BEST PAPERS IN INFECTIOUS DISEASES 2023

TUBERCOLOSI

Carlo Cerini

END TB

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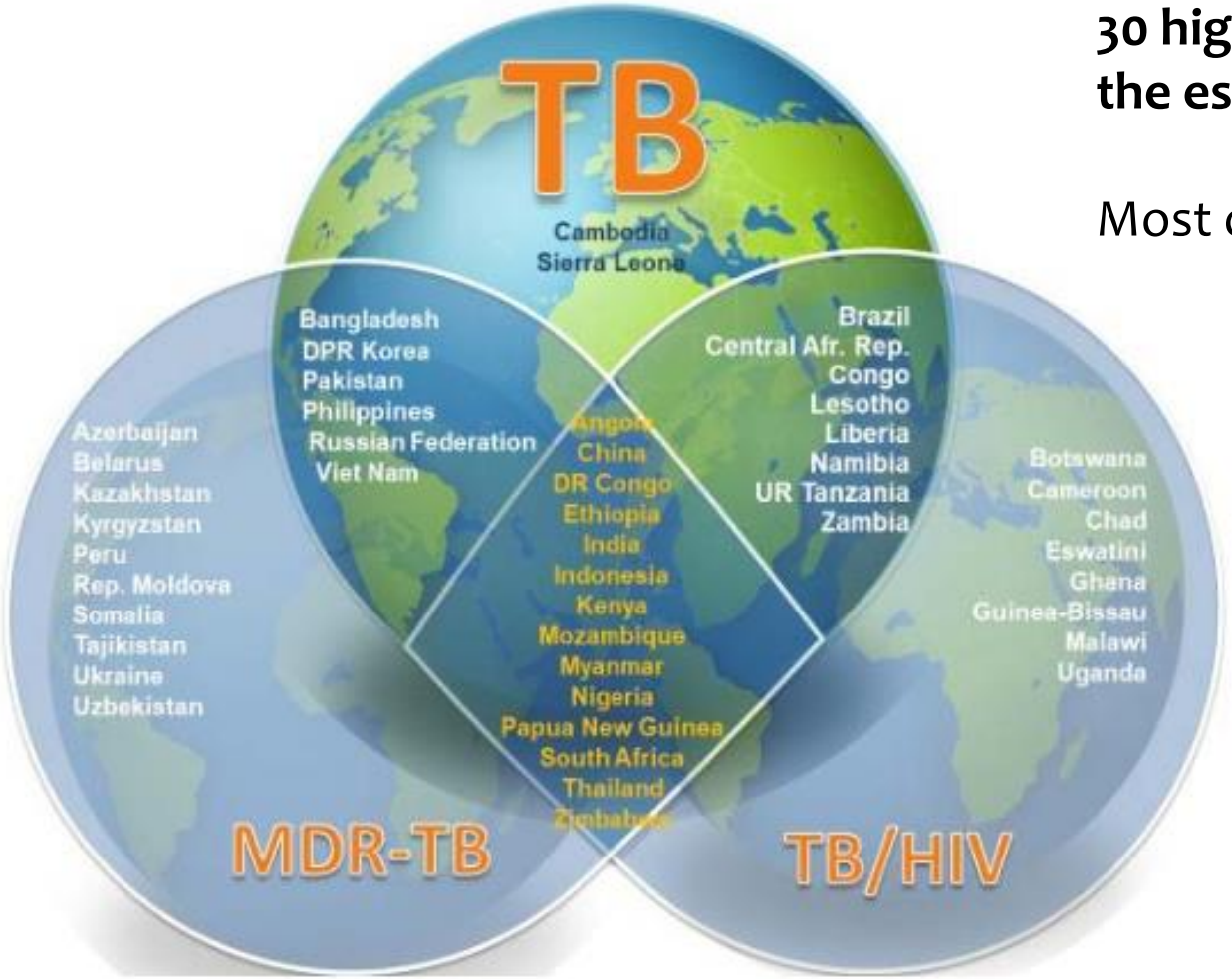
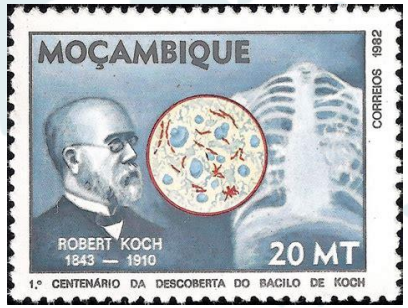
2022 WHO report: estimated **10.6 million incident cases of TB** in 2021,
approximately 1.2 million (11%) occurred among children <15 years of age



