomegaly, cavitary lesions, consolidation, fibrosis, emphysema, hilar enlargement, opacities and pleural effusions.

The Qure.ai qXR v2.0 reports the TB scores and summarises the chest X-ray by the following categorisations: 'high-risk TB screening (HRTBS)', 'routine TB screening (RTBS)', 'abnormal' and 'no significant abnormality'. The Qure.ai qXR v2.0 software assigns a score of at least 0.45 for X-rays with features of TB, which include cavitating lesions, nodules, fibrosis, consolidation and pleural effusions, which may be classified as diagnoses other than active TB by the human reader. The software summarises as abnormal all features that are not suggestive of TB, along with X-ray features that do not fit within the spectrum of the classifications allowed by the software.

We used the predefined classifications for TB likelihood provided by the software report (HRTBS and RTBS). The classification of 'no significant abnormality' was transcribed as 'normal'. Cardiomegaly as a feature was recorded on its own, thus leaving the classification 'abnormal' to be used only for X-ray features that do not fit within the spectrum of the classifications allowed by the software.

Chronic obstructive airways disease on X-ray was defined as the presence of hyperexpanded hazy lungs, flattened diaphragm or increased broncho-vascular markings on chest X-ray. High blood pressure was defined as at least two readings with a systolic value of >140 mmHg and/or a diastolic value of >85 mmHg. Patients with a pre-existing diagnosis of asthma or a history and chest X-ray suggestive of lung disease due to previous TB or chronic obstructive airways disease were summarised as chronic lung diseases. Patients with a pre-existing diagnosis of diabetes were classified as having diabetes as the tent clinic was not equipped to screen for and diagnose new cases of diabetes. Patients with a history that was strongly suggestive of diabetes were classified as 'possible diabetes'. Patients with a pre-existing diagnosis of heart disease, or a history and examination strongly suggestive of a heart pathology with or without chest X-ray abnormalities were classified as 'heart disease'. All pathologies were defined syndromically based on history and examination [23,24], with support from the chest radiograph where appropriate (Table S1). Bacteriologically confirmed TB was defined as at least one positive laboratory investigation (smear microscopy, Xpert MTB/RIF or culture).

Statistical analysis

The primary study outcome was to define the prevalence of pathologies causing abnormal chest radiography at TB

screening, disaggregated into communicable and non-communicable diseases causes. The secondary outcome was to compare X-ray classifications by the radiographers, physician and Qure.ai qXR v2.0 software.

A random sample of 387 prevalence survey participants classified as normal by the radiographer was selected from the main SCALE prevalence survey database using Stata (version 14.2) (Statacorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The classification of X-rays by the physician was used as the reference as this reflects the best-case scenario in primary and secondary care facilities in Blantyre and was compared to the radiographer and the computer-aided classifications.

Statistical analyses were performed using R (version 4.0.0), 2020 (Vienna, Austria: R Foundation for Statistical Computing), and Stata. Participant distribution was described using mean and standard deviation (SD) for numerical data and proportions for categorical data. Baseline characteristics were compared between those who were identified to have an abnormal versus a normal chest X-ray by the field radiographer using Chi-square tests and Fisher's exact tests.

RESULTS

Tracing of participants

Of the 15,897 participants in the prevalence survey, 13,490 (84.9%) underwent a CXR – Figure 1. Of these 13,490, 648 (4.8%) participants were identified to have an abnormal chest X-ray by the field radiographer and were referred to the community-based X-ray clinic for evaluation by a physician. Of the booked participants, 261 (40.3%) did not attend the clinic leaving 387 (59.7%) participants who attended and were reviewed by a physician. A 1:1 random sample of 387 prevalence survey participants who were classified as normal by the field radiographer were selected for X-ray classification by the physician and computer-assisted algorithm and compared with the clinic attendees.

Baseline characteristics

Table 1 describes the baseline characteristics of the participants of the tent clinic. A total of 774 X-rays were reviewed by the physician and the Qure.ai qXR v2.0 automated system. The median age of the participants was 37 (IQR 25.0–50.0), with participants referred with an abnormal X-ray being significantly older than those with normal X-rays (median age 43 [IQR 32.5–58.5] vs. 28 [IQR 22.0–40.0], respectively). The overall proportion of women was 62.0% (480/720), with no difference in gender distribution between the two groups.

Participants with abnormal CXRs by the field radiographer interpretation had poorer self-reported health than those with normal X-rays (76/387 [19.7%] vs. 19/387 [4.9%], respectively). A larger proportion of those with an abnormal X-ray compared to those with a normal X-ray reported having at least one TB symptom (170/387 [43.9%] vs. 54/387 [14.0%] p-value < 0.001). There was no significant difference in risk behaviour (smoking and alcohol consumption) between the groups (59/387 (15.3%) vs. 53/387 (13.7%) for smoking [p-value 0.540] and 10/387 (2.6%) vs. 14/387 (3.6%) for any amount of alcohol use [p value 0.407]).

