Massive Diagnostic Yield of HIV-Associated Tuberculosis Using Rapid Urine Assays in S. Africa

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Stephen D. Lawn,[1,2,3] Andrew D. Kerkhoff,[2,4] Rosie Burton,[3,5,6] Charlotte Schutz,[3,7] Gavin van Wyk,[3,5] Monica Vogt,[2] Pearl Pahlana,[2]
Mark P. Nicol,[8,9] Graeme Meintjes[3,7]

1 Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK; 2 Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine (IIDMM), University of Cape Town, Cape Town, South Africa; 3 Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; 4 George Washington University School of Medicine and Health Sciences, Washington DC, USA; 5 GF Jooste Hospital, Manenberg, Cape Town, South Africa; 6 Khayelitsha District Hospital, Cape Town, South Africa; 7 Clinical Infectious Diseases Research Initiative, IIDMM, University of Cape Town, Cape Town, South Africa; 8 Division of Medical Microbiology and IIDMM, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; 9 National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa

Stephen.lawn@lshtm.ac.uk

ABSTRACT

Background: Autopsy studies of HIV/AIDS deaths in medical in-patients in sub-Saharan Africa have all reported a high frequency of disseminated tuberculosis (TB), indicating frequent failure of diagnosis. This observational study aimed to identify improved means of rapid TB diagnosis.

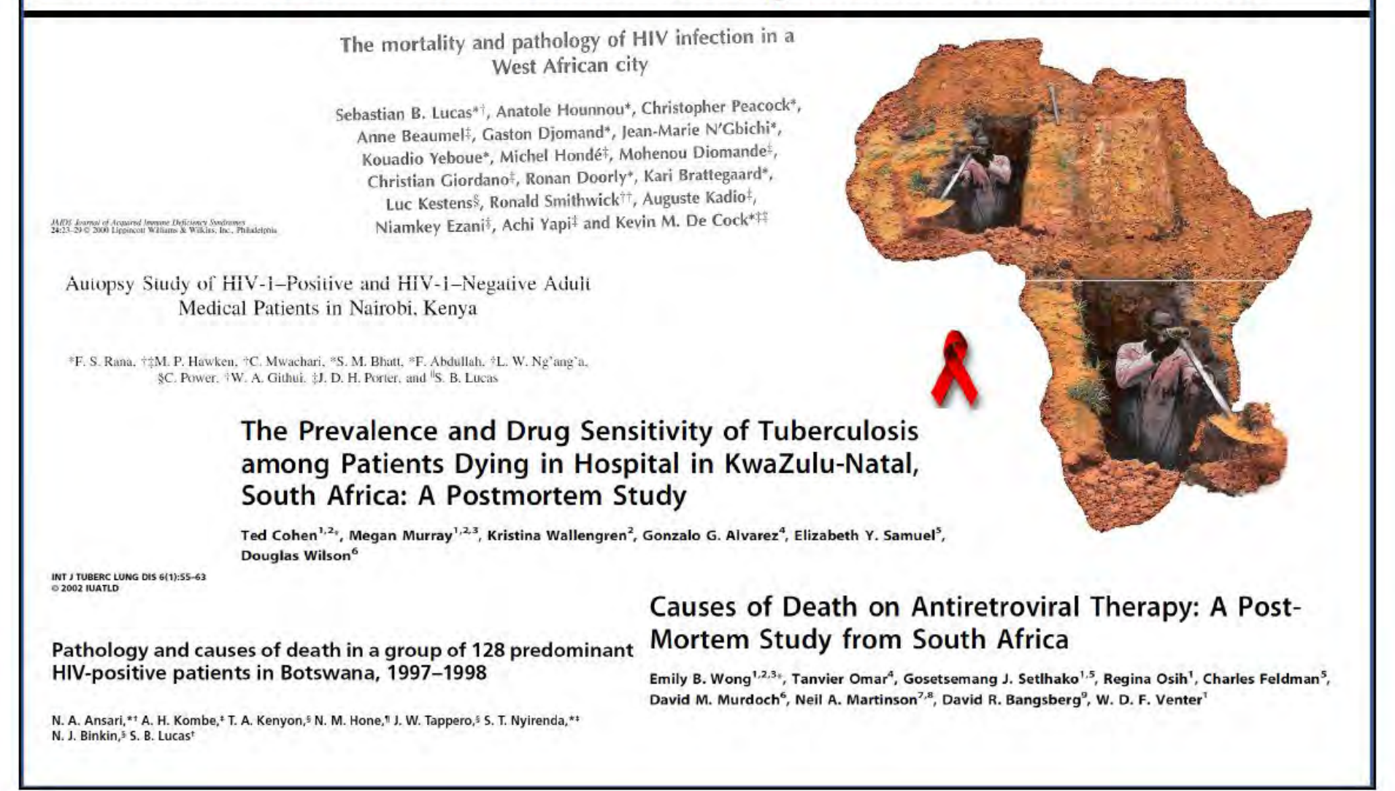
Methodology: Unselected HIV-infected medical admissions to a South African district hospital were intensively investigated. Sputum, urine and blood specimens were systematically obtained within the first 24 hours. Multiple additional respiratory and non-respiratory samples were obtained throughout admission as clinically indicated. Sputum samples were tested using fluorescence microscopy, liquid culture and Xpert MTB/RIF (Xpert). Urine samples were tested using Xpert (urine-Xpert of both unconcentrated and concentrated samples) and Determine TB-LAM (urine-LAM). Other non-respiratory samples were cultured. TB diagnoses were defined by detection of *Mycobacterium tuberculosis* in any sample using culture or Xpert.