30 high TB burden Countries accounts for 86-90% of the estimated global incidence

Most of them are Limited Resources Countries (LRC)



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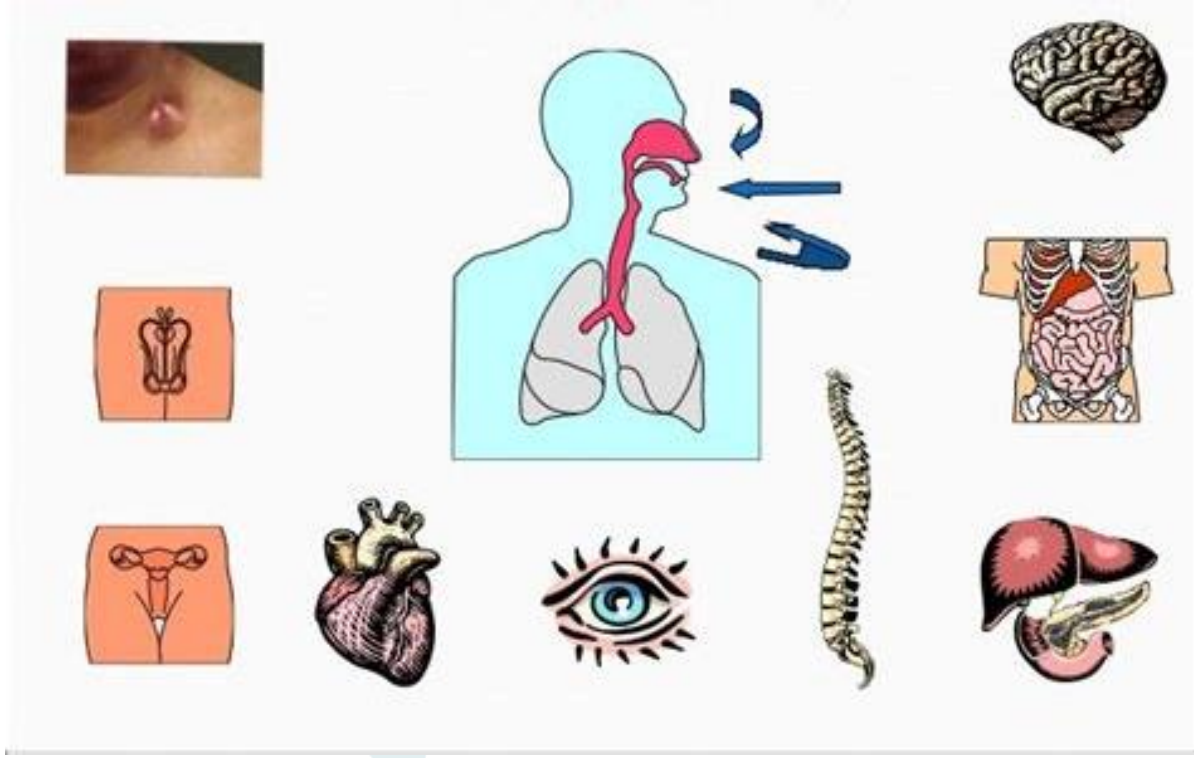
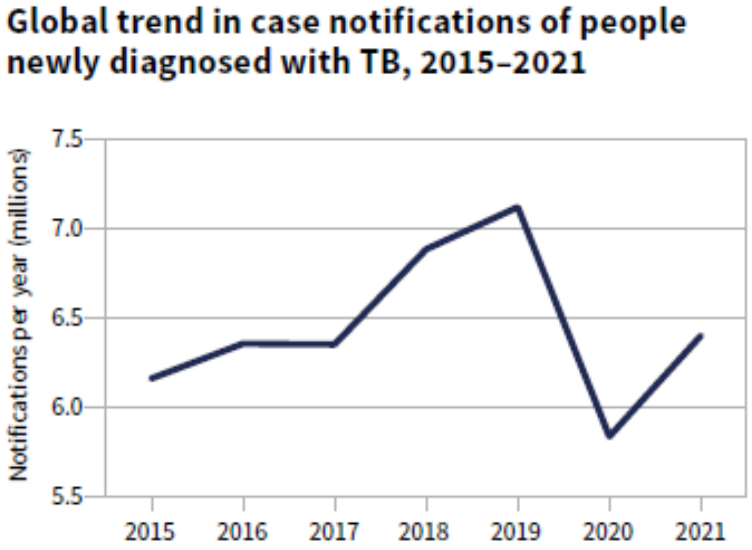
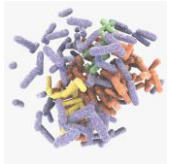
Extrapulmonary TB (EPTB) constitutes about 15%-20% of all TB patients (50% among HIV-coinfected and children) → real data underestimated





