

# **CRYPTOCOCCAL SCREENING IN SOUTH AFRICA**

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# OUTLINE

Introduction

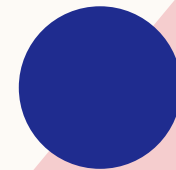
Cryptococcosis refresher

CrAg screening in SA

Results for Action and ethical obligations

Challenges in implementation

Conclusion



# INTRODUCTION

What makes for a good screening programme?

WHO defines the characteristics of an ideal screening test

important health problem

the natural history understood

recognisable latent/  
early symptomatic stage

easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific

accepted treatment recognised for the disease

treatment should be more effective if started early

policy on who should be treated

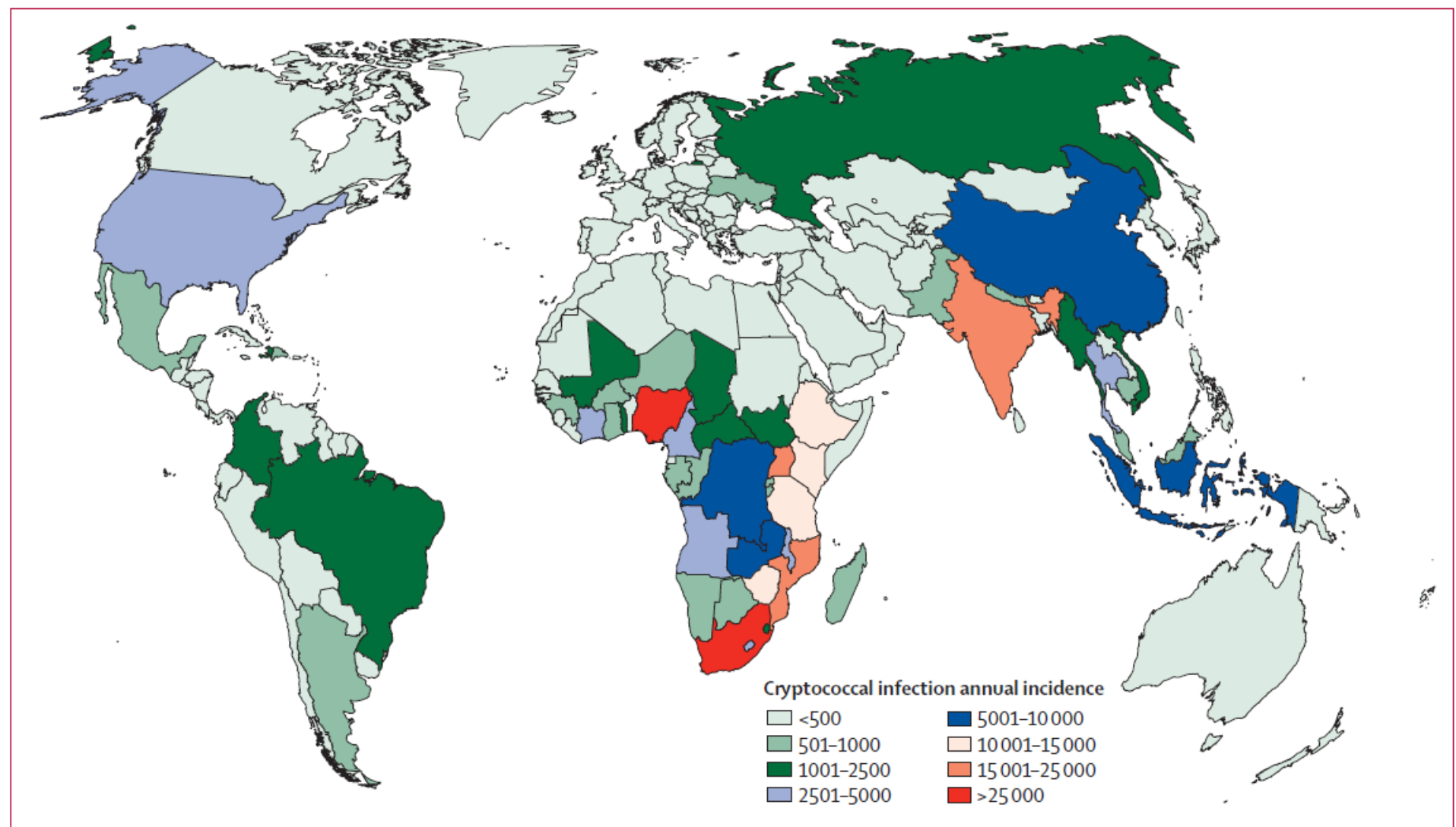
case-finding should be a continuous process

