Cryptococcosis

Preventing a Deadly Fungal Disease Together

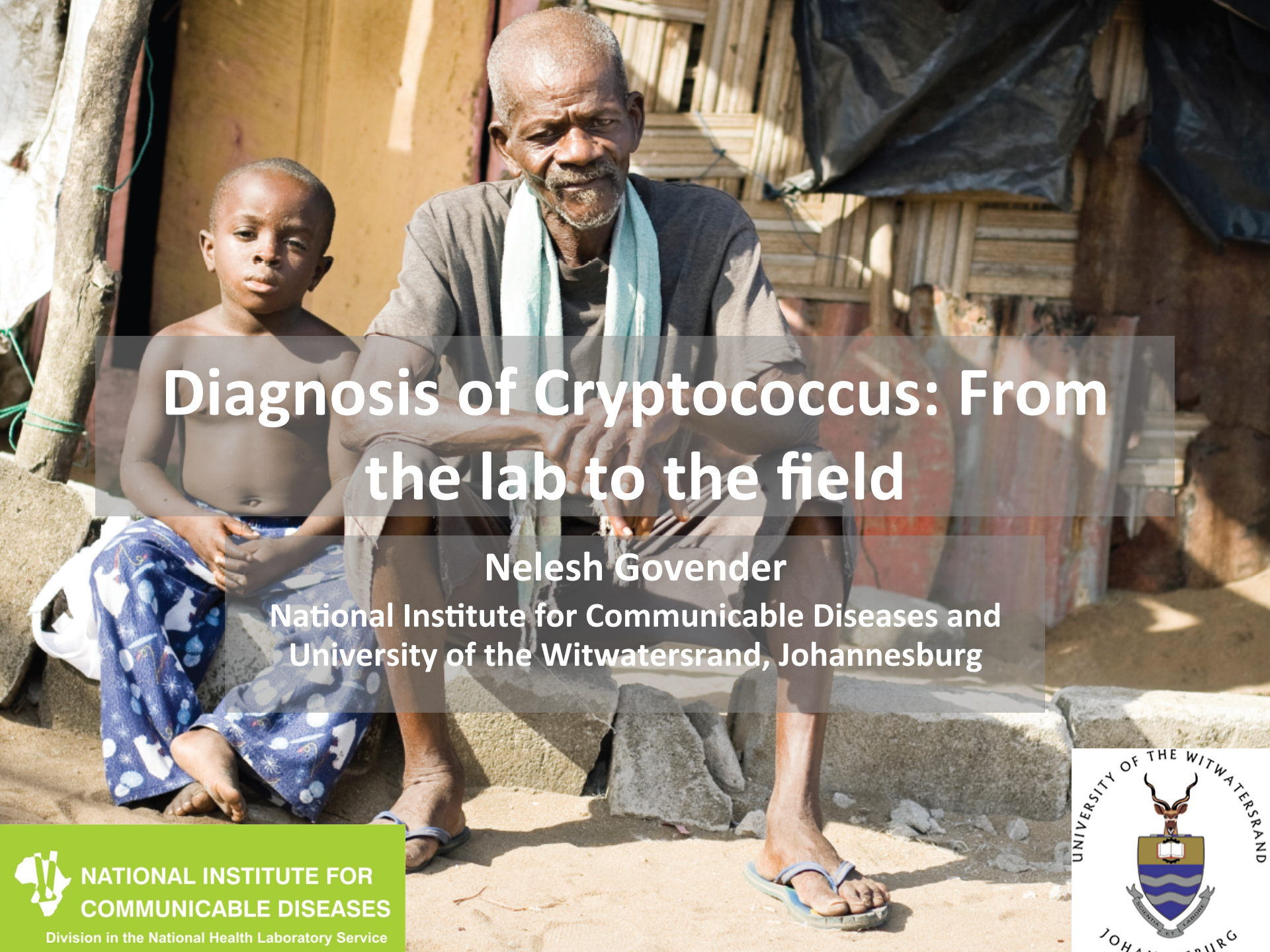
THANK YOU

Cryptococcosis

Preventing a Deadly Fungal Disease

Round table programme update:

Time	Title	Speaker
17:30-17:45	**Diagnosis of Cryptococcus: From the lab to the field**	Dr. Nelesh Govender *(NICD)*
17:45-18:05	**Lateral flow assay demonstration**	Sean Bauman *(Immy)*
18:05-18:20	**The South African Screening program**	Dr. Samuel Oladoyinbo *(CDC South Africa)* Dr. Thapelo Maotoe *(USAID South Africa)*
18:20-18:35	**Clinical management**	Graeme Meintjes *(University of Cape Town)*
18:35-18:50	**Cryptococcal screening in Uganda**	David Meya *(Makerere University)* David Boulware *(University of Minnesota)*
18:50-19:00	**Q&A**	All