Results: HIV-status was ascertained in 1,013 of 1,018 (99.5%) admissions and 585 of 609 (96.1%) HIV-infected patients were enrolled. All those without an existing TB diagnosis (n=427) were included in this analysis. 3,471 TB investigations were done on 1,745 samples from a median of 3 anatomic sites per patient. TB was diagnosed in 139 patients (median CD4 count, 80 cells/µL) and symptoms were very poorly predictive. TB prevalence was 32.6% (95%CI, 28.1-37.2). Disease was extrapulmonary in 83% of cases and pulmonary in just 54% (P<0.001). Using samples obtained in the first 24-hours, the proportions of final diagnoses made by sputum microscopy, sputum-Xpert, urine-LAM and urine-Xpert (30-40 ml concentrated urine) were 19.4%, 26.6%, 38.1% and 59.0%, respectively. Rapid urine tests used together diagnosed 69.1% (96 of 139) of cases. This further increased to 80.6% (112 of 139) of cases when combined with sputum Xpert testing. Of those with CD4 counts <100 cells/µL, 85.1% (63 of 74) could be diagnosed with urine rapid tests alone.

Conclusions: The prevalence of TB was so high and the presentation so non-specific that routine microbiological investigation for TB should be done in all HIV-infected medical in-patients in high-burden settings. Compared to Xpert testing of one sputum sample alone, the addition of urine-based testing increased the diagnostic yield of the initial TB screen 3.0-fold from 26.6% to 80.6% (P<0.001). Urine-based rapid diagnostics should be considered for routine use in this patient population.

THE PROBLEM:

Post-mortem studies of HIV+ medical in-patient deaths in sub-Saharan Africa (1993-2013) report finding TB in 32% - 67% of cadavers. Much of this remained undiagnosed at the time of death.



JAIDS Journal of Acquired Immune Deficiency Syndromes 24:23–29 © 2000 Lippincott Williams & Wilkins, Inc., Philadelphia

The mortality and pathology of HIV infection in a West African city

Sebastian B. Lucas*†, Anatole Hounnou*, Christopher Peacock*, Anne Beaumel‡, Gaston Djomand*, Jean-Marie N'Gbichi*, Kouadio Yeboue*, Michel Hondé‡, Mohenou Diomande‡, Christian Giordano‡, Ronan Doorly*, Kari Brattegaard*, Luc Kestens§, Ronald Smithwick††, Auguste Kadio‡, Niamkey Ezani‡, Achi Yapi‡ and Kevin M. De Cock*†‡

Autopsy Study of HIV-1–Positive and HIV-1–Negative Adult Medical Patients in Nairobi, Kenya

*F. S. Rana, †‡M. P. Hawken, †C. Mwachari, *S. M. Bhatt, *F. Abdullah, †L. W. Ng'ang'a, §C. Power, †W. A. Githui, ‡J. D. H. Porter, and ||S. B. Lucas

The Prevalence and Drug Sensitivity of Tuberculosis among Patients Dying in Hospital in KwaZulu-Natal, South Africa: A Postmortem Study

Ted Cohen[1,2*], Megan Murray[1,2,3], Kristina Wallengren[2], Gonzalo G. Alvarez[4], Elizabeth Y. Samuel[5], Douglas Wilson[6]