About one in five of the participants declined HIV testing (160/774, 20.7%). This was significantly higher in those who were identified to have a normal chest X-ray by the field radiographer than those who were referred to the X-ray clinic (109/387 [28.2%] vs. 51/387 [13.2%] p-value < 0.001). Overall, 133/774 (17.2%) of the participants were HIV-positive, with only 8/774 (1.0%) being new positive diagnoses. The majority

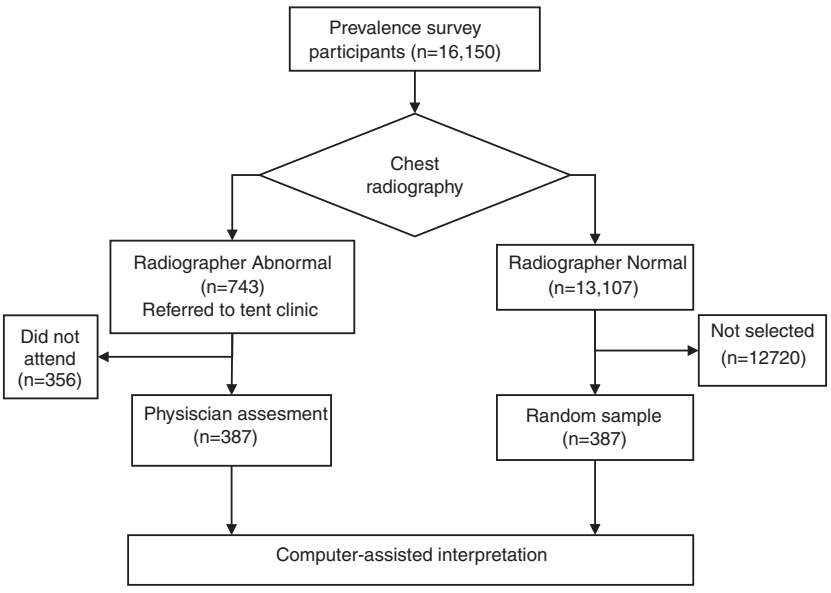

FIGURE 1 Simplified study flowchart

TABLE 1 Demographic characteristics of prevalence survey participants.

Characteristic	Overall	Referred as radiographer abnormal	Sampled as radiographer normal	*p*-value
Total	774	387	387	
Female sex (%)	480 (62.0)	235 (60.7)	245 (63.3)	0.505
Median age, (IQR)	37.0 (25.0–50.0)	43.0 (32.5–58.5)	28.0 (22.0–40.0)	<0.001
Age group (%)				<0.001
15–24	185 (23.9)	42 (10.9)	143 (37.0)	
25–35	170 (22.0)	69 (17.8)	101 (26.1)	
35–44	173 (22.4)	94 (24.3)	79 (20.4)	
45–54	88 (11.4)	61 (15.8)	27 (7.0)	
55–65	75 (9.7)	59 (15.2)	16 (4.1)	
>65	83 (10.7)	62 (16.0)	21 (5.4)	
Literate (%)	690 (89.7)	334 (86.3)	356 (92.0)	0.015
Self-reported health status (%)				<0.001
Very good	105 (13.6)	44 (11.4)	61 (15.8)	
Good	482 (62.3)	211 (54.5)	271 (70.0)	
Fair	92 (11.9)	56 (14.5)	36 (9.3)	
Poor	76 (9.8)	61 (15.8)	15 (3.9)	
Very poor	19 (2.5)	15 (3.9)	4 (1.0)	
Previous or current TB (%)	65 (8.4)	51 (13.2)	14 (3.6)	<0.001
Cough of any duration (%)	147 (19.0)	130 (33.6)	17 (4.4)	<0.001
Night sweats (%)	80 (10.3)	63 (16.3)	17 (4.4)	<0.001
Weight loss (%)	57 (7.4)	35 (9.0)	22 (5.7)	0.099
Fever (%)	57 (7.4)	45 (11.6)	12 (3.1)	<0.001
TB symptom screen positive (%)	224 (28.9)	170 (43.9)	54 (14.0)	<0.001
HIV test result (%)				<0.001
Refused to test	160 (20.7)	51 (13.2)	109 (28.2)	
Negative	481 (62.1)	246 (63.6)	235 (60.7)	
Positive	133 (17.2)	90 (23.3)	43 (11.1)	
New HIV	8 (1.0)	5 (1.3)	3 (0.8)	<0.001
HIV-positive participants on ART	125/133 (94.0)	85/90 (94.4)	40/43 (93.0)	0.747
Proportion who have ever smoked (%)	112 (14.5)	59 (15.3)	53 (13.7)	0.540
Proportion who have ever consumed any alcohol (%)	24 (3.1)	10 (2.6)	14 (3.6)	0.407
Mid-upper arm circumference (MUAC) (mean (SD))	39.71 (27.15)	38.80 (26.76)	40.74 (27.77)	0.685
Bacteriologically confirmed TB (microscopy/Pert/ culture) (%)	11 (1.4)	11 (2.8)	0 (0.0)	0.002
Qure.ai qXR v2.0 (%)				<0.001
Abnormal, consistent with TB	80 (10.3)	79 (20.4)	1 (0.3)	
Abnormal, not consistent with TB	220 (28.4)	131 (33.9)	89 (23.0)	
Normal	474 (61.2)	177 (45.7)	297 (76.7)	
Physician reading (%)				<0.001
Normal	490 (63.3)	184 (47.5)	306 (79.1)	
Old TB	38 (4.9)	37 (9.6)	1 (0.3)	
Other abnormalities	200 (25.8)	124 (32.0)	76 (19.6)	
Possible TB	46 (5.9)	42 (10.9)	4 (1.0)	