Diagnosis of Cryptococcus: From the lab to the field

Nelesh Govender

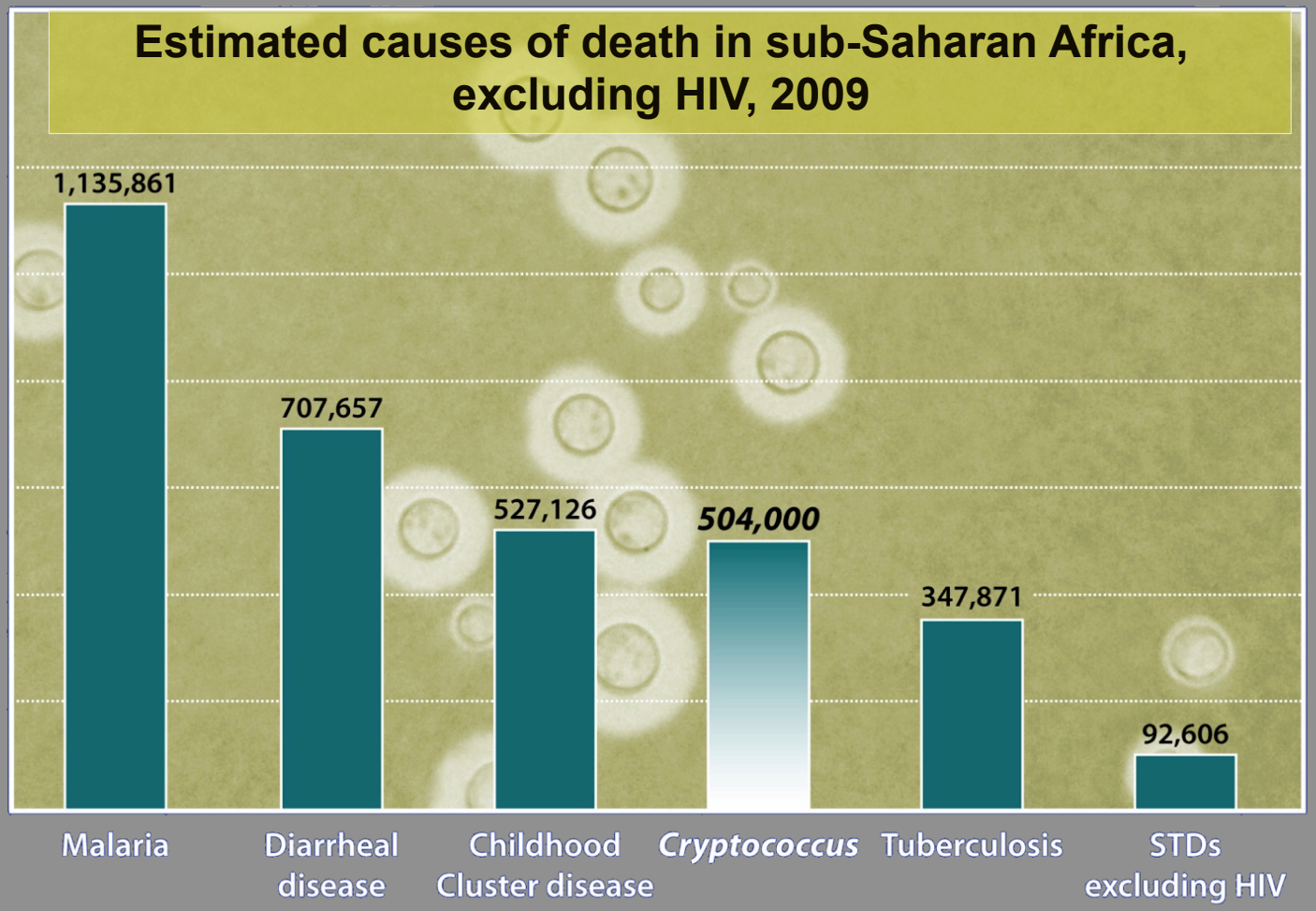
National Institute for Communicable Diseases and University of the Witwatersrand, Johannesburg

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

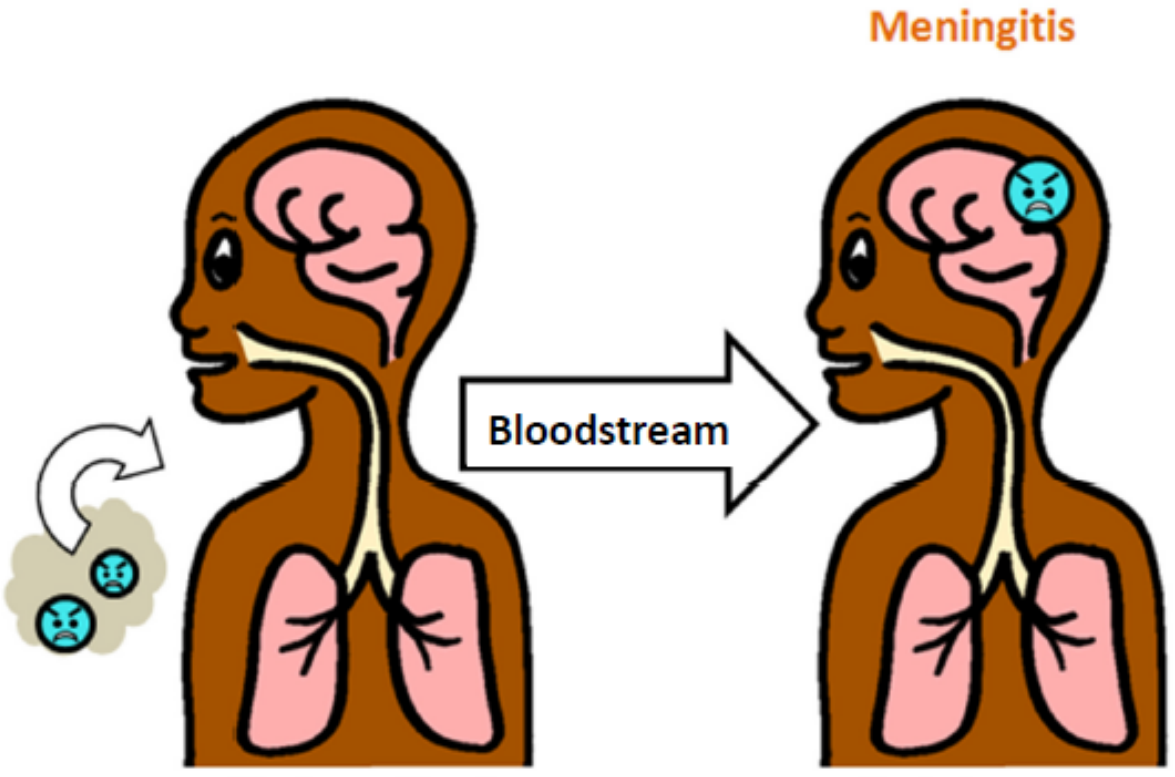
Division in the National Health Laboratory Service