INT J TUBERC LUNG DIS 6(1):55–63
© 2002 IUATLD

Pathology and causes of death in a group of 128 predominant HIV-positive patients in Botswana, 1997–1998

N. A. Ansari,*† A. H. Kombe,‡ T. A. Kenyon,§ N. M. Hone,¶ J. W. Tappero,§ S. T. Nyirenda,*‡ N. J. Binkin,§ S. B. Lucas†

Causes of Death on Antiretroviral Therapy: A Post-Mortem Study from South Africa

Emily B. Wong[1,2,3*], Tanvier Omar[4], Gosetsemang J. Setlhako[1,5], Regina Osih[1], Charles Feldman[5], David M. Murdoch[6], Neil A. Martinson[7,8], David R. Bangsberg[9], W. D. F. Venter[1]

Is Rapid Urine-Based TB Diagnosis a Solution?

Determine TB-LAM

- Simple, low-cost, lateral flow assay
- Detects cell wall antigen lipoarabinomannan (LAM)
- Can be used at point-of-care
- Provides result within 30 minutes

Xpert MTB/RIF Assay

- Cartridge-based rapid molecular assay
- Detects DNA in *Mycobacterium tuberculosis* bacilli in many different clinical sample types
- Yield in urine can be increased by concentration

AIMS AND SETTING

AIMS: To determine TB prevalence among unselected HIV+ medical admissions and to determine the comparative yield from different diagnostic approaches, including rapid urine-based diagnostics.

SETTING: G.F. Jooste District Hospital serving township communities in Cape Town, South Africa

PATIENTS AND METHODS

Prospective descriptive cohort study

Unselected patient sample of new admissions to medical wards

- ALL were offered testing for HIV infection
- ALL HIV+ patients investigated for TB regardless of symptoms / presentation

Yields from different samples and assays were determined

Yields from sputum-based vs urine-based vs other samples were compared

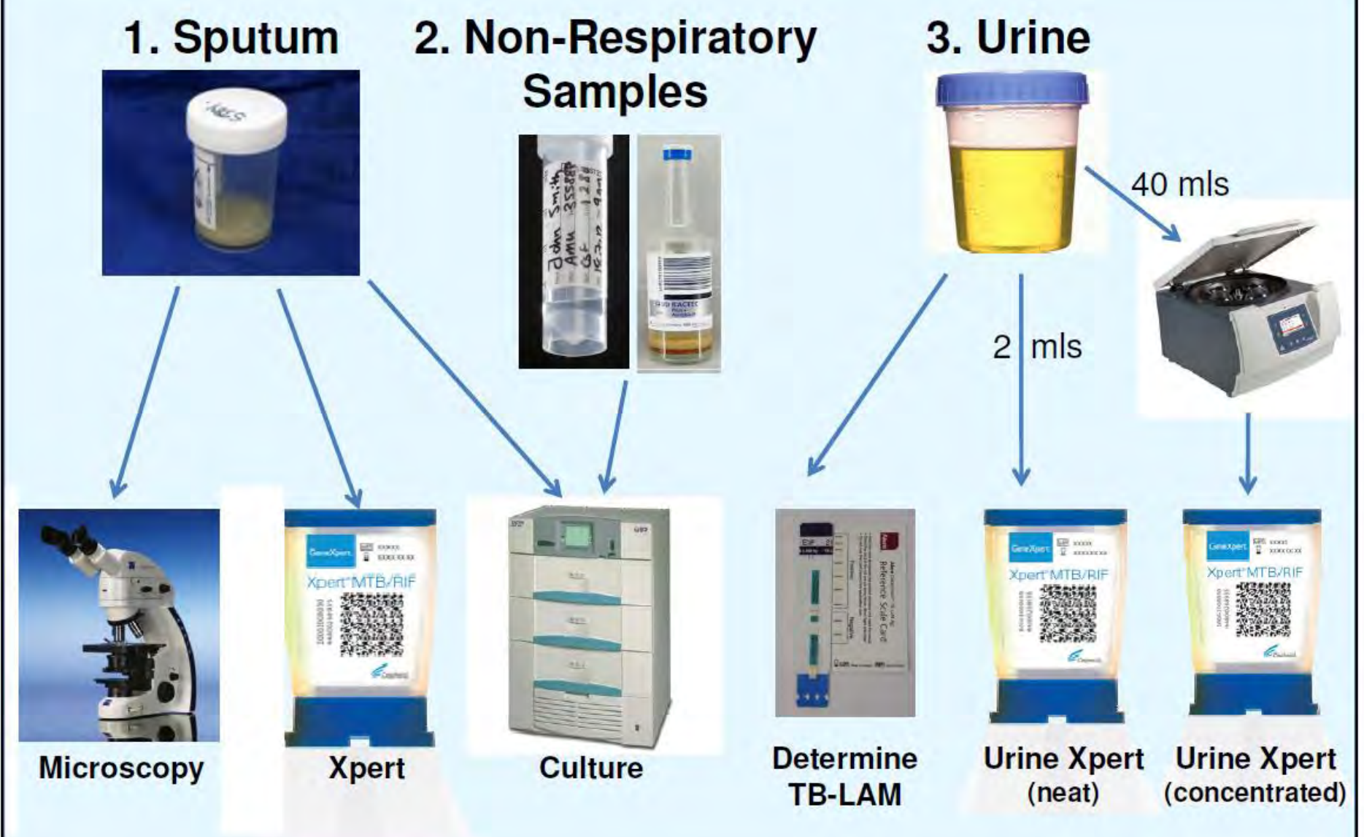
Times when samples were obtained:

Day 1: Study TB Screen | **Multiple other TB investigations as required during remainder of admission period**

Systematic screen:
Sputum
Urine
Blood cultures

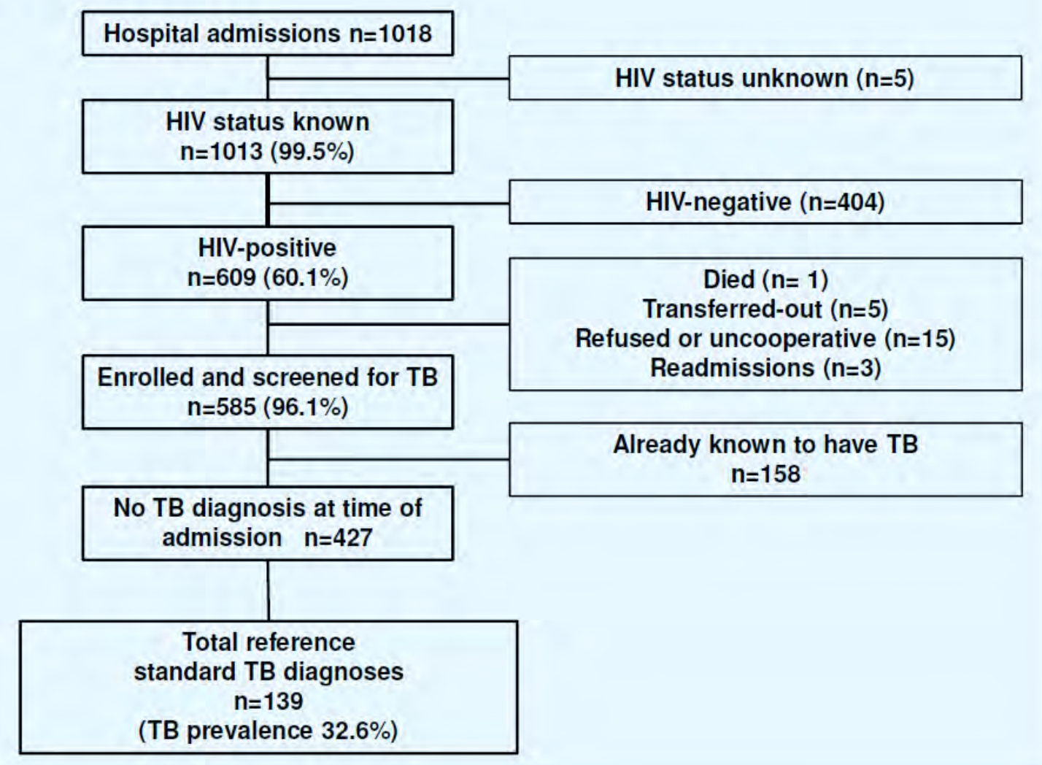
Additional samples:
Sputum; Blood cultures; Pleural fluid / biopsy; CSF; Lymph node aspirates / biopsies; Bone Marrow; Urine culture etc