diagnosis and treatment should be cost-effective



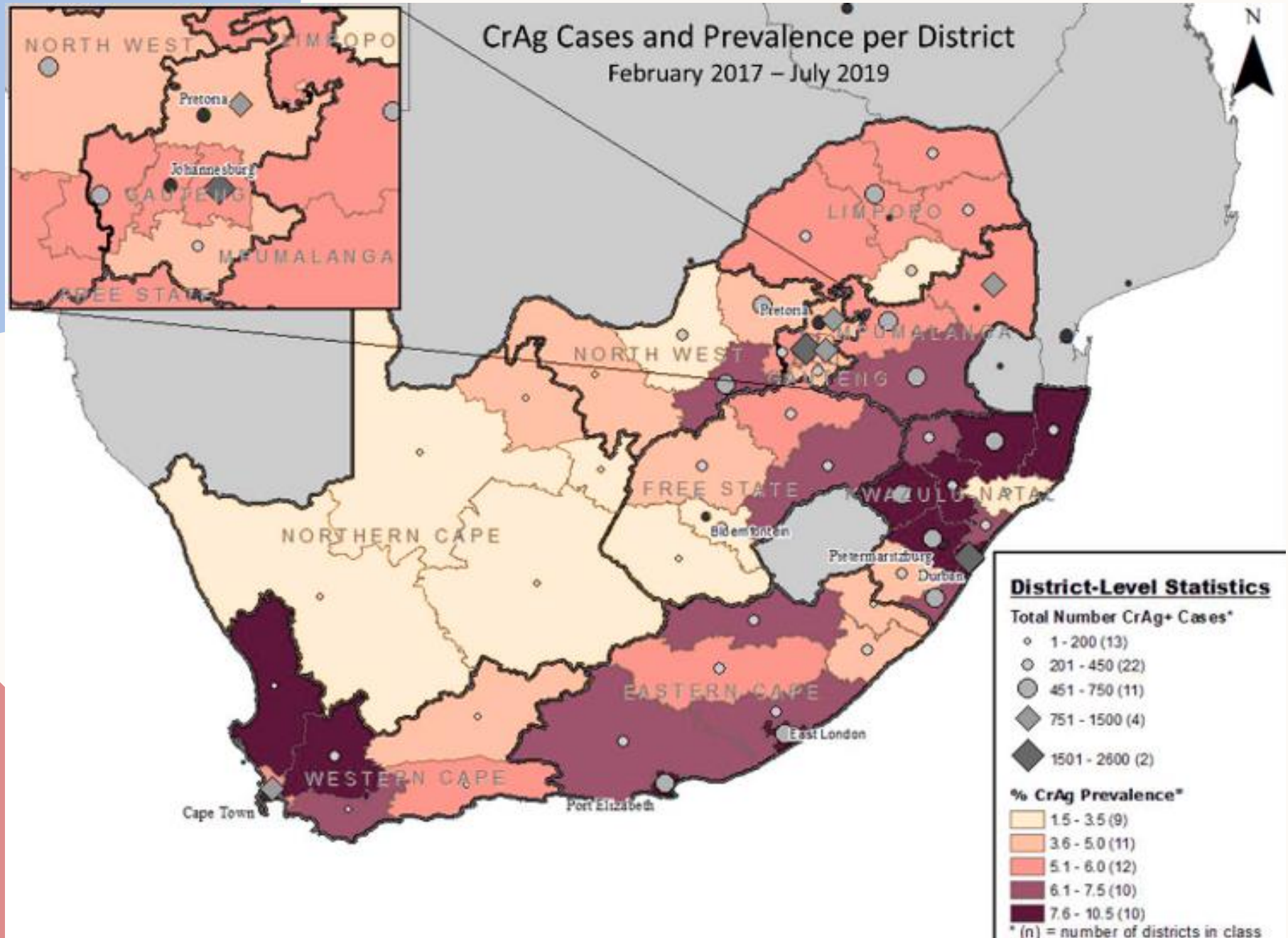
# **BURDEN OF DISEASE**

Worldwide and national prevalence of  
cryptococcal antigenaemia and meningitis



**Figure 2: Annual incidence of cryptococcal infection by country**

The annual number of people positive with cryptococcal antigenaemia estimated at 278 000 (95% CI 195 500–340 600) globally in 2014. We estimated 223 100 annual incident cases of cryptococcal meningitis in 2014..