In 2020 LRC TB diagnoses were microbiologically confirmed in only one-third of persons treated for tuberculosis, partly owing to limited access to diagnostics

Colture often impossible



Xpert still not widely available / limited sensitivity in sputum-negative cases

Non-sputum samples

LAM (Lipoarabinomannan) - WHO approval only on urine, low specificity (NTM)

ADA (Adenosine Deaminase): variables sensibility and specificity

Empirical treatment often performed

- unnecessary treatment
- diagnostic delay
- over-burden of pills in HIV+

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FASH

Focused **a**ssessment with **s**onography for **HIV** and tuberculosis **(FASH) is a ultrasonographic (US) protocol** developed to detect signs of extrapulmonary tuberculosis

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pleural and pericardial effusion

ascites, and abnormalities of the terminal ileum wall

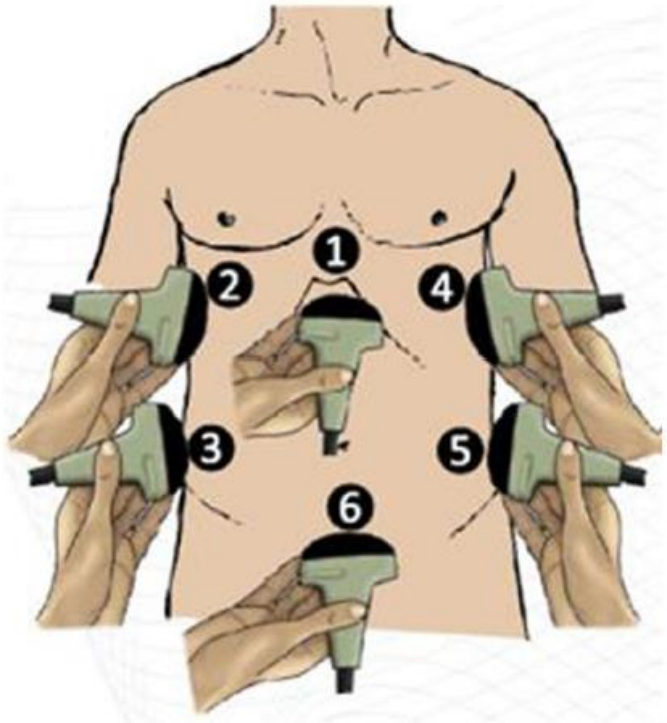

Figure 1 Schematic drawing of the ultrasound probe positions during the FASH examination.

ORIGINAL ARTICLE Open Access

Focused assessment with sonography for HIV-associated tuberculosis (FASH): a short protocol and a pictorial review

Tom Heller[1*], Claudia Wallrauch[1], Sam Goblirsch[2] and Enrico Brunetti[3]

splenic and hepatic abscesses

abdominal lymph nodes

FASH protocol was expanded by adding US of the chest, axillary and cervical lymph nodes, and the inferior vena cava diameter as a sign of heart failure, naming it extended FASH **(eFASH)** — an examination taking about 15 minutes

FASH

- *Previous studies have shown low to moderate diagnostic accuracy for abdominal US as a stand-alone test for definite tuberculosis, although the presence of ≥3 US predictors increased the specificity to as high as 93%*

- *In a previous study including HIV-positive and HIV-negative patients, we showed that the absence of FASH signs combined with a normal chest radiograph and absence of fever might exclude tuberculosis*