UNIVERSITY OF THE WITWATERSRAND

Death from cryptococcal meningitis in sub-Saharan Africa



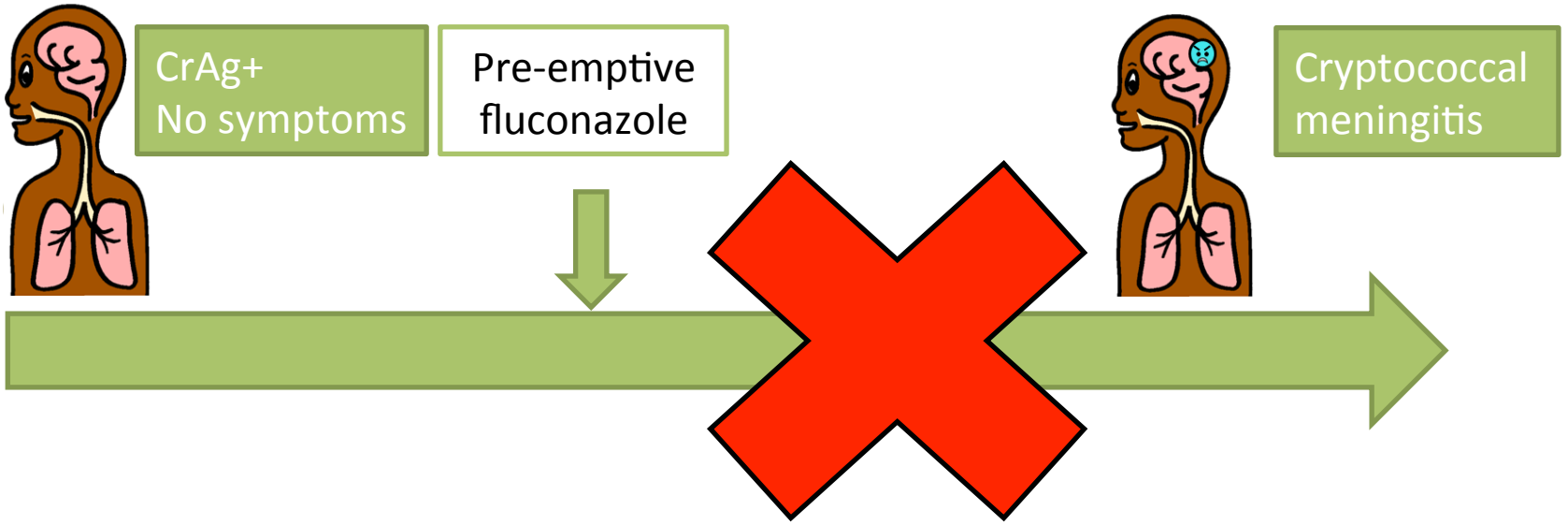
Pathogenesis of disease



Garcia-Hermoso D, et al. *J Clin Microbiol* 1999
French N, et al. AIDS 2002.

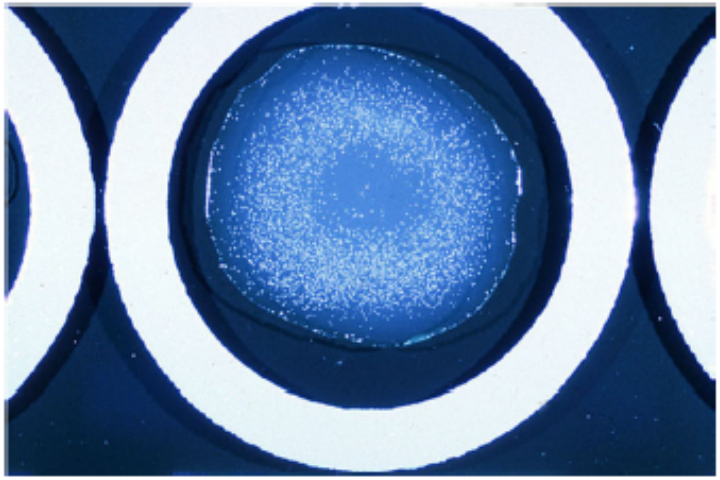
How cryptococcal screening works

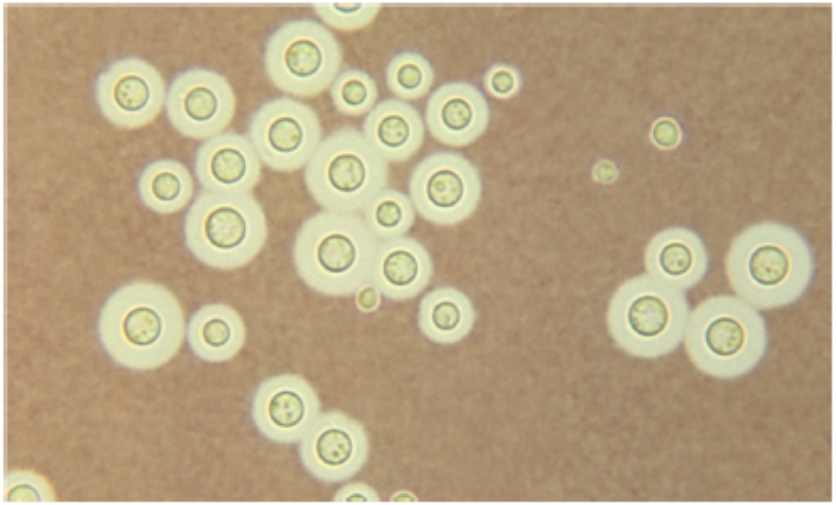
- Identify HIV-infected patients with CD4<100
- Test for cryptococcal antigenaemia before symptom onset
- Treat with oral fluconazole
- Prevent cryptococcal meningitis and deaths