Laboratory Investigations for TB



RESULTS

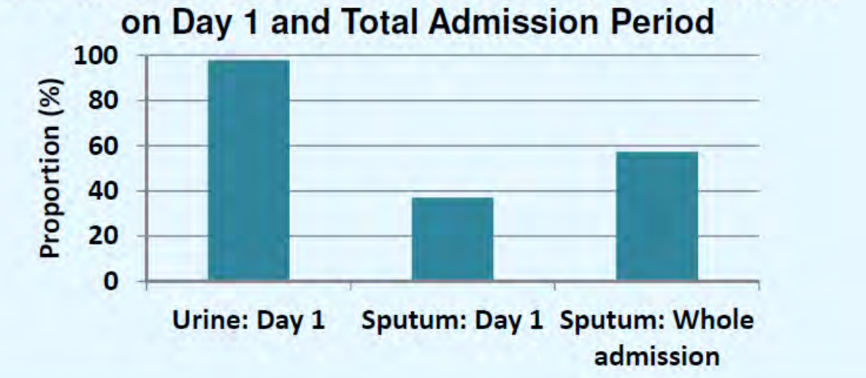
Patient Recruitment



Samples Obtained From Patients (n=427)

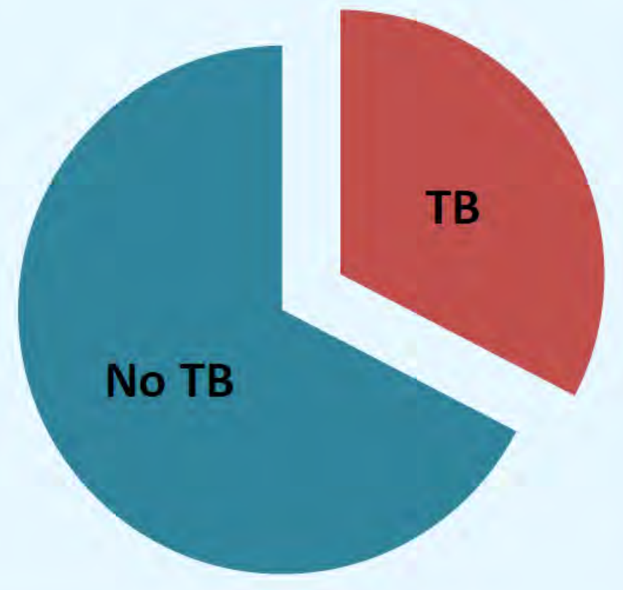
Sample Types	First 24 hour Samples	Total Admission Samples	Total TB Tests
Sputum	379	615	1,378
Urine	418	418	1,251
Other Non-respiratory	-	712	842
TOTAL	**697**	**1,745**	**3,471**

% Patients Able to Produce Urine / Sputum Samples on Day 1 and Total Admission Period



TB Prevalence

- TB diagnoses = 139 (Xpert or culture of any sample)
- TB Prevalence = 32.6% (28.1-37.2)