# EPIDEMIOLOGY

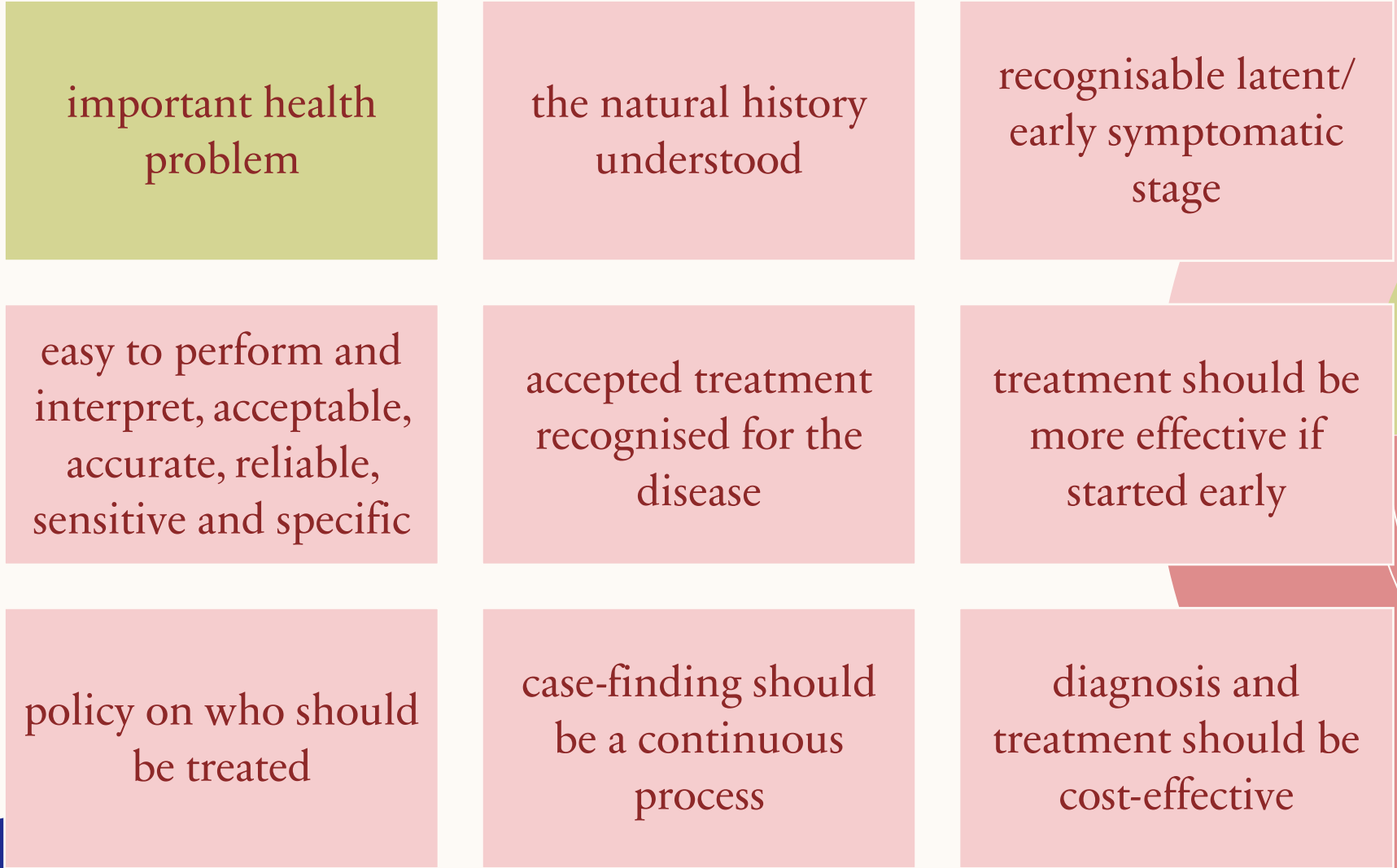
## CRYPTOCOCCOSIS:

- Majority of infection likely reactivation of dormant cells
- Global incidence of antigenaemia
  - ~ **6.5% of people with CD4 <100/uL**
  - ~2% in with CD4 100-200/uL
- **Global annual deaths ~ 181100 people** (mainly CM)
- Treatment of cryptococcosis reduces progression to CM

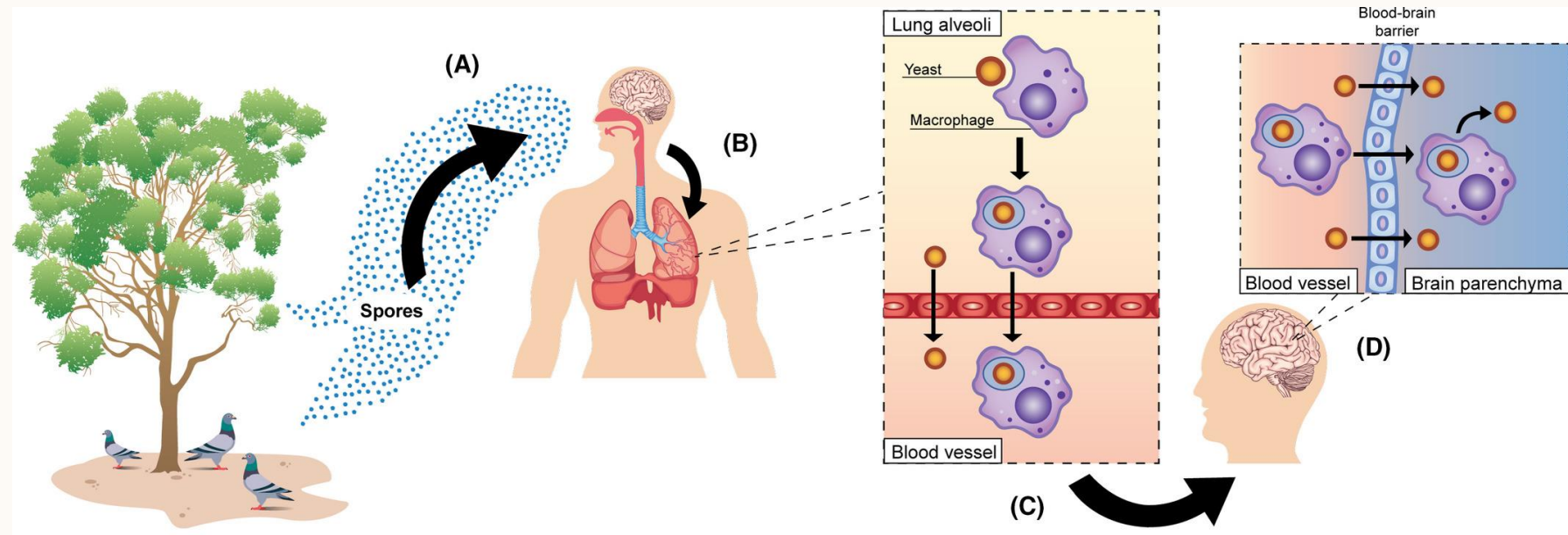
## CRYPTOCOCCAL MENINGITIS (CM):