TABLE 2 Prevalence and qXR median scores of WHO-IMAI radiological diagnoses with accompanying characteristics

WHO-IMAI Radiological diagnosis	Prevalence		qXR scores	Field interpretation by radiographer		Bacteriological confirmed TB (microscopy/Xpert/culture)
	N = 774	% (95% CI)	Median, IQR	Normal N(387), % (95% CI)	Abnormal N(387), % (95% CI)	N(11), % (95% CI)
Cardiomegaly	160	20.7% (18.0–23.7)	0.2 (0.2–0.3)	70/160, 43.8% (36.2–51.6)	90/160, 56.3% (48.4–63.8)	1/160, 0.6% (0.1–4.3)
COAD	40	5.2% (3.8–7.0)	0.3 (0.2–0.4)	6/40, 15.0% (6.8–29.9)	34/40, 85.0% (70.1–93.2)	0/40, 0.0% (NA)
Normal	490	63.3% (59.8–66.6)	0.1(0.02–0.2)	306/490, 62.4% (58.1–66.6)	184/490, 37.5% (33.4–41.9)	4/490, 0.8% (0.3–2.2)
Old TB	38	4.9% (3.6–6.7)	0.7 (0.6–0.8)	1/38, 2.6% (0.4–16.9)	37/38, 97.4% (83.1–99.6)	1/38, 2.6% (0.4–16.9)
Pleural effusion	8	1% (0.5–2.1)	0.3 (0.2–0.5)	0/8, 0.0% (NA)	8/8, 100% (NA)	0/8, 0.0% (NA)
Pneumonia	20	2.6% (1.7–4.0)	0.6 (0.4–0.6)	3/20, 15.0% (4.8–38.8)	17/20, 85.0% (61.6–95.2)	1/20, 5.0% (0.7–29.4)
Possible TB	18	2.3% (1.5–3.7)	0.8 (0.5–0.8)	1/18, 5.6% (0.7–32.0)	17/18, 94.4% (68.0–99.3)	4/18, 22.2% (8.3–47.3)

of people with HIV were already on ART (125/133, 94.0%). Participants who were referred to the community clinic had a significantly higher HIV prevalence than those who had been identified to have a normal CXR by the field radiographer (90 [23.3%] versus 43 [11.1%] p-value < 0.001).

Abnormalities identified on chest X-ray

Cardiomegaly was the commonest abnormality identified on chest X-ray at 20.7% (95% CI 18.0–23.7) of all chest X-rays reviewed (Table 2). The age distribution of the participants with cardiomegaly is shown in Figure 2. Cardiomegaly affected all age groups involved in the survey. The proportion of cardiomegaly increased with increasing age group. Cardiomegaly was significantly higher in participants with high blood pressure than those with normal blood pressure (54/90 [51.92%] vs. 36/90 [12.77%], p-value < 0.001). Other common X-ray abnormalities were features of chronic obstructive airways disease (5.2%, 95% CI 3.8–7.0) and features of old TB (4.9%, 95% CI 3.6–6.7).

One in five (81/387) chest X-rays were misclassified by the radiographer. Cardiomegaly (70/81 [86.4%]) was the commonest X-ray abnormality misidentified by the radiographer, followed by features of chronic obstructive airways disease (6/81 [7.4%]) – Table 2.

Physician diagnoses of clinic attendees based on physician assessment

Table 3 displays the diagnoses made by the physician at the community-based tent clinic. The commonest diagnosis

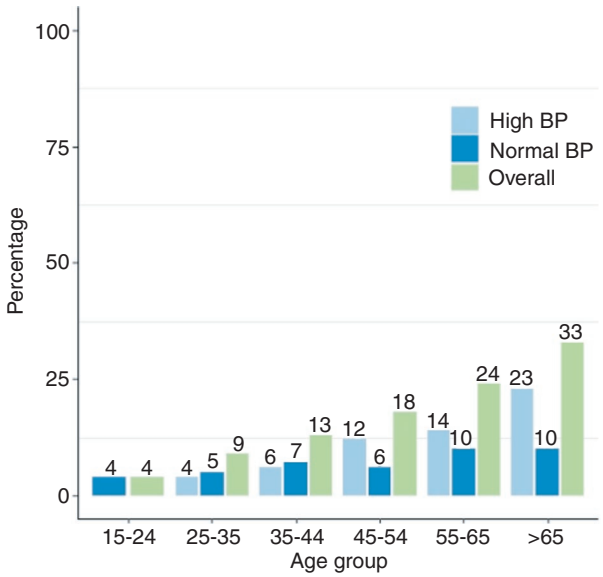

FIGURE 2 Age distribution of participants with cardiomegaly on chest X-ray. Mean age was 39.42 (SD 17.31). The overall proportion of participants with cardiomegaly on chest X-ray was 20.6% (95% CI 17.6–24.1)