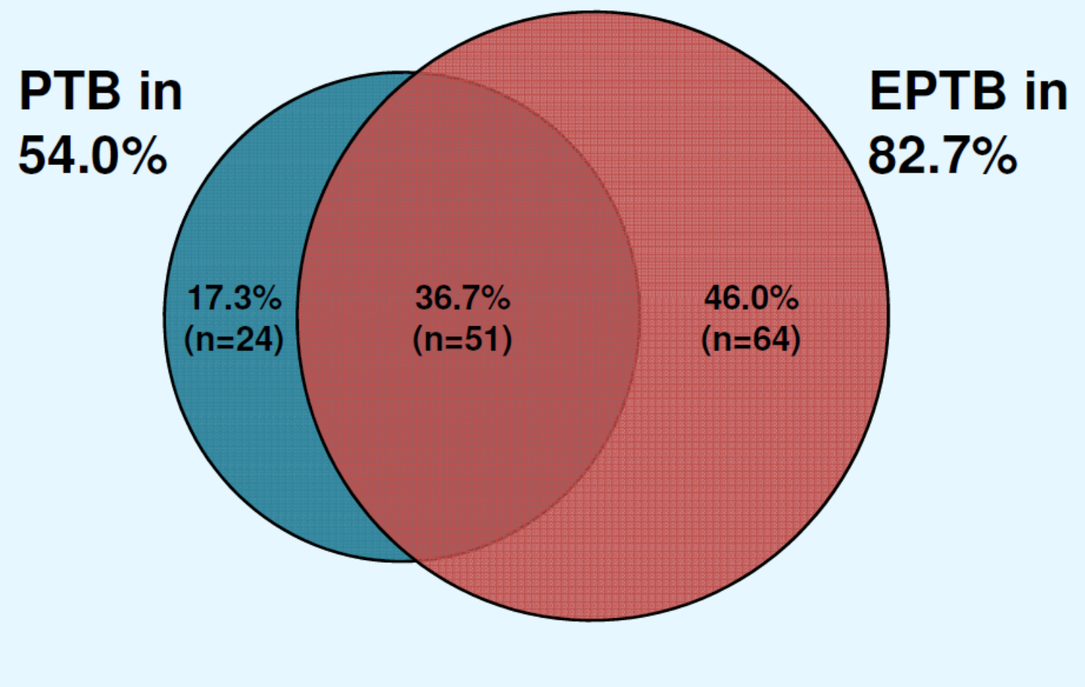


Median CD4 Count in TB cases = 80 cells/µL

Cough >2 weeks in just 13% of TB cases

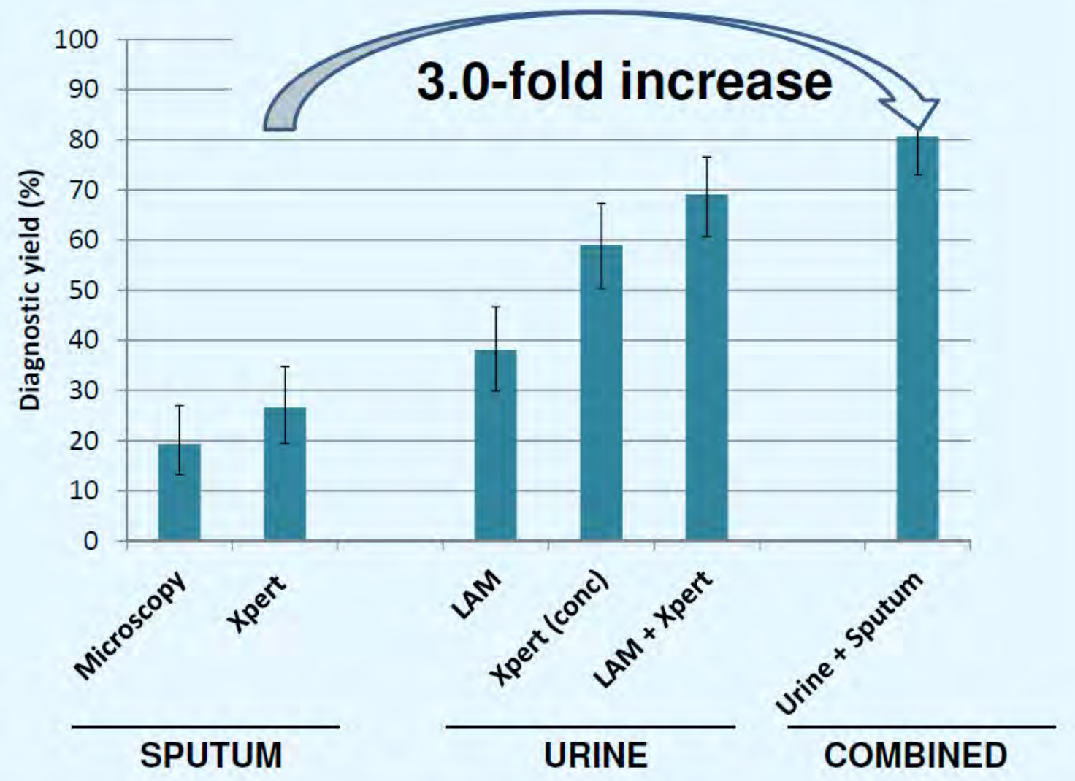
WHO symptom screen positive in 92% of total patients studied: NOT predictive for TB