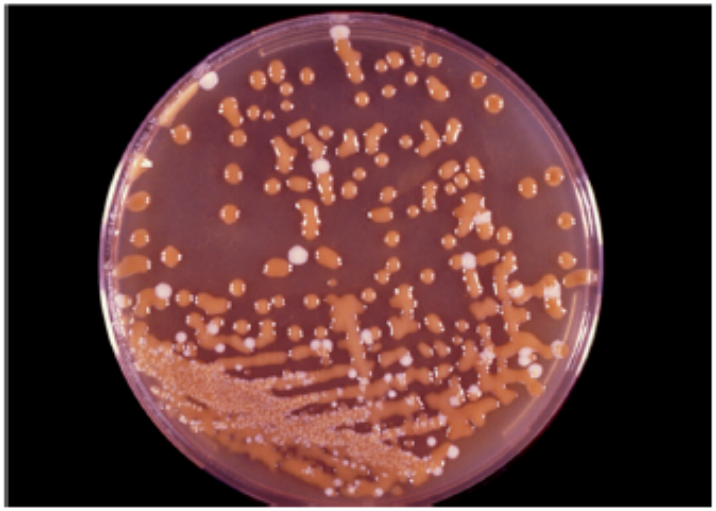


Conventional diagnostic tests

- Microscopy
- Antigen detection
- Culture





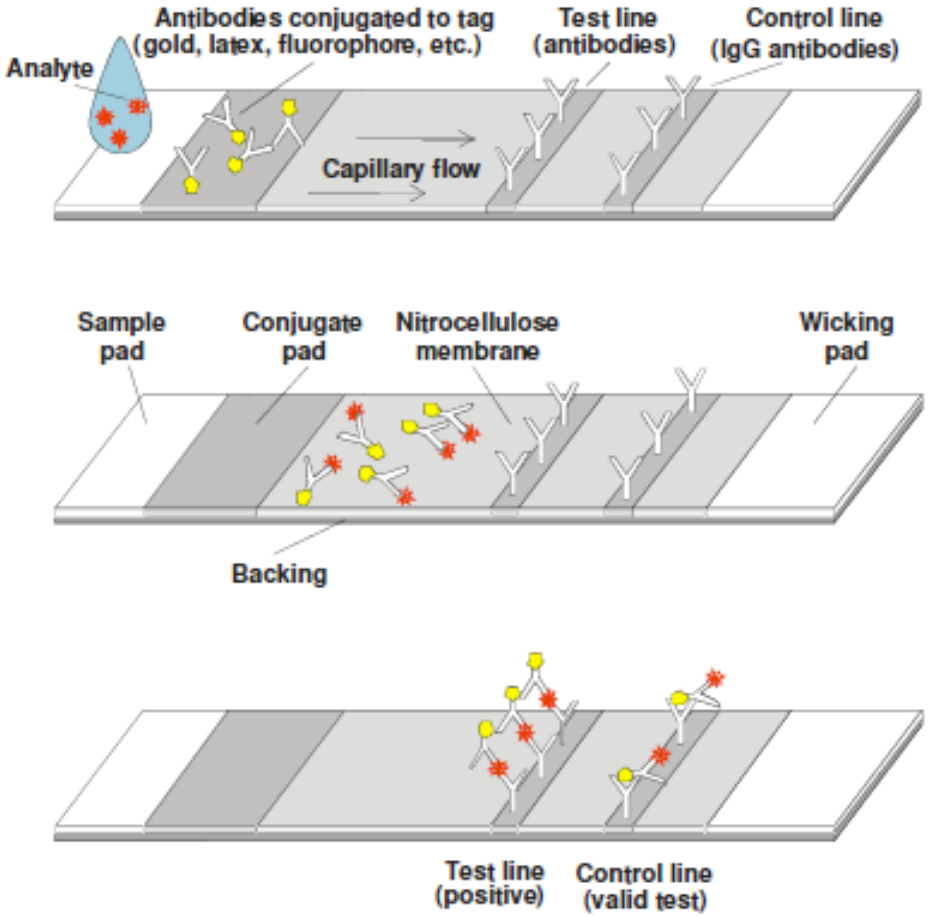


Expanded range of diagnostic tests

WHO ASSURED criteria	India ink	Culture	LA	LFA	EIA
Affordable	+	++++	+++	++	++++
Sensitive	73% - 94%	Reference	90% - 100%	98% - 100%	93% - 100%
Specific	95% - 100%	Reference	83% -100%	95% - 100%	93% - 100%
User-friendly	+++	++	++	++++	+
Rapid and robust	5 min	Days	35 min	10 min	Hours
Equipment-free	+++	+	++	++++	+
Delivered	+++	+	++	++++	++

WHO Rapid Advice Guidelines. December 2011.

Cryptococcal lateral flow assay



Sean Bauman, IMMY

LFA performance as a diagnostic test

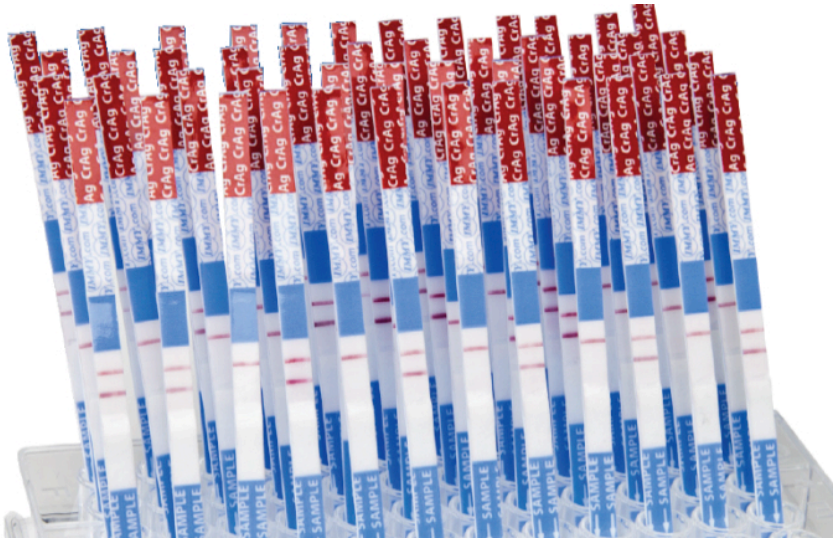
Reference	Study site	Number	Study population	Sensitivity	Specificity	Reference
Jarvis JN, et al. Clin Infect Dis 2011	Cape Town, South Africa	62	HIV+ adults with prior culture-confirmed cryptococcal meningitis	100% (serum and plasma); 98% (urine)	Not determined	CSF culture
Lindsley M, et al. Clin Infect Dis 2011	Thailand	704	HIV+ adults with pneumonia	90% (serum); 70% (urine)	99% (serum)	EIA
Lindsley M, et al. Clin Infect Dis 2011	Thailand	18	HIV+ adults with pneumonia	100% (serum); 92% (urine)	Not determined	Blood culture
Rolfes M, CROI 2012	Kampala, Uganda	102	ART-naïve adults with and without cryptococcal meningitis	100% (CSF, serum and plasma), 99% (urine)	99% (CSF), 96% (serum), 100% (plasma), 98% urine	CSF culture
Govender NP, unpublished	Johannesburg, South Africa	295	HIV+ adults with and without cryptococcal meningitis	100% (CSF), 99% (whole blood, serum, plasma), 95% (urine)	100% (CSF, whole blood, plasma, urine), 99% (serum)	CSF culture