TABLE 3 Diagnoses made at community-based tent clinic amongst clinic attendees ($N = 387$)

Diagnosis[a]	Overall $N = 304$ % (95% CI)	Cardiomegaly $N = 97$ % (95% CI)	Other CXR abnormality $N = 116$ % (95% CI)	Normal CXR $N = 91$ % (95% CI)
Chronic Lung Diseases (CLD)	69 22.7% (18.3–27.7)	2/69 2.9% (0.8–10.0)	62 89.9% (80.5–95.0)	5 7.2% (3.1–15.9)
Diabetes	9 3.0% (1.6–5.5)	6/9 66.7% (35.4–87.9)	0/9 0.0% (0.0–30.0)	3/9 33.3% (12.1–64.6)
Gastritis	16 5.3% (3.3–8.4)	0/16 0.0% (0.0–19.4)	2/16 12.5% (3.5–36.0)	14/16 87.5% (64.0–96.5)
Heart disease	21 6.9% (4.6–10.3)	13/21 61.9% (40.9–79.2)	0/21 0.0% (0.0–15.5)	8/21 38.1% (20.8–59.1)
High blood pressure	104 34.2% (29.1–39.7)	61/104 58.7% (49.0–67.6)	23/104 22.1% (15.2–31.0)	20/104 19.2% (12.8–27.8)
Malignancy	4 1.3% (0.5–3.3)	1 25.0% (4.6–69.9)	2 50.0% (15.0–85.0)	1 25.0% (4.6–69.9)
Musculoskeletal pathologies	23 7.6% (5.1–11.1)	10 43.5% (25.6–63.2)	3 13.0% (4.5–32.1)	10 43.5% (25.6–63.2)
Other[b]	9 3.0% (1.6–5.5)	0 0.0% (0.0–29.9)	0 0.0% (0.0–29.9)	9 100.0% (70.0–100.0)
Suspected Pneumocystis jirovercii pneumonia	1 0.3% (0.1–1.8)	0 0.0% (0.0–79.3)	1 100.0% (20.7–100.0)	0 0.0% (0.0–79.3)
Pneumonia	17 5.6% (3.5–8.8)	0 0.0% (0.0–18.4)	17 100.0% (81.6–100.0)	0 0.0% (0.0–18.4)
Pulmonary TB	8 2.6% (1.3–5.1)	1 12.5% (2.2–47.1)	3 37.5% (13.7–69.4)	4 50.0% (21.5–78.5)
Extra-pulmonary TB	3 1.0% (0.3–2.9)	0 0.0% (0.0–56.1)	2 66.7% (20.8–94.0)	1 33.3% (6.1–79.2)
Upper Respiratory Tract Infections (URTI)	20 6.5% (4.3–9.9)	3 15.0% (5.2–36.0)	1 5.0% (0.9–23.6)	16 80.0% (58.4–91.9)

[a]Not unique summaries. Some participants had more than one pathology, while others had none.
[b]Other includes skin pathologies, hernias and prostatic disease.

made among those attending the X-ray clinic was high blood pressure (104/304, [34.2%, 95% CI of 29.1–39.7]). This was seconded by chronic lung diseases (CLD) with 69 (22.7%, 95% CI of 18.3–27.7) cases. Other common pathologies were musculoskeletal pathologies (7.6%, 95% CI of 5.1–11.1), heart disease (6.9%, 95% CI of 4.6–10.3) and gastritis (5.3%, 95% CI of 3.3–8.4). About 70% (213/304) of diagnosed pathologies had an abnormality on CXR. There was a high proportion of cardiomegaly amongst patients with diabetes (66.7%, 95% CI of 35.4–87.9), heart disease (61.9%, 95% CI of 40.9–79.2) and high blood pressure (58.7%, 95% CI of 49.0–67.6). Only 7.2% (95% CI of 3.1–15.9) of patients with CLD had a normal CXR.

Qure.ai qXR v2.0 classification of X-rays

23.3% (90/387) of all X-rays classified as normal by the radiographer were identified as abnormal by the automated system – Table 1. Table 4 shows the physician interpretation of the automated X-ray classifications. 38/387 X-rays were classified as HRTBS by the automated system, of whom 50% (19/38) were classified as with old TB by the physician. The physician classification of cardiomegaly corresponded very closely with that of the computer (109/118, 92.4%). The software classification of abnormal was mainly classified as COAD (19/102, 18.6%) and cardiomegaly (16/102, 15.7%) by the physician.