- *The presence of 2 or more independent PoCUS predictors (intra-abdominal lymphadenopathy, ascites, and pericardial effusion) had moderate discrimination for HIV-associated tuberculosis in patients presenting to the emergency center.*

- *In South Africa, the Emergency Medicine Association adopted FASH as a module in their US training curriculum and uses it in the emergency-room setting.*

Point-of-Care Ultrasound Predictors for the Diagnosis of Tuberculosis in HIV-Positive Patients Presenting to an Emergency Center

Daniël Jacobus Van Hoving, MBChB, Dip PEC (SA), MMed (EMed), MMedSci (Clin Epi),[a,b] Andre P. Kenge, MD, DScS, PhD,[c,d] Gary Maartens, MMed (Int Med),[e] and Graeme Meintjes, MBChB, FCP(SA), FRCP(Glasg), MPH, PhD[e,f]

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NOTES FROM THE FIELD

Diagnostic value of FASH ultrasound and chest X-ray in HIV-co-infected patients with abdominal tuberculosis

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Sonography to Rule Out Tuberculosis in Sub-Saharan Africa: A Prospective Observational Study

Robert Ndege,[1,2,a] Maja Weisser,[1,3,4,5,a] Luigia Elzi,[5,6] Flavia Diggelmann,[5] Farida Bani,[1,2] Winfrid Gingo,[2] George Sikalengo,[1,2] Herry Mapesi,[1,2] Elisante Mchomvu,[2] Lujeko Kamwela,[1] Dorcas Mnzava,[1] Manuel Battegay,[3,5] Klaus Reither,[4,5] Daniel H. Paris,[4,5] and Martin Rohacek[1,2,4,5]

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Ultrasound in managing extrapulmonary tuberculosis: a randomized controlled two-center study

Robert Ndege[1,2*†], Omary Ngome[1,3†], Farida Bani[1,2], Yvan Temba[1,3], Herieth Wilson[1,2], Fiona Vanobberghen[4,5], Jerry Hella[1], Winfrid Gingo[2], Mohamed Sasamalo[1], Dorcas Mnzava[1], Namvua Kimera[1], Helen Hiza[1], John Wigayi[1], Herry Mapesi[1], Irene B. Kato[3], Francis Mhimbira[1], Klaus Reither[4,5], Manuel Battegay[6,5], Daniel H. Paris[4,5], Maja Weisser[1,5,6] and Martin Rohacek[1,2,4,5*]

rural Saint Francis Referral Hospital, Ifakara

urban Mwananyamala Regional Referral Hospital, Dar es Salaam

Clinical Infectious Diseases

MAJOR ARTICLE

Ultrasononography in Managing Extrapulmonary Tuberculosis: A Randomized, Controlled, Parallel, Superiority, Open-Label Trial

Robert Ndege,[1,2,3,4,a] Omary Ngome,[1,5,a] Fiona Vanobberghen,[3,4,©] Farida Bani,[1,2] Yvan Temba,[1,5] Herieth Wilson,[1] Jerry Hella,[1] Winfrid Gingo,[2] Mohamed Sasamalo,[1] Dorcas Mnzava,[1] Namvua Kimera,[1] Hellen Hiza,[1,3,4] John Wigayi,[1] Herry Mapesi,[1,3,4] Irene B. Kato,[5] Francis Mhimbira,[1] Klaus Reither,[3,4] Manuel Battegay,[4,6] Daniel H. Paris,[3,4] Maja Weisser,[1,3,4,6] and Martin Rohacek[1,2,3,4]

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eligible participants

September 2018 - October 2020
(follow-up till march 2021)

HIV-positive and HIV-negative patients aged ≥18 years

clinical signs of extrapulmonary tuberculosis, with or without concomitant signs of pulmonary tuberculosis

fever of any duration
night sweats within the last 3 weeks
weight loss

+

* nuchal, cervical, axillary or generalized lymphadenopathy
* abdominal pain
* ascites
* neurological symptoms
* hemoglobin level <8 g/dL in HIV-positive participants receiving HAART
* skeletal disorders suggesting tuberculosis
* genitourinary disorders suggesting tuberculosis
* chest radiograph showing a miliary pattern, pleural or suspected pericardial effusion, upper lobe infiltrate, or a cavernous lesion

diagnostic panel

^ Baseline eFASH examinations were reviewed remotely by an independent board-certified sonographer