Thokozile Gloria Zulu – FRIDAY, 7 NOVEMBER

A comprehensive screening programme

- Who should be screened and where?
- Develop clinical algorithm
- Integrate screening into ART and TB programmes
- Train healthcare personnel
- Educate patients
- Perform monitoring and evaluation to determine effectiveness

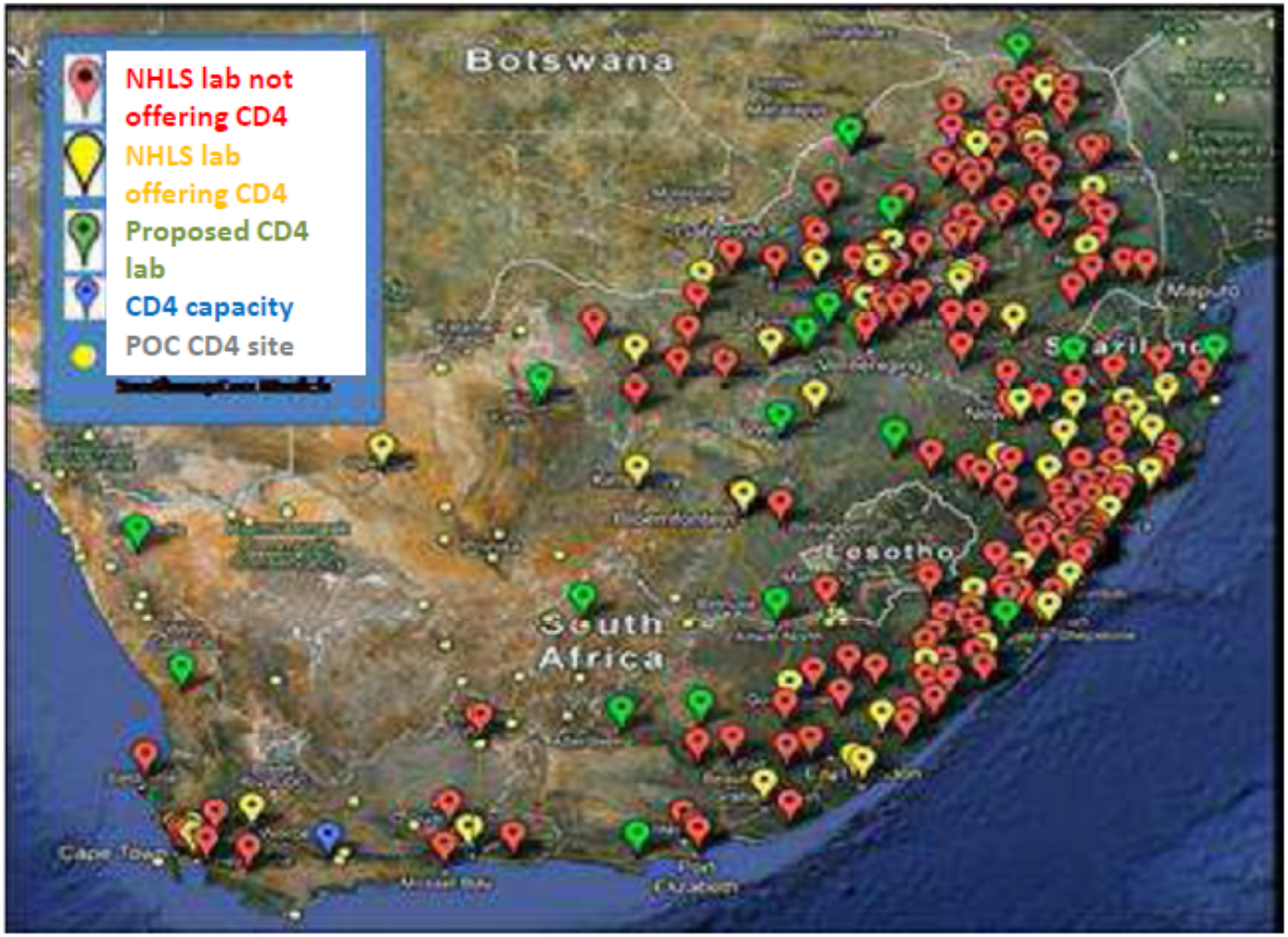
Strategy	1. Reflex LAB	2. Clinician-initiated LAB	3. Clinician-initiated POC
Coverage	▪ Potentially broader	▪ Restricted	▪ Restricted
Test location	▪ CD4 laboratory	▪ Microbiology laboratory	▪ Point-of-care
Required specimen	▪ CD4 EDTA-blood sample	▪ Separate sample submitted by clinician	▪ Whole blood or urine
Test format	▪ Lateral flow assay	▪ Latex agglutination test or lateral flow assay	▪ Lateral flow assay
Test request	▪ Reflex	▪ Depends on clinician awareness	▪ Depends on clinician awareness
Clinician training	▪ Augmented clinician training required because test not specifically requested	▪ Clinician training useful adjunct	▪ Clinician training useful adjunct
Patient selection	▪ All samples screened regardless of clinical background – including repeat CD4 samples from the same patient	▪ Clinicians select patients, e.g. ART-naïve vs. ART-experienced, no prior CM, adult, asymptomatic, no prior screening test	▪ Clinicians select patients, e.g. ART-naïve vs. ART-experienced, no prior CM, adult, asymptomatic, no prior screening test