- Accounts for **17%** of global AIDS-related deaths (2<sup>nd</sup> leading cause after TB)
- Annual incidence of CM ~278 000 individuals
  - **73% of CM (223 000) occurs in Sub-Saharan Africa**
- ~50% of CM patients die within 10 weeks of diagnosis
- In-hospital CM mortality is high 44%
- Early detection and treatment (+ adherence support) reduces mortality by 28%





# CRYPTOCOCOSIS



# PATHOGENESIS



## CRYPTOCOCCAL DISEASE IS A SPECTRUM

### ASYMPTOMATIC

CrAg aemia detected through screening, may have calcified nodule/s on chest x-ray

### PULMONARY DISEASE

Pneumonia -> ARDS, multiple non-calcified nodules/ effusions, LNs, non-contiguous consolidation and cavitation on CXR

### SYSTEMIC SPREAD

May have positive BC  
Can involve any site, usually skin, lungs, bones, prostate, eye, CNS

### MENINGITIS

Up to 1/3 may STILL be asymptomatic  
Meningitis (headache, photophobia, neck stiffness), raised ICP, SOL (with focal or global deficits), coma

### DEATH

Untreated, 100% of cases will be fatal  
Overwhelming SIRS, coning, seizures etc.

important health problem

the natural history understood

recognisable latent/early symptomatic stage

easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific

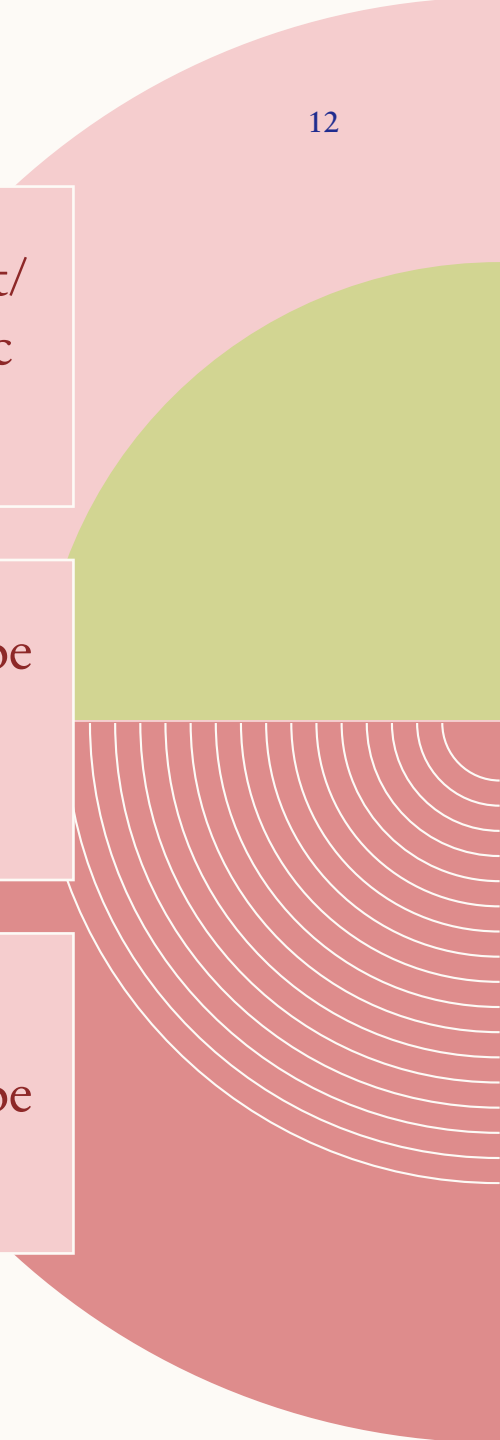
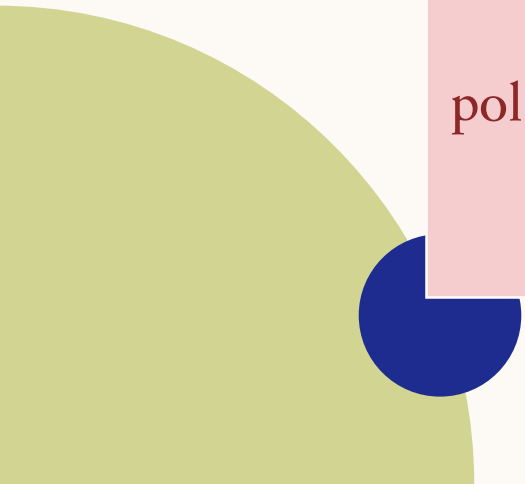
accepted treatment recognised for the disease