Pulmonary vs Extrapulmonary Disease

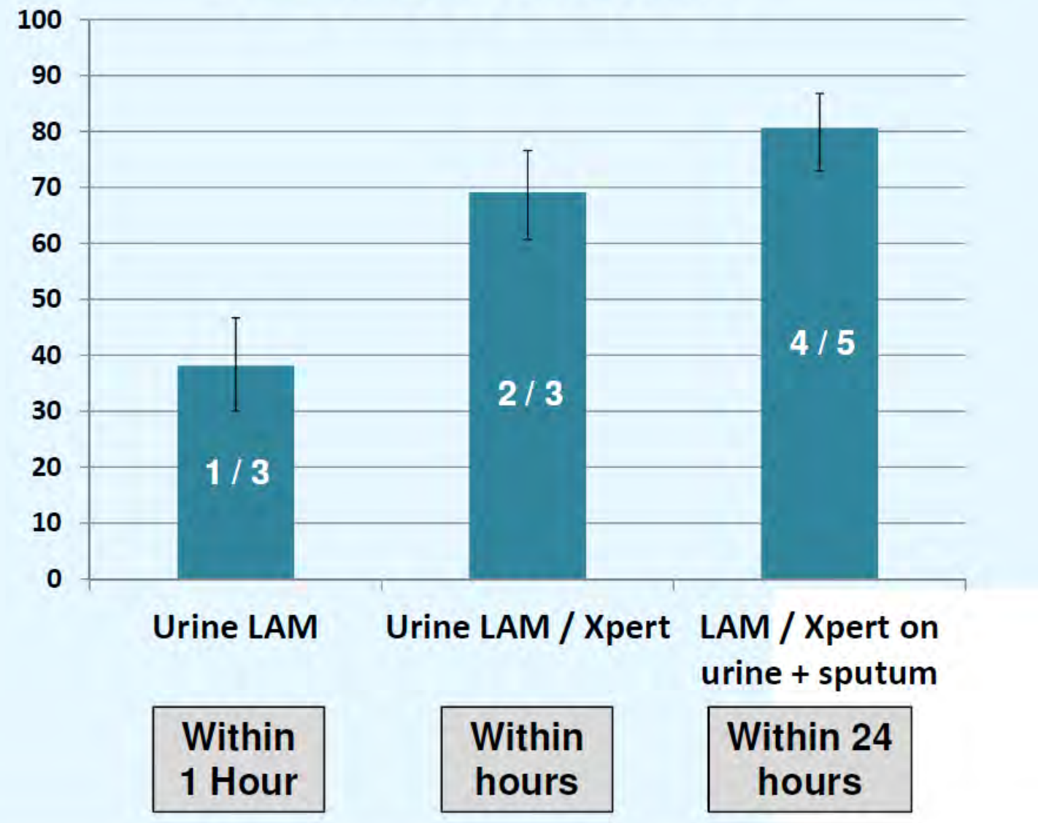


...so why do we rely primarily on sputum testing?

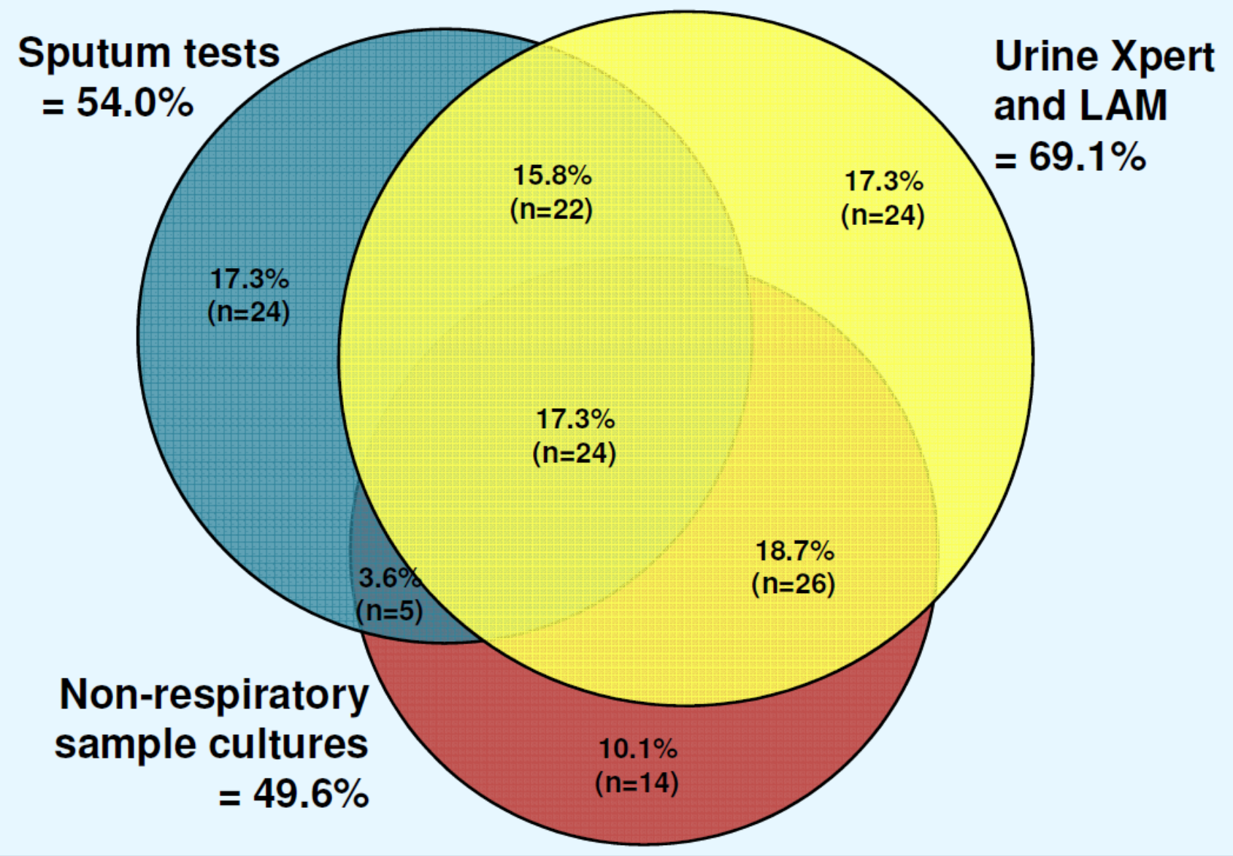
Diagnostic Yield From Rapid Testing of Sputum and Urine Obtained in First 24 Hrs