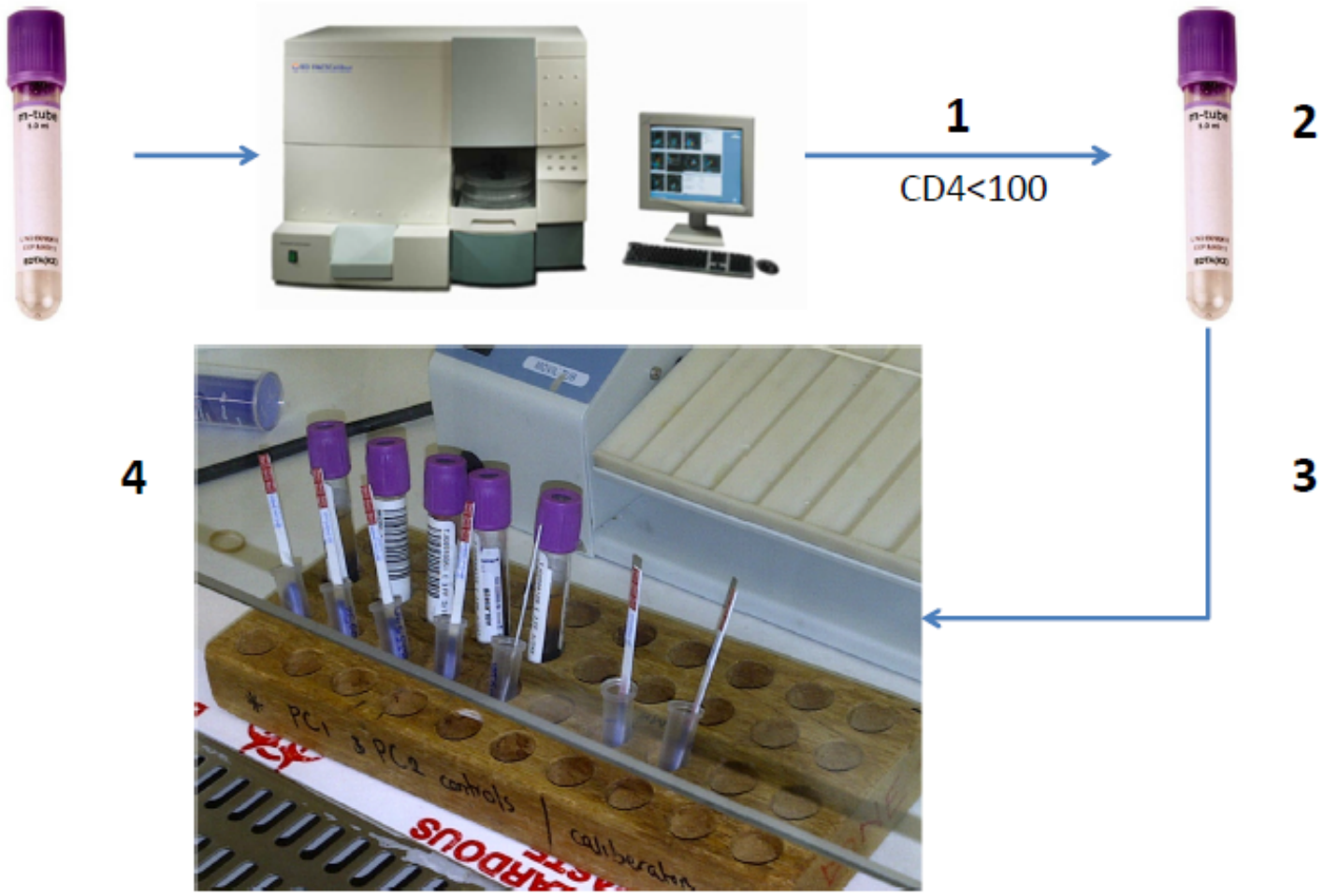
SCREENING STRATEGIES

1. REFLEX LABORATORY SCREENING

NHLS CD4 lab footprint



Reflex Laboratory Screening



National Health
Laboratory Service
(Pr5200296)
NHLS Laboratoratoy Complex
Johannesburg Hospital
Jubilee Street,
Parktown, 2193

Call Centre 24 hours
Tel: (011) 489-8571/2/4/5
Fax: (011) 489-8409/10
After Hours
Tel: (011) 489-8433

Johannesburg Hospital Laboratory Complex

Patient

Age(Sex)DoB

Ref Dr
Ward-Hosp

Hosp No
Taken
Report

LABORATORY REPORT

Clinical data No clinical details supplied
Specimen Blood
Tests ordered CD4,Crypt

LYMPHOCYTE SUBSET ANALYSIS		Flags	Ref Ranges
CD45 +ve White Cell Count	9.27 x 10^9/l		
CD4% of Lymphocytes	2.63 %		
Absolute CD4	20 X 10^6/l	L-	500 - 2010

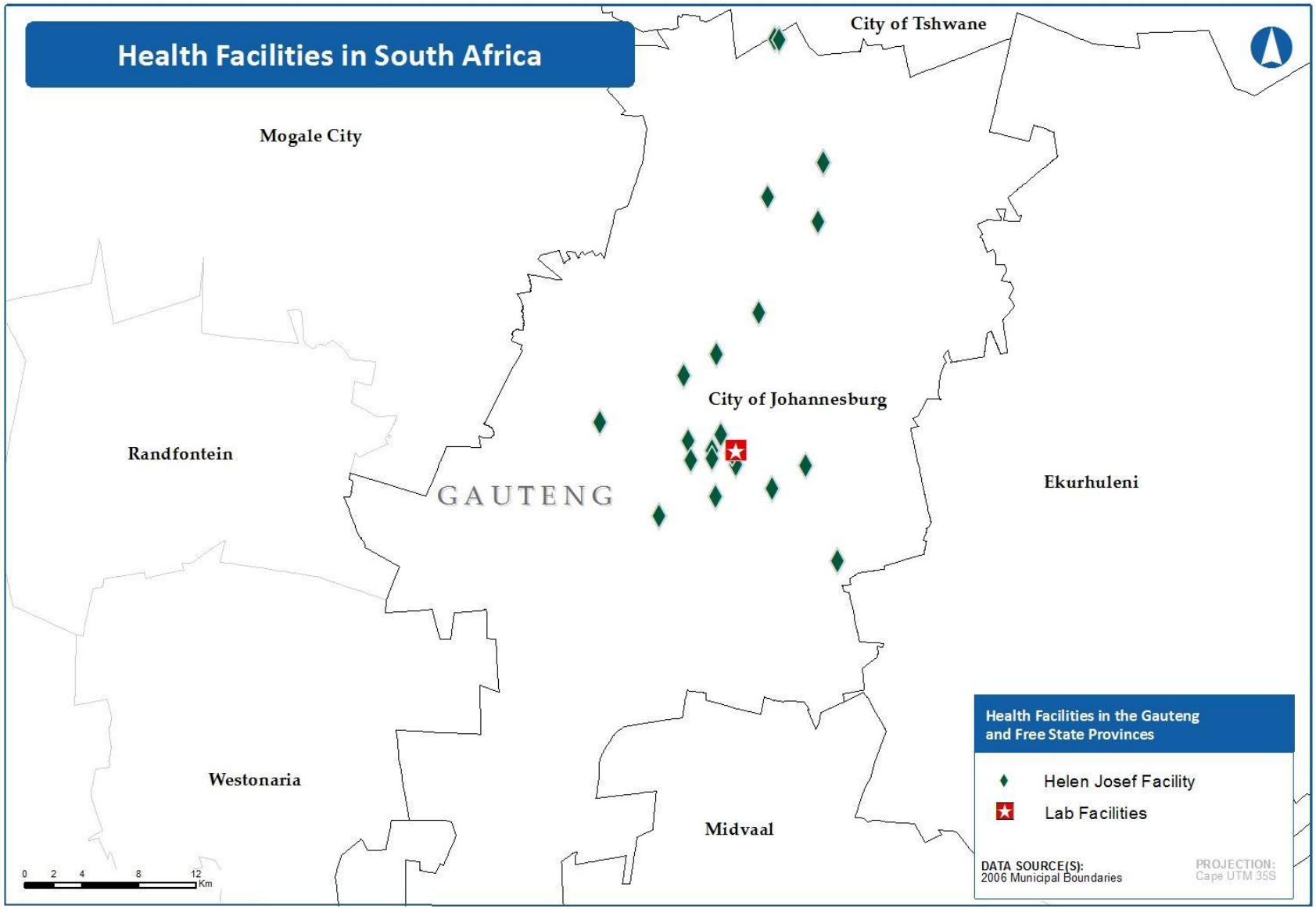
CRYPTOCOCCAL ANTIGEN TEST
Cryptococcal antigen .... **Positive**