- ❑ Clinical evaluation
- ❑ Chest radiography
- ❑ Blood tests
- ❑ sputum with **Xpert MTB/RIF assay** and **culture***
- ❑ **Urine samples** with **Xpert MTB/RIF Ultra assay**
- ❑ If sterile samples were obtained from pleural, ascitic, or pericardial fluids or from pus from lymph nodes, **Xpert MTB/ RIF Ultra assay** and **liquid culture** were performed.
- ❑ **Adenosine deaminase (ADA)** was measured in pleural and pericardial fluid and from ascites.
- ❑ Fine-needle aspiration biopsy specimens of lymph nodes were analyzed by means of **Giemsa and Papanicolaou stains for cytomorphology, Ziehl-Neelsen stain, Xpert MTB/RIF Ultra assay**, and **culture**.
- ❑ **eFASH**

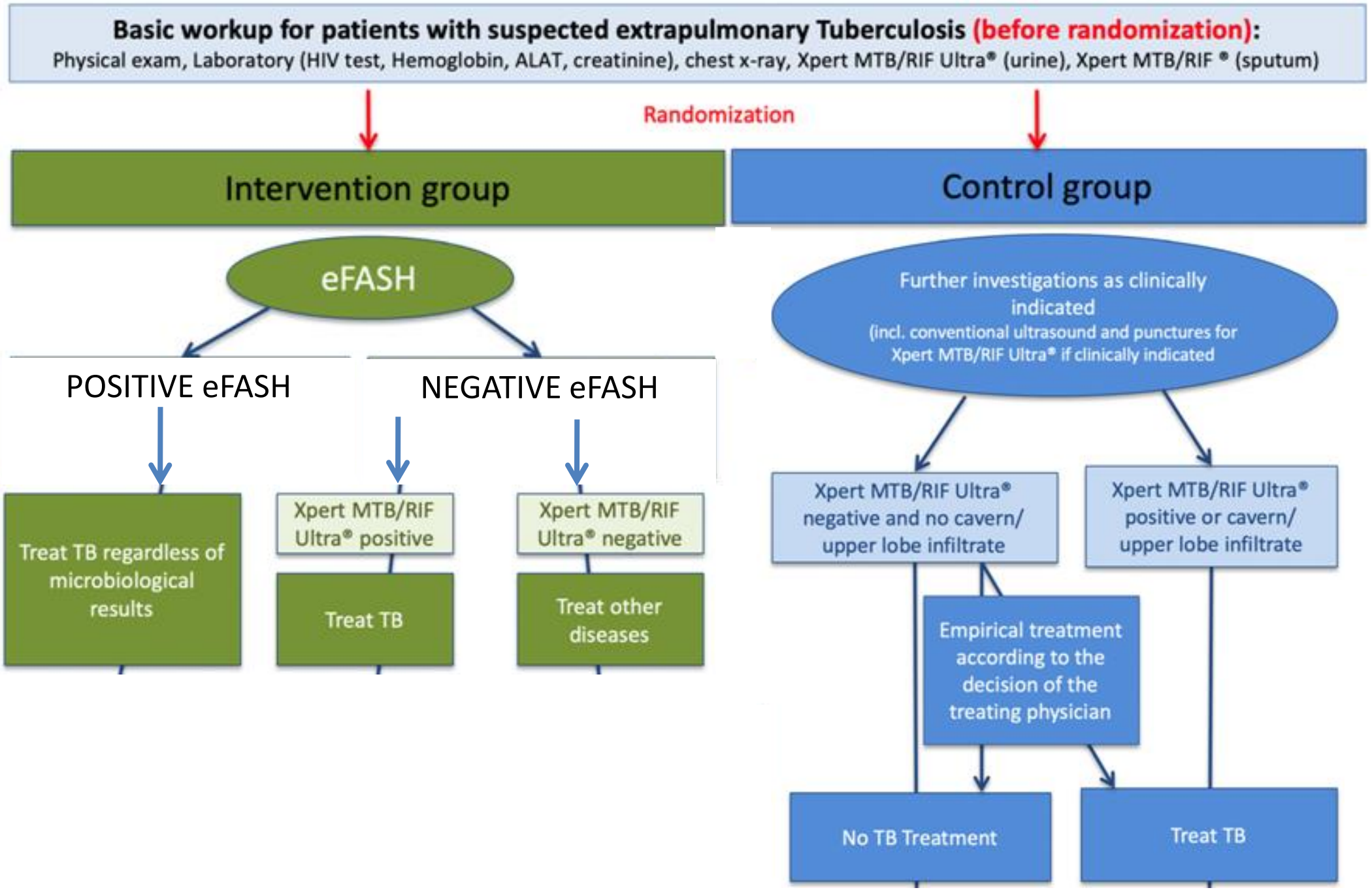
eFASH criteria^

ONLY INTERVENTION GROUP

eFASH results were considered positive if ≥1 of the following was present:

(1) multiple hypoechogenic lesions in the spleen or the liver;
(2) pericardial effusion without other clinical explanation;
(3) pleural effusion and no clinical or US signs for heart failure (normal inferior vena cava);
(4) subpleural granular artifacts with B-lines;
(5) abdominal, axillary, nuchal, or cervical lymph nodes >1.5 cm and no other explanation;
(6) thickened ileum wall >4 mm and loss of wall architecture and at least another eFASH sign;
(7) ascites and ≥1 additional eFASH sign

**The Xpert MTB/RIF assay for sputum was used because of its higher specificity compared with the Xpert MTB/RIF Ultra assay [2] and because it was the national standard for sputum samples during the study period.*


Basic workup for patients with suspected extrapulmonary Tuberculosis (before randomization):
Physical exam, Laboratory (HIV test, Hemoglobin, ALAT, creatinine), chest x-ray, Xpert MTB/RIF Ultra® (urine), Xpert MTB/RIF ® (sputum)