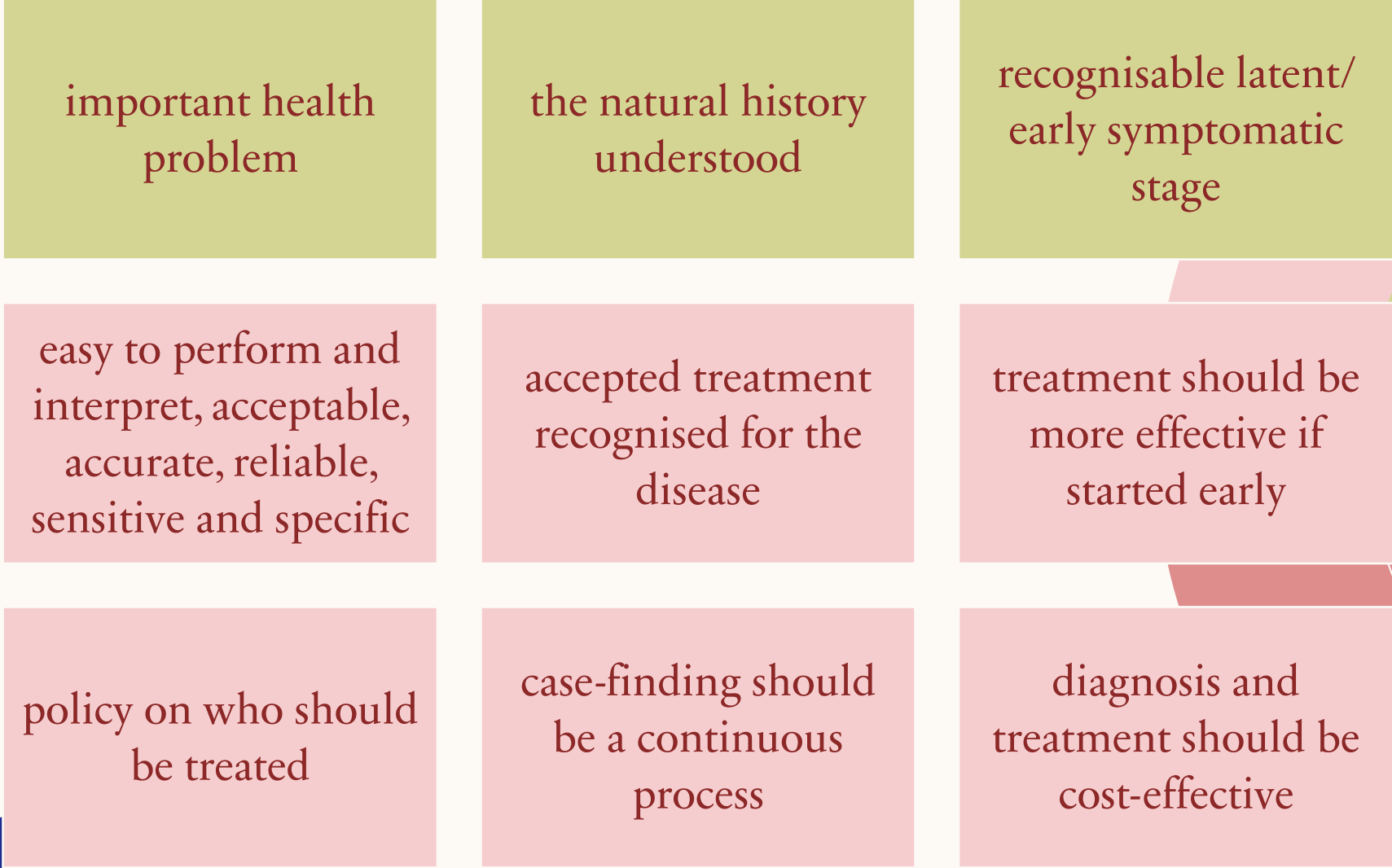
treatment should be more effective if started early

policy on who should be treated

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diagnosis and treatment should be cost-effective