*Reflex testing for cryptococcal antigen has been performed because the patient's CD4+ T-cell count is below 100 cells/µl. Cryptococcal antigen **has** been detected.*
If the patient has been previously diagnosed with cryptococcal disease, please ensure that the patient continues antifungal treatment.
If this is a new diagnosis, the patient should be evaluated for signs and symptoms of disseminated disease, including meningitis. Symptomatic patients will need a lumbar puncture to exclude meningitis while asymptomatic patients should be started on fluconazole after evaluation for special conditions.

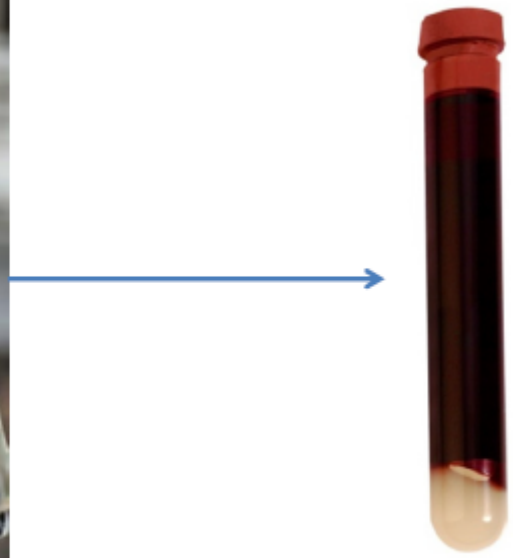
Authorised by :