Randomization
Intervention group
Control group
eFASH
POSITIVE eFASH
NEGATIVE eFASH
Treat TB regardless of microbiological results
Xpert MTB/RIF Ultra® positive
Treat TB
Xpert MTB/RIF Ultra® negative
Treat other diseases
Further investigations as clinically indicated
(incl. conventional ultrasound and punctures for Xpert MTB/RIF Ultra® if clinically indicated
Xpert MTB/RIF Ultra® negative and no cavern/ upper lobe infiltrate
Xpert MTB/RIF Ultra® positive or cavern/ upper lobe infiltrate
Empirical treatment according to the decision of the treating physician
No TB Treatment
Treat TB

definitions

definite tuberculosis if any microbiological test result was positive or if the ADA level was elevated (≥40 U/mL in pleural [16], ≥35 U/mL in ascitic [17], or ≥35 U/mL in pericardial fluid [18]).

A correctly managed participant

(PRIMARY OUTCOME)

= definite or probable tuberculosis and treated with antituberculosis treatment at baseline

or

= NO tuberculosis and not treated with antituberculosis treatment at baseline

(SECONDARY OUTCOME)

- ✓ proportions of asymptomatic participants at 2 and 6 months
- ✓ proportions of participants with alternative diagnoses
- ✓ proportions of participants with invasive procedures
- ✓ time to death

Results

1036
elegibles

Excluded (n = 335)
- Age <18 y (n = 11)
- No constitutional signs/symptoms (n = 52)
- No extrapulmonary tuberculosis signs/symptoms (n = 185)
- Other explanation for signs/symptoms (n = 32)
- Pregnant (n = 1)
- Already on tuberculosis treatment (n = 1)
- Refused to sign informed consent (n = 26)
- Not available for follow-up (n = 27)

701
enrolled

351
control group

350
intervention group

The median age at enrollment was 39 years (IQ range, 29–50 years)