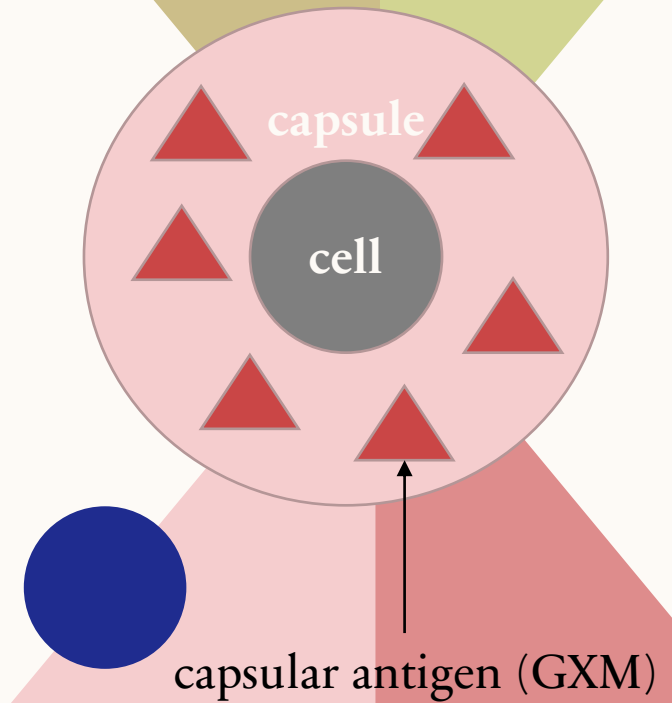




# CRAG SCREENING WITH IMMY LFA



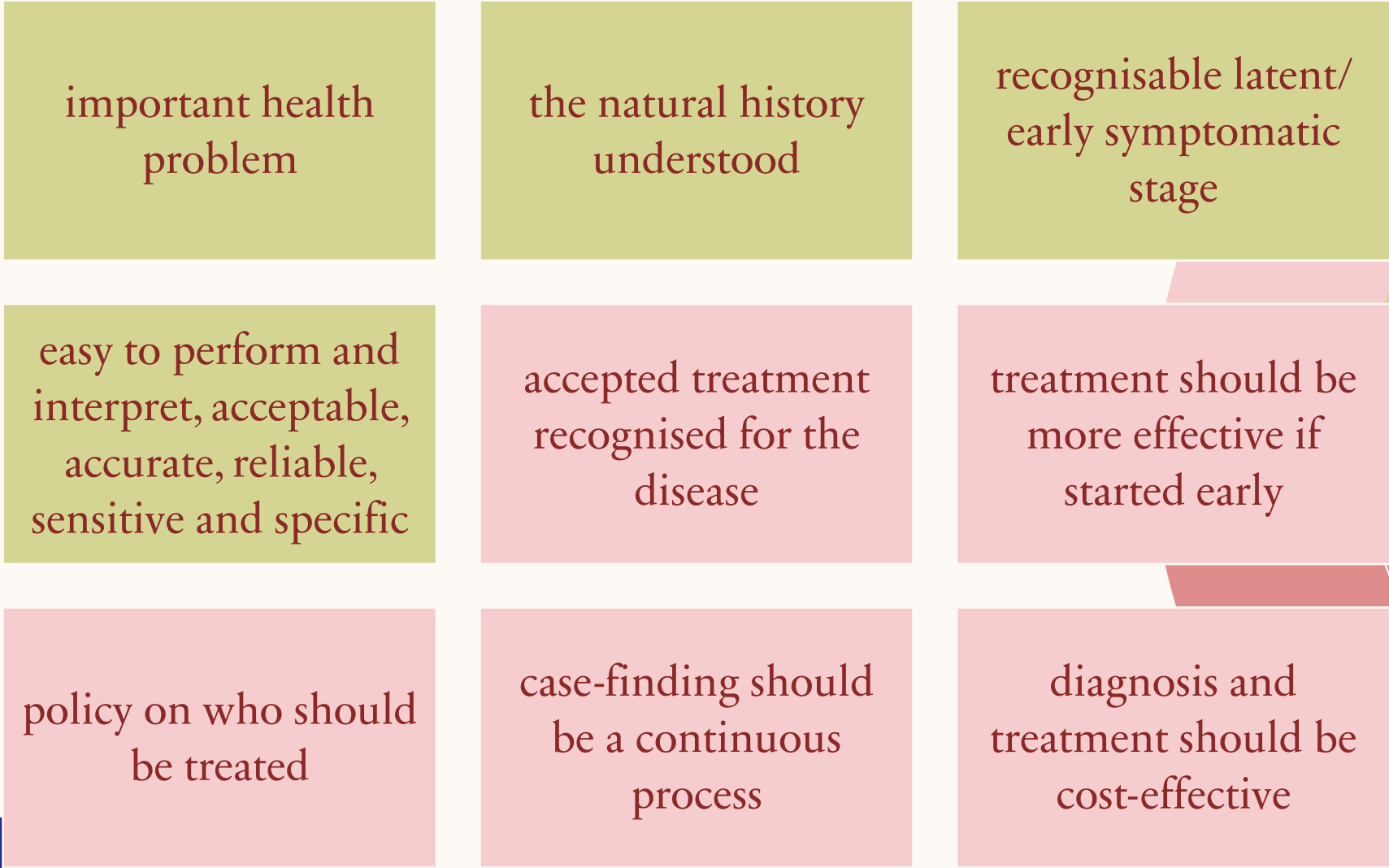
Can be performed on blood or CSF, in lab or at point of care.





## **CRAG SCREENING TO DATE**

<b>CrAg reflex <u>tests</u> run:</b>	<b>1 238 237 (98.9%)</b>
<b>Positive reflex CrAg <u>tests</u>:</b>	<b>76 085 (6.1%)</b>
<b>Eligible <u>patients</u> screened:</b>	<b>1 012 493 (99.1%)</b>
<b>CrAg+ <u>patients</u> identified:</b>	<b>64 310 (6.0%)</b>