Test(s): CD4
Test(s): Crypt

--- End of Laboratory Report ---



NHLS-CMJAH CD4 lab node and 25 facilities



SCREENING STRATEGIES

2. CLINICIAN-INITIATED LABORATORY SCREENING

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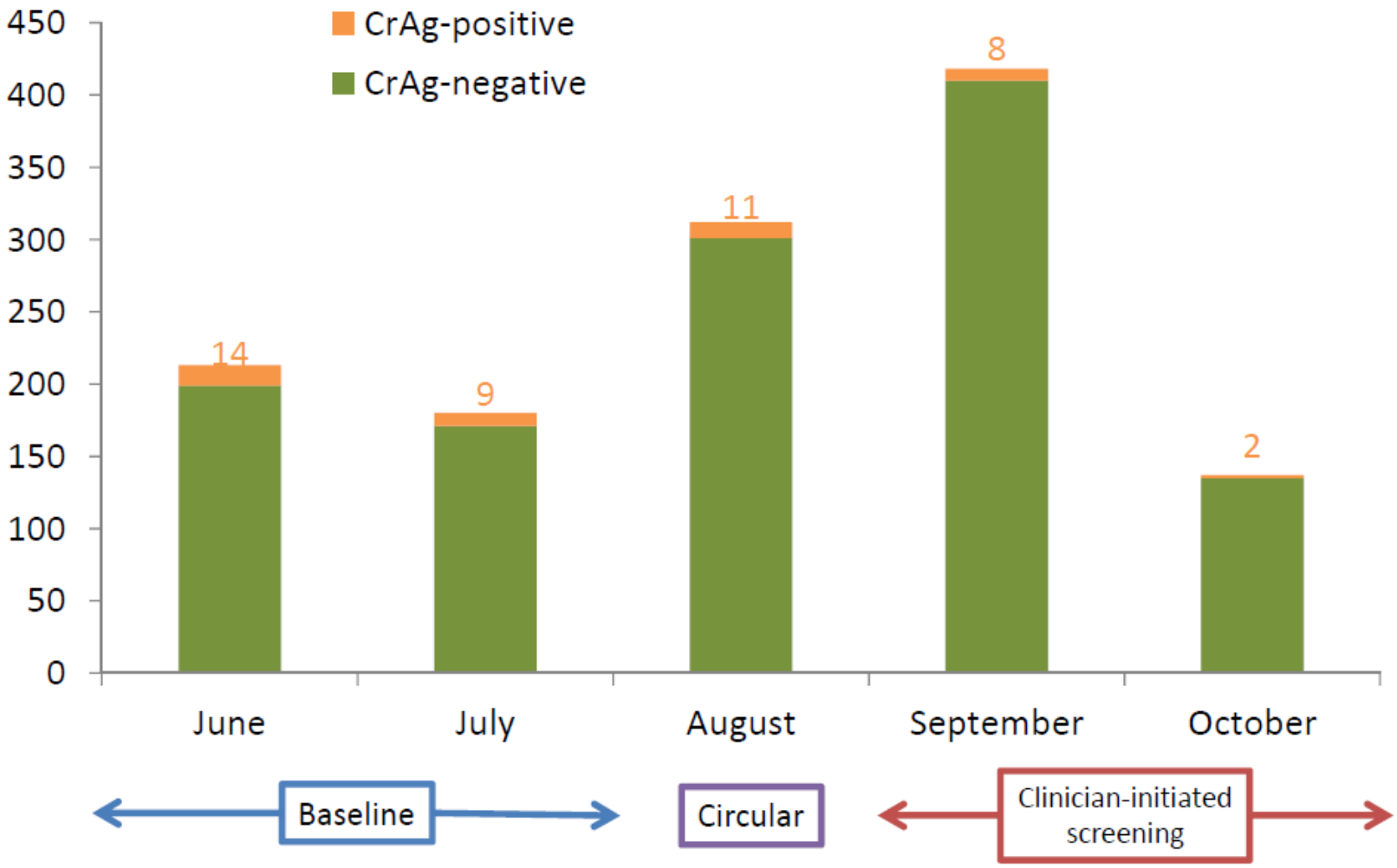
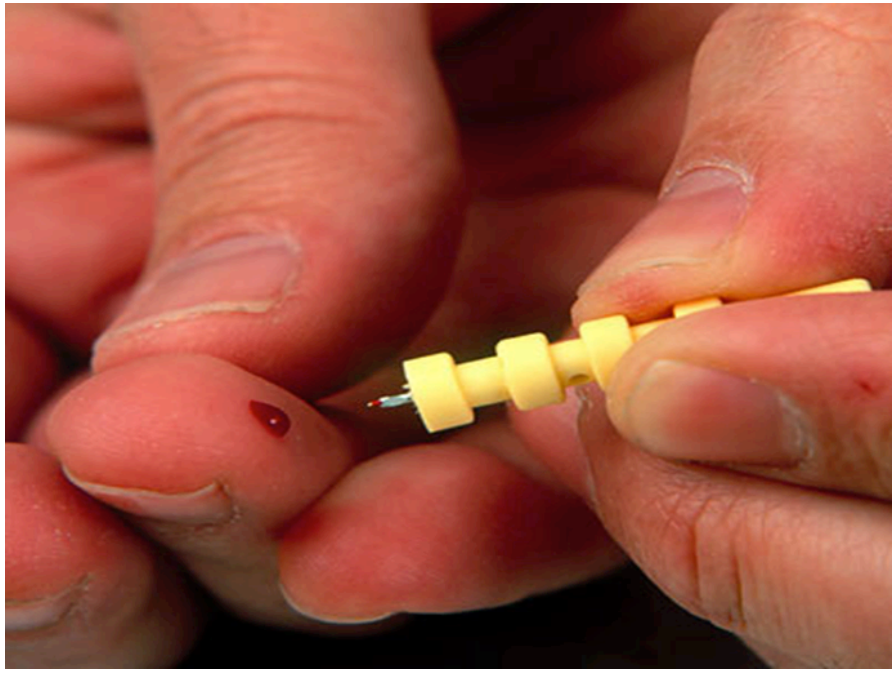
Figure 1: Number of blood specimens screened for CrAg at NHLS laboratories by month, Western Cape, 1 June to 8 Oct 2012





SCREENING STRATEGIES

3. CLINICIAN-INITIATED POINT-OF-CARE SCREENING

Point-of-care testing

- LFA is being validated for use in whole blood and/or urine
  - Diagnostic test for meningitis (n=295)
    - Whole blood: 99% sensitive; 100% specific
    - Urine: 95% sensitive; 100% specific
  - Screening
    - 100% correlation with whole blood and plasma in CD4 lab
    - Finger prick whole blood testing underway for screening
- Could occur in combination with POC CD4 testing or with clinical WHO staging in settings where POC CD4 testing is not available
- CrAg-positive patients still need referral for LP
- **Advantage**: minimises patient loss to follow-up and treatment delays
- **Disadvantage**: lack of quality control, requires clinician awareness

Summary

- Screening can detect cryptococcal disease earlier and prevent deaths
- The simple, quick and accurate lateral flow assay expands the number of implementation strategies for screening
- The choice of screening strategy depends on infrastructure, clinician practices and ability to train

Acknowledgements

Members of the South African Cryptococcal Screening Initiative Group: National Department of Health: Yogan Pillay, Thobile Mbengashe; Gauteng Department of Health: Zukiswa Pinini, Lucky Hlatshwayo, Nobantu Mpela; Free State Department of Health: Yolisa Tsibolane; Right to Care: David Spencer, Inge Harlen, Barbara Franken, Shabir Banoo, Pappie Majuba, Ian Sanne; Wits Reproductive and HIV Research Institute: W.D. Francois Venter, Ambereen Jaffer, Bongiwe Zondo, Judith Mwansa, Andrew Black, Thilligie Pillay, Mamotho Khotseng, Vivian Black; Aurum: Dave Clark, Lauren de Kock; Health Systems Trust: Waasila Jassat, Richard Cooke, Petro Rousseau; Anova: James McIntyre, Kevin Rebe, Helen Struthers; BroadReach: Mpuma Kamanga, Mapule Khanye, Madaline Feinberg, Mark Paterson; Technical Advisors: Tom Chiller (CDC Atlanta), Monika Roy (CDC Atlanta), Joel Chehab (CDC Atlanta), Ola Oladoyinbo (CDC South Africa), Adeboye Adelakan (CDC South Africa), Thapelo Maotoe (USAID South Africa); Expert Clinicians: Jeffrey Klausner, Tom Harrison, Joseph Jarvis, Tihana Bicanic, Ebrahim Variawa, Nicky Longley, Robin Wood, Stephen Lawn, Linda-Gail Bekker, Gary Maartens, Francesca Conradie; Data Safety and Monitoring Committee: Graeme Meintjes, Yunus Moosa, Halima Dawood, Kerrigan McCarthy, Alan Karstaedt; National Health Laboratory Service: Wendy Stevens, Lindi Coetzee, Debbie Glencross, Denise Lawrie, Naseem Cassim, Floyd Olsen; National Institute for Communicable Diseases/NHLS: Verushka Chetty, Nelesh Govender.