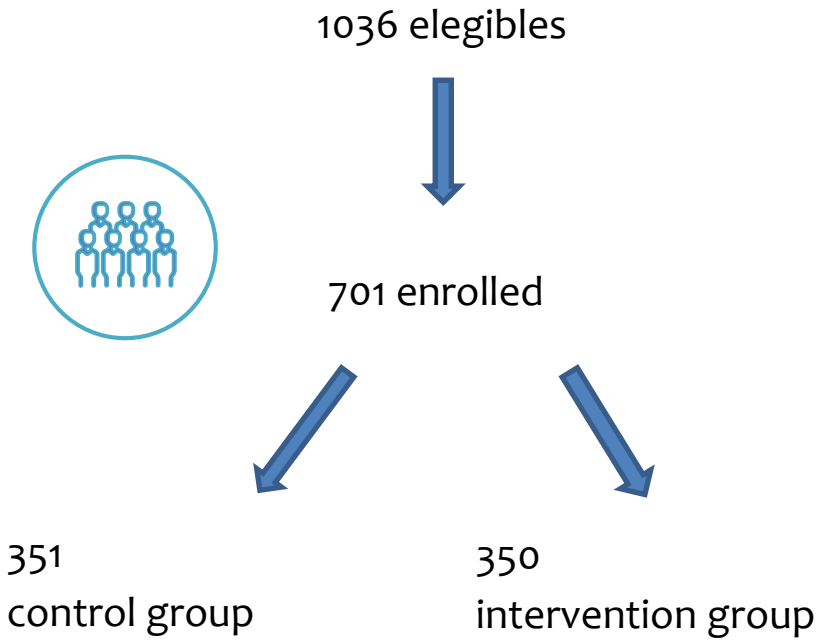
415 participants (59%) were male

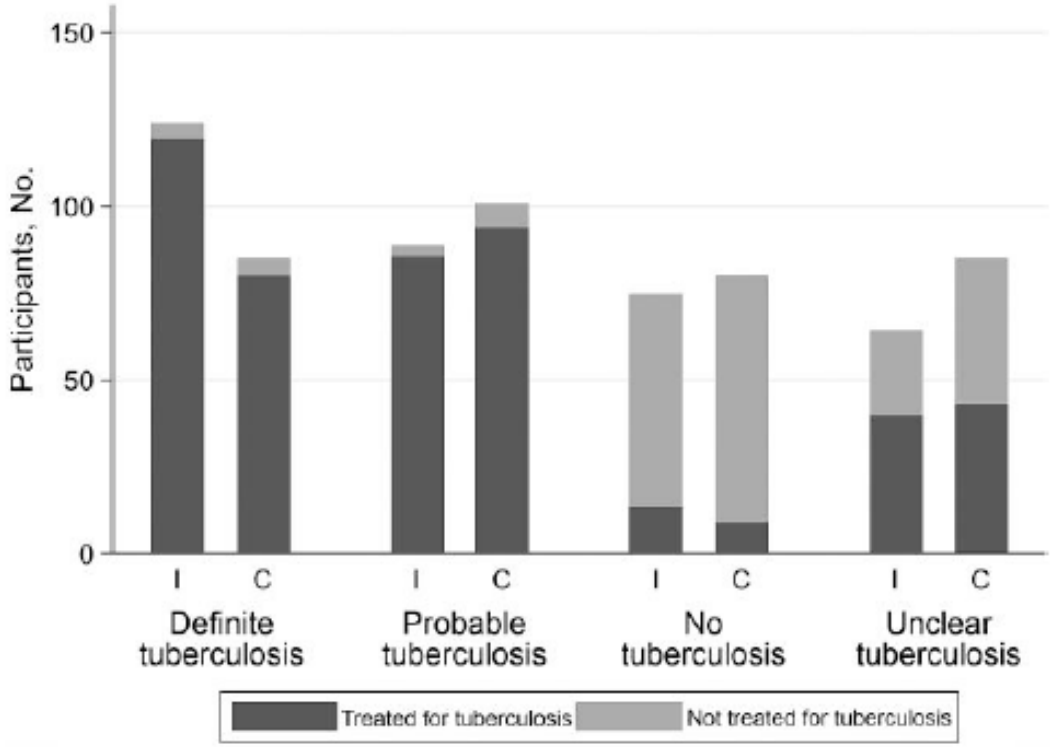
268 (38%) were HIV positive

65% (227/351)

74% (258/350)

Results





➢ <u>NO DIFFERENCE in the primary outcome between the 2 groups;</u>
a high proportion of participants were correctly managed: 266 of 286 (93%) in the intervention versus 245 of 266 (92%) in the control group (adjusted odds ratio, 1.14 [95% confidence interval: .60–2.16]; *P*=.68)