# CURRENT TREATMENT



**FLUCONAZOLE**



**AMPHOTERICIN B  
DEOXYCHOLATE**



**FLUCYTOSINE**

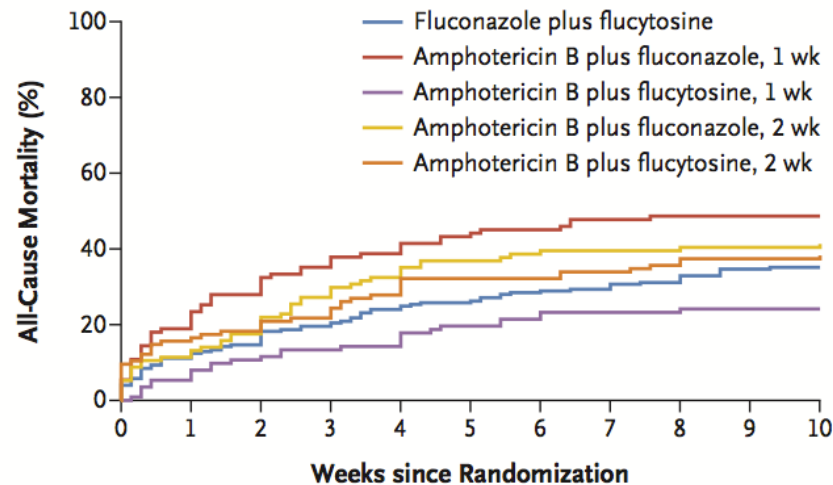


**LIPOSOMAL  
AMPHOTERICIN B**

# ADVANCES TO DATE

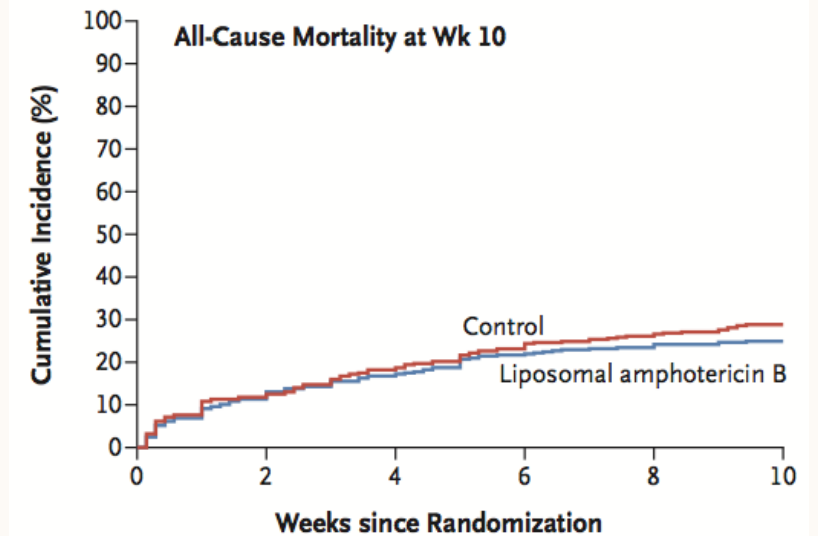
## THE ACTA TRIAL

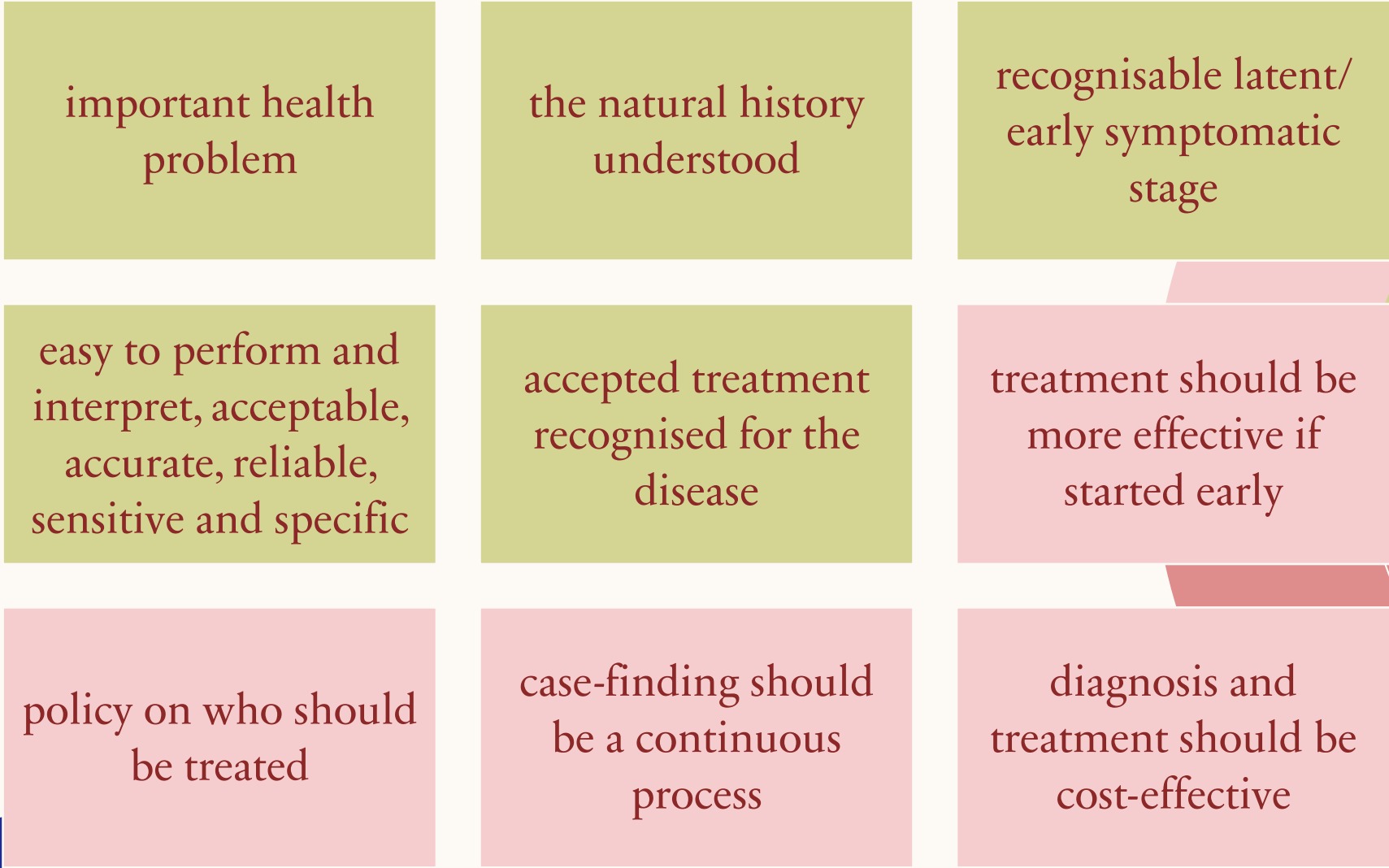
- Determined 5FC to be key
- Adopted into WHO guidelines
- Now SA guidelines