The overall mean Qure.ai qXR v2.0 score for all reviewed X-rays was 0.23 (SD 0.20). Images classified as normal and abnormal by the physician scored 0.14 (SD 0.13) and 0.37 (SD 0.23), respectively. The mean score of X-rays from confirmed TB patients was 0.62 (SD 0.34), while the mean score for patients with negative laboratory investigations was 0.22 (SD 0.20). The highest mean Qure.ai qXR v2.0 score denoted features of active PTB (0.68, SD 0.21), followed by features suggestive of old TB (0.67, SD 0.19) – Figure 3.

DISCUSSION

This study describes the abnormalities found on CXR screening for TB at the community level. There was a high prevalence of non-tuberculous abnormalities described by a physician during this survey. The study also found a high burden of high blood pressure and cardiomegaly, a

TABLE 4 Comparison between physician X-ray classifications and qXR classifications ($N = 774$)

		Physician WHO-IMAI X-ray classification						
Computer-assisted classification	**Overall**	**Normal**	**Possible TB**	**Cardiomegaly**	**Old TB**	**COAD**	**Pleural effusion**	**Pneumonia**
Normal	474 (62.2%)	431 (90.9%)	0 (0.0%)	31 (6.5%)	2 (0.4%)	9 (1.9%)	1 (0.2%)	0 (0.0%)
HRTBS	38 (4.9%)	0 (0.0%)	11 (28.9%)	1 (2.6%)	19 (50.0%)	3 (7.9%)	0 (0.0%)	4 (10.5%)
Cardiomegaly	118 (15.2%)	3 (2.5%)	0 (0.0%)	109 (92.4%)	0 (0.0%)	5 (4.2%)	1 (0.8%)	0 (0.0%)
RTBS	42 (5.4%)	11 (26.2%)	3 (7.1%)	3 (7.1%)	11 (26.2%)	4 (9.5%)	1 (2.4%)	9 (21.4%)
Abnormal	102 (13.1%)	45 (44.1%)	4 (3.9%)	16 (15.7%)	6 (5.9%)	19 (18.6%)	5 (4.9%)	7 (6.9%)

Abbreviations: HRTBS, High-risk TB screening; RTBS, Routine TB screening; COAD, Chronic obstructive airways disease; IMAI, Integrated management of adult illnesses.

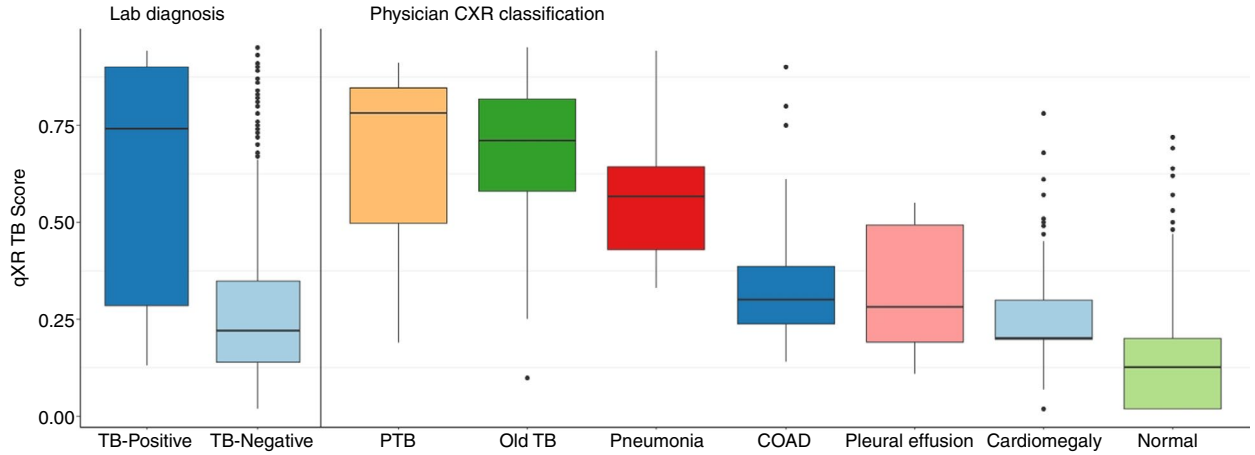

FIGURE 3 Qure.ai qXR v2.0 TB scoring for laboratory and radiological diagnoses. PTB, pulmonary tuberculosis

lower-than-expected prevalence of CXR abnormalities amongst those with the previous TB, and a high concordance between the automated CXR and physician X-ray interpretation. Cardiomegaly was found to be a prominent feature on chest radiography in cases of diabetes, heart disease and high blood pressure.

We found 160/774 (20.7%) participants with cardiomegaly on chest X-ray screening in the community. This concurs with a similar study by Mungai et al., describing chest X-ray abnormalities in a community-wide TB prevalence survey [4]. Their studies found the prevalence of cardiomegaly on chest X-ray to be 23.1% (95% CI 20.6%–25.6%) [4]. These are higher values than an earlier survey in South Africa, which found a prevalence of cardiomegaly on chest X-ray of 12.7% (95% CI 9.6%–15.8%) [25]. The changing socio-economic paradigm and urbanisation may be implicated here, with more and more people being exposed to fast foods and sedentary lifestyles at home and work [6].