➢ <u>A greater proportion of participants in the intervention group had definite tuberculosis diagnosed</u>
(124 [35%] vs 85 [24%] in the control group)

Limitations

- high rates of early deaths and loss to follow-up (24-18%)
- findings might not be generalizable to other settings and populations with a lower morbidity (45-39%)
- almost one-third of participants had probable tuberculosis

Conclusions

- This study is one of the first randomized clinical trials evaluating the effects of the introduction of a diagnostic algorithm with eFASH on the management of EPTB, realized in a real African context and on a large number of participants.

- Greater proportion of definite tuberculosis in intervention group (35%) vs control group (24%), primarily due to a higher proportion of invasive procedures.

  The absence of complications after invasive procedures in our and other studies motivates the use of US-guided invasive procedures to increase the proportion of patients with definite tuberculosis. This is of epidemiological importance, especially in the context of drug resistance.

- As already highlighted in other studies, training of healthcare personnel is rapidly effective (*strong agreement on eFASH signs between the study physician and an independent board-certified sonographer*) → potential far-reaching benefit in terms of public health if the protocol is introduced in rural settings.

Considerations

- Not-so-much limited resources setting…
- Suggestive clinical criteria…

World Health Organization

Rapid communication:
Key changes to the treatment of drug-resistant tuberculosis

May 2022

- The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).

- This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.

The available evidence was limited to patients aged above 14 years and there were no data on the use of these regimens during pregnancy or in severe forms of extrapulmonary TB (e.g. TB meningitis). Thus, the evidence provided by the TB-PRACTECAL and ZeNix studies will support new recommendations for the programmatic use of the two regimens.

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Table 3. Primary and Secondary Outcomes

Outcome	Participants, No. With Outcome/Total No. (%)			
	Control Group (n = 351)	Intervention Group (n = 350)	OR (95% CI)[a]	*P* Value[b]
Primary outcome: correct management[c]	245/266 (92)	266/286 (93)	1.14 (.60–2.16)	.68
Effect modification of primary outcome				
Site				
Ifakara (rural)	98/107 (92)	115/124 (93)	1.18 (.45–3.08)	.94
Mwananyamala (urban)	147/159 (92)	151/162 (93)	1.12 (.48–2.62)	
HIV status				
Positive	84/91 (92)	100/108 (93)	1.05 (.36–3.01)	.84
Negative	161/175 (92)	166/178 (93)	1.20 (.54–2.68)	
Secondary outcomes				
Free of symptoms at 2 mo	80/183 (44)	79/216 (37)	0.77 (.50–1.17)	.22
Free of symptoms at 6 mo	124/168 (74)	114/163 (70)	0.84 (.51–1.37)	.49
Diagnosis other than tuberculosis at 6 mo[d]	159/351 (45)	138/350 (39)	0.78 (.57–1.05)	.11
Underwent an invasive procedure	18/351 (5)	202/350 (58)	25.6 (15.2–43.1)	<.001
Any safety outcome[e]	0	0	NA	NA
Death	90/351 (26)	91/350 (26)	HR: 0.91 (.67–1.23)	.54

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; NA, not applicable; OR, odds ratio.

[a]Results are intervention effects reported as ORs from logistic regression models, except for the result for death, reported as HR from Cox proportional hazards models, adjusted for the randomization stratification factors of site and HIV status.

[b]*P* values represent the intervention effect, except for the analysis of effect modification of the primary outcome, where the *P* values represent effect modification.

[c]Correct management was defined as initiating antituberculosis treatment at baseline with probable or definite tuberculosis determined by 6 months, or not initiating antituberculosis treatment at baseline and the absence of tuberculosis determined by 6 months. Tuberculosis status results are according to assessment by an independent end-point review committee; results correspond to a rate ratio of 1.01 (95% CI: .96–1.06) and risk difference of 0.009 (−.03 to .05), with standard errors estimated using the delta method.

[d]Including concomitant second diagnoses in participants with definite, probable, unclear, or no tuberculosis.

[e]Predefined as pneumothorax during thoracentesis, major bleeding during puncturing, or postexpansion pulmonary edema.