Cumulative Yield of Diagnoses Achievable in First 24 Hours of Admission



Final Total Diagnoses (n=139) Made From Three Types of Samples Obtained During Total Admission Period



Conclusions

- **Huge burden of HIV-TB in this clinical population:**
  - symptoms very poorly predictive
  - much TB remains 'under the radar'
- **Traditional diagnostic approaches are v. limited:**
  - identifying 'suspects' greatly limits the diagnostic yield
  - reliance on sputum is unhelpful: many patients cannot produce sputum and much disease is extrapulmonary
- **Need a paradigm shift(s) in diagnostic approach:**
  - Active screening regardless of symptoms is needed
  - Consider routine use of urine-based rapid tests (Determine TB-LAM and urine Xpert MTB/RIF) in the initial diagnostic screen

References

- Lawn SD, Kerkhoff AD, Vogt M, Wood R. Diagnostic accuracy of a low-cost, urine antigen, point-of-care assay for screening for HIV-associated tuberculosis prior to antiretroviral therapy: a descriptive study. Lancet Infect Dis 2012; 12: 201-209.
- Lawn SD, Kerkhoff AD, Vogt M, Wood R. High diagnostic yield of tuberculosis from screening urine samples from HIV-infected patients with advanced immunodeficiency using the Xpert MTB/RIF assay. J Acquir Immunodefic Syndr 2012; 60: 289-294.
- Lawn SD. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. BMC Infect Dis 2012; 12: 103.
- Lawn SD Kerkhoff AD, Vogt M, Wood R. Clinical significance of lipoarabinomannan (LAM) detection in urine using a low-cost point-of-care diagnostic assay for HIV-associated tuberculosis. AIDS 2012; 26: 1635-1643.
- Lawn SD, Dheda K, Kerkhoff AD, Peter J, Dorman S, Boehme CC, Nicol M. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. BMC Infect Dis 2013; 13: 407.
- Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Medicine 2013; 11: 231.
- Peter JG, Theron G, Muchinga TE, Govender U, Dheda K: The diagnostic accuracy of urine-based Xpert MTB/RIF in HIV-infected hospitalized patients who are smear-negative or sputum scarce. PLoS ONE 2012, 7:e39966.
- Peter JG, Theron G, Zyl-Smit R, Haripersad A, Mottay L, Kraus S, Binder A, Meldau R, Hardy A, Dheda K: Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. Eur Respir J 2012, 40:1211-1220.
- Dorman S., Manabe Y, Nicol M, Nakiyingi L, Moodley M, Zemanay W, Holshouser M, Perkins M, Alland D, Ellner J. Accuracy of Determine TB-LAM Lateral Flow Test for Diagnosis of TB in HIV+ Adults: Interim Results from a Multicenter Study. Program and Abstracts of the 19th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington 3-8 March 2012. Abstract # 149aLB.

Funding : wellcome trust

Improving health worldwide www.lshtm.ac.uk