There remains a gap in the implications of cardiomegaly in otherwise healthy populations. Studies on cardiomegaly in hospitalised populations suggest that it is a potential screening and triaging tool for cardiovascular disease in those patients [25,26]. A retrospective, descriptive study in Zambia suggested that 87.9% of cardiomegaly on chest X-ray had some cardiovascular abnormality on echocardiogram [27]. A systematic review done by Loomba et al included seven descriptive papers and found that cardiomegaly had a sensitivity of 83.3% and a specificity of 42.4% in the prediction of an abnormal left ventricular end-diastolic dimension [28]. These studies support the utilisation of cardiomegaly on CXR as a triaging tool for cardiovascular disease in in-hospital populations and provide the basis for exploration of the potential role of cardiomegaly on CXR as a community-level screening tool for CVD.

The proportions of cardiomegaly on CXR in cases of diabetes, heart disease and high blood pressure were 66.7%, 61.9% and 58.7%, respectively. These conditions are of public health significance associated with premature mortality [25,29]. Studies are required to investigate the risks of progression of cardiomegaly found in these patient populations to heart disease and death, informing decisions on the use of cardiomegaly in screening and triaging algorithms for NCD care pathways in low-resource settings. Community-level interventions such as health messaging on the prevention of NCDs may also be integrated into these screening programmes.

Based on the WHO IMAI classification, non-TB-related pulmonary abnormalities identified in this survey included features of COAD, pneumonia and effusions (9.4%, 68/774). Features of COAD alone accounted for 5.2% (40/774) of

the described non-TB chest X-ray anomalies. This is relatively higher than the 3.2% (95% CI 2.3%–4.4%) reported by Mungai et al. [4] Although chest X-ray has high interobserver variability [30], the high sensitivity for diagnosing features of emphysema [30,31] provides a potential for its application as a screening tool at the community level, informing decision for spirometry and other respiratory function tests.

Features of old TB accounted for 4.9% of all chest X-ray abnormalities. This would account for roughly 50% of all participants who had previous TB (38/65, 58.5% – Tables 1 and 2). This value is much lower than in a South African and a Zimbabwean study, wherein 96% and 83% of the patients with post-TB CLD to had abnormal CXRs, respectively [32,33]. A systematic review by Meghji et al. in 2016 discovered a high prevalence of radiographic abnormalities in post-TB lung disease, the commonest of which was fibrosis (prevalence 25.0–70.4%) [34]. This was higher still in post-multidrug-resistant TB cases [34]. These studies were all conducted in countries with higher socio-economic status than Malawi, included patients with the diagnosis of chronic lung disease secondary to the previous TB and did not fully describe interactions with other environmental confounders, such as air quality, smoking and mining. Inclusion of more sensitive tests such as CT scans may help define the true burden of radiographic abnormalities in patients who have had previous TB [4].

One in four (104/387, 26.9%) people were found to have high blood pressure on screening at the community-based tent clinic (referred by the radiographer as having an abnormal chest X-ray). This is comparable to the projected proportion of the population with raised blood pressure by the WHO in 2015 [35]. The 2009 Malawi National STEPS Survey demonstrated the overall prevalence of raised blood pressure in urban regions was 27.9% [36].

The prevalence of HIV in our study was 17.2% (133/774) with >90% ART coverage (94.0% of all PLHIV were on ART). According to the 2015–2016 Malawi Population-based HIV Impact Assessment (MPHIA) report, the overall HIV prevalence among adults aged 15–64 was 10.6% [37], a much lower proportion than we found in our study. However, disaggregated data demonstrate that the HIV prevalence in Blantyre City to be 17.1%, which is similar to what our study found [37].

Automated systems for CXR interpretation for the assessment of TB are useful in this setting. Qure.ai qXR v2.0 generates a report with recommendations for TB screening and does not require the user to interpret a TB probability score [22]. Qure.ai qXR v2.0 has high sensitivity (93% to 98%) [22,38] and is tailored towards making recommendations for focused TB screening. The computer-assisted technology has been portrayed to be a tool for use in low-resource settings where specialist opinion is lacking [38]. Qure.ai qXR v2.0 reporting system thus allows for a more harmonised approach to CXR classification, making it easier to create guidelines based on its performance. Our study found that 50% of images that were recommended for HRTBS by the software had features of old TB by physician interpretation. Secondary-level testing using cartridge-based nucleic acid amplification tests (CBNAATs) such as Xpert MTB/RIF Ultra is still required to inform clinical decisions [39].

The automated diagnostics system has several potential areas where it can be applied. CADXR may have a role in outlining treatment algorithms, which assign patient groups to shorter treatment regimens, as evidenced by a review by Imperial et al. [40], which described adult patients with minimal TB disease (as defined by low smear grade or the absence of cavitation) as having a lower baseline risk for unfavourable outcomes [40]. The CADXR system may also be used to track TB treatment progress [41]. Physicians can then use the CADXR system to respond earlier to potential TB treatment failure, resulting in improved treatment outcomes. Further, the CADXR programme can be integrated into the Integrated Chronic Care community clinics that some districts in Malawi already have in plac. [42].

There are several limitations to our study. Due to the limited testing capacity at the tent, the true burden of infectious and non-communicable diseases could not be discerned. Additionally, the limited access to diagnostic tests meant the clinic physician had to rely on a syndromic approach to arrive at most diagnoses, and thus, the range of diagnoses that could be made was narrow. There was a low referral turn up (52.1%) to the tent clinic, which could have introduced selection bias, and patients were not followed up to ascertain reasons for failure to attend. Although all images from the study were posteroanterior radiographs, data were not collected on other X-ray quality factors. We did not have access to radiologists in the study and had to use a physician for X-ray interpretation. The strength of the human X-ray interpretations may thus be low, but they do reflect the true picture of the health systems in the region.

CONCLUSION

There is a high burden of cardiomegaly on chest X-ray at the community level, especially in cases of diabetes, heart disease and high blood pressure. TB prevalence surveys that incorporate CXR screening of participants offer a platform for integrated screening of TB and cardiovascular NCDs in communities. There is also a need to propose resource sparing interventions to strengthen primary prevention of cardiovascular NCDs at primary care levels.

ACKNOWLEDGEMENTS

We acknowledge the SCALE study team for identifying the participants for the X-ray clinic.

REFERENCES

1. World Health Organization. Global Tuberculosis Report. Blood. Geneva, Switzerland: World Health Organization; 2015. Available from: http://www.who.int/tb/publications/global_report/en/index.html
2. MacPherson P, Khundi McEwen, Nliwasa M, Choko AT, Phiri VK, Webb EL, et al. Disparities in access to diagnosis and care in Blantyre,

Malawi, identified through enhanced tuberculosis surveillance and spatial analysis. BMC Med. 2019;17(1):1–11.
3. Ho J, Fox GJ, Marais BJ. Passive case finding for tuberculosis is not enough. Int J Mycobacteriol. 2016;5(4):374–8.
4. Mungai BN, Joekes E, Masini E, Obasi A, Manduku V, Mugi B, et al. "If not TB, what could it be?" Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey. Thorax. 2021;76(6):607–14.
5. Murphy K, Habib SS, Zaidi SMA, Khowaja S, Khan A, Melendez J, et al. Computer aided detection of tuberculosis on chest radiographs: An evaluation of the CAD4TB v6 system. Sci Rep. 2020;10(1):1–11.
6. Elsey H, Agyepong I, Huque R, Quayyem Z, Baral S, Ebenso B, et al. Rethinking health systems in the context of urbanisation: challenges from four rapidly urbanising low-income and middle-income countries. BMJ Glob Heal. 2019;4(3):1–6.
7. Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. Trans R Soc Trop Med Hyg. 2006;100(3):191–9.
8. Peer N. The converging burdens of infectious and non-communicable diseases in rural-to-urban migrant Sub-Saharan African populations: A focus on HIV/AIDS, tuberculosis and cardio-metabolic diseases. Trop Dis Travel Med Vaccines. 2015;1(1):1–8.
9. de-Graft Aikins A. Ghana's neglected chronic disease epidemic: a developmental challenge. Ghana Med J. 2007;41(4):154–9.
10. Cundale K, Wroe E, Matanje-Mwagomba BL, Muula AS, Gupta N, Berman J, et al. Reframing noncommunicable diseases and injuries for the poorest Malawians: The Malawi national NCDI poverty commission. Malawi Med J. 2017;29(2):194–7.
11. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Medicine. 2006;3(11):2011–30.
12. Allain TJ, Aston S, Mapurisa G, Ganiza TN, Banda NP, Sakala S, et al. Age related patterns of disease and mortality in hospitalised adults in Malawi. PLoS One. 2017;12(1):1–13.
13. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: The colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respiratory J. 2010;35(1):27–33.
14. Traoré Y, Bensghir R, Ihbibane F, OuladLashen A, Sodqi M, Marih L, et al. Diabetes and human immunodeficiency virus infection: Epidemiological, therapeutic aspects and patient experience. Press Medicale. 2016;45(6):e139–43.
15. Salindri AD, Wang J-Y, Lin H-H, Magee MJ. Post-tuberculosis incidence of diabetes, myocardial infarction, and stroke: Retrospective cohort analysis of patients formerly treated for tuberculosis in Taiwan, 2002–2013. Int J Infect Dis. 2019;84:127–30.
16. Huaman MA, Henson D, Ticona E, Sterling TR, Garvy BA. Tuberculosis and cardiovascular disease: linking the epidemics. Trop Dis Travel Med Vaccines. 2015;1(1):1–7.
17. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: The impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7:1–8.
18. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. Lancet. 2015;385(9967):540–8.
19. Hirschhorn LR, Kaaya SF, Garrity PS, Chopyak E, Fawzi MCS. Cancer and the "other" noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. AIDS. 2012;26(Suppl):S65–75.
20. Petersen M, Yiannoutsos CT, Justice A, Egger M. Observational research on NCDs in HIV-positive populations: conceptual and methodological considerations. J Acquir Immune Defic Syndr. 2014;67(Suppl 1):S8–S16.
21. World Health Organization. Acute Care – Integrated Management of Adolescent and Adult Illness (IMAI) modules [Internet]. WHO/CDS/IMAI/2004.1 Rev. 2; 2005. 16–17 p. Available from: http://www.who.int/3by5/publications/documents/imai/en/
22. Engle E, Gabrielian A, Long A, Hurt DE, Rosenthal A. Performance of Qure.ai automatic classifiers against a large annotated database of patients with diverse forms of tuberculosis. PLoS One. 2020;15(1):1–19.
23. Wilkinson IB, Raine T, Wiles K, Goodhart A, Hall C, O'Neill H. Oxford Handbook of Clinical Medicine, 10th edn. Oxford University Press; 2017.
24. Malawi Standard Treatment Guidelines (MSTG). Ministry of Health Malawi, 5th edn; 2015.
25. Esmail H, Oni T, Thienemann F, Omar-Davies N, Wilkinson RJ, Ntsekhe M. Cardio-thoracic ratio is stable, reproducible and has potential as a screening tool for HIV-1 related cardiac disorders in resource poor settings. PLoS One. 2016;11(10):1–10.
26. Schwartz T, Magdi G, Steen TW, Sjaastad I. HIV as a risk factor for cardiac disease in Botswana: A cross-sectional study. Int Health. 2012;4(1):30–7.
27. Gwaba N, Isaacs F, Harneck M. Serosurvey and factors associated with Leishmania donovani infection in febrile HIV infected individuals attending Abuja Teaching Hospital, Nigeria. Med J Zambia. 2018;45(4):216–25.
28. Loomba RS, Shah PH, Nijhawan K, Aggarwal S, Arora R. Cardiothoracic ratio for prediction of left ventricular dilation: a systematic review and pooled analysis. Future Cardiol. 2015;11(2):171–5.
29. Mensah GA, Roth GA, Sampson UKA, Moran AE, Feigin VL, Forouzanfar MH, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: A systematic analysis of data from the Global Burden of Disease Study 2013. Cardiovasc J Afr. 2015;26(2):S6–10.
30. Miniati M, Monti S, Stolk J, Mirarchi G, Falaschi F, Rabinovich R, et al. Value of chest radiography in phenotyping chronic obstructive pulmonary disease. Eur Respir J. 2008;31(3):509–14.
31. Washko GR. Diagnostic imaging in COPD. Semin Respir Crit Care Med. 2010;31(3):276–85.
32. Mkoko P, Naidoo S, Mbanga LC, Nomvete F, Muloiwa R, Dlamini S. Chronic lung disease and a history of tuberculosis (Post-tuberculosis lung disease): Clinical features and in-hospital outcomes in a resource-limited setting with a high HIV burden. South African Med J. 2019;109(3):169–73.
33. Chin AT, Rylance J, Makumbirofa S, Meffert S, Vu T, Clayton J, et al. Chronic lung disease in adult recurrent tuberculosis survivors in Zimbabwe: a cohort study. Int J Tuberc Lung Dis. 2019;23(2):203–11.
34. Meghji J, Simpson H, Squire SB, Mortimer K. A systematic review of the prevalence and pattern of imaging defined post-TB lung disease. PLoS One. 2016;11(8):1–17.
35. WHO. Noncommunicable Diseases Country Profiles 2018 [Internet], vol. 369. World Health Organization; 2018:1336–43 p. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24088093
36. World Health Organisation. Malawi National STEPS Survey for Chronic Non-Communicable Diseases and their Risk Factors Final Report. 2009;(June):1–131. Available from: http://www.who.int/chp/steps/Malawi_2009_STEPS_Report.pdf
37. Ministry of Health Malawi. Malawi Population-based HIV Impact Assessment (MPHIA) 2015-16; 2018.
38. Qin ZZ, Sander MS, Rai B, Titahong CN, Sudrungrot S, Laah SN, et al. Using artificial intelligence to read chest radiographs for tuberculosis detection: A multi-site evaluation of the diagnostic accuracy of three deep learning systems. Sci Rep. 2019;9(1):1–10.
39. McCarthy K, Fielding K, Churchyard GJ, Grant AD. Empiric tuberculosis treatment in South African primary health care facilities - For whom, where, when and why: Implications for the development of tuberculosis diagnostic tests. PLoS One. 2018;13(1):1–14.
40. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nat Med. 2018;24(11):1708–15.
41. Lieberman R, Kwong H, Liu B, Huang HK. Computer-assisted detection (CAD) methodology for early detection of response to

pharmaceutical therapy in tuberculosis patients. Med Imaging 2009 Comput Diagnosis. 2009;7260:726030.
42. Kachimanga C, Cundale K, Wroe E, Nazimera L, Jumbe A, Dunbar E, et al. Novel approaches to screening for noncommunicable diseases: Lessons from Neno, Malawi. Malawi Med J. 2017;29(2):78–83.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.