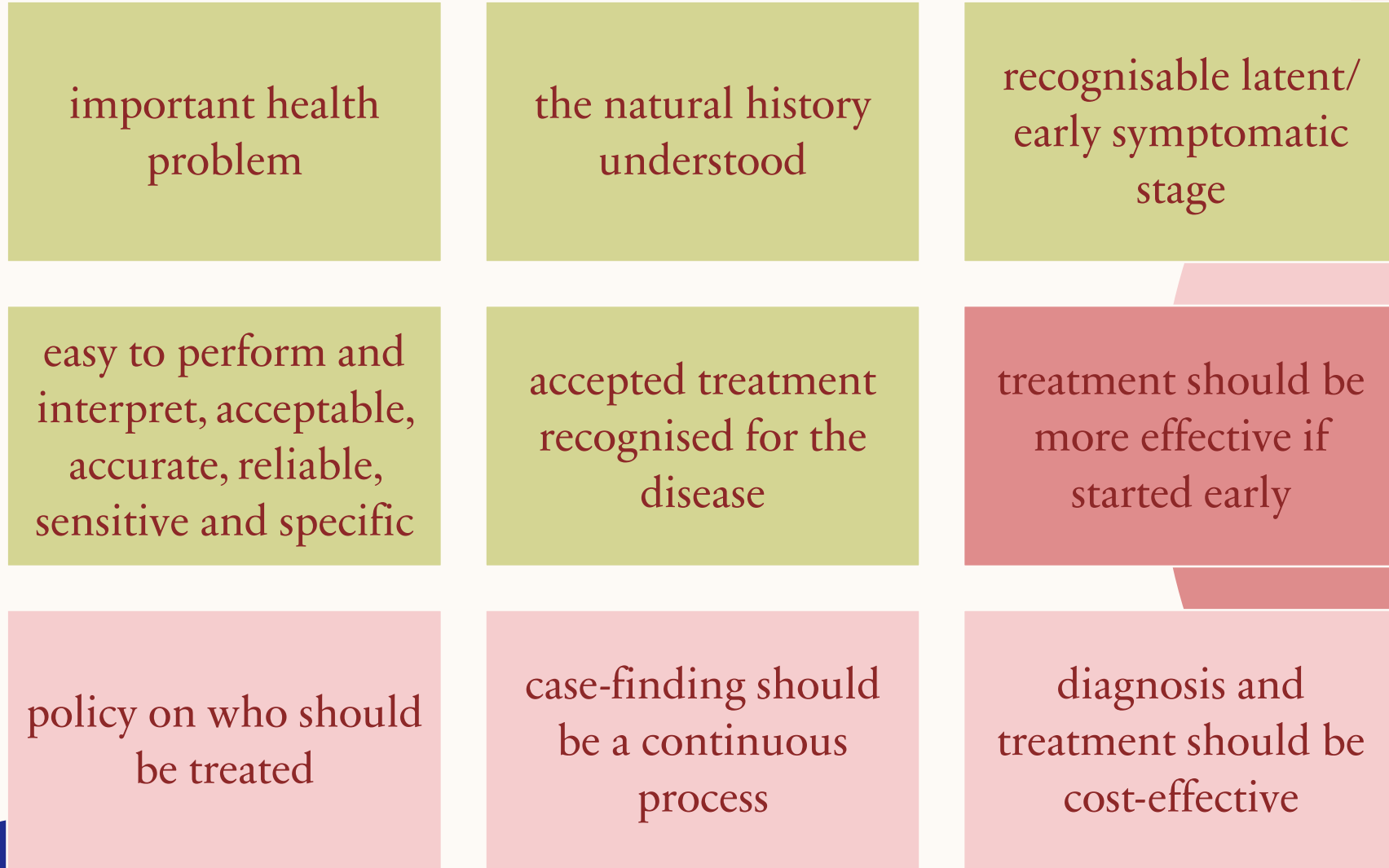


## THE AMBITION TRIAL

- Determined liposomal amphotericin B (single high dose) with FLU and 5FC non-inferior to ACTA with better safety profile and tolerability
- Rapid advice from WHO to implement







# **CURRENT GUIDELINES**

Where are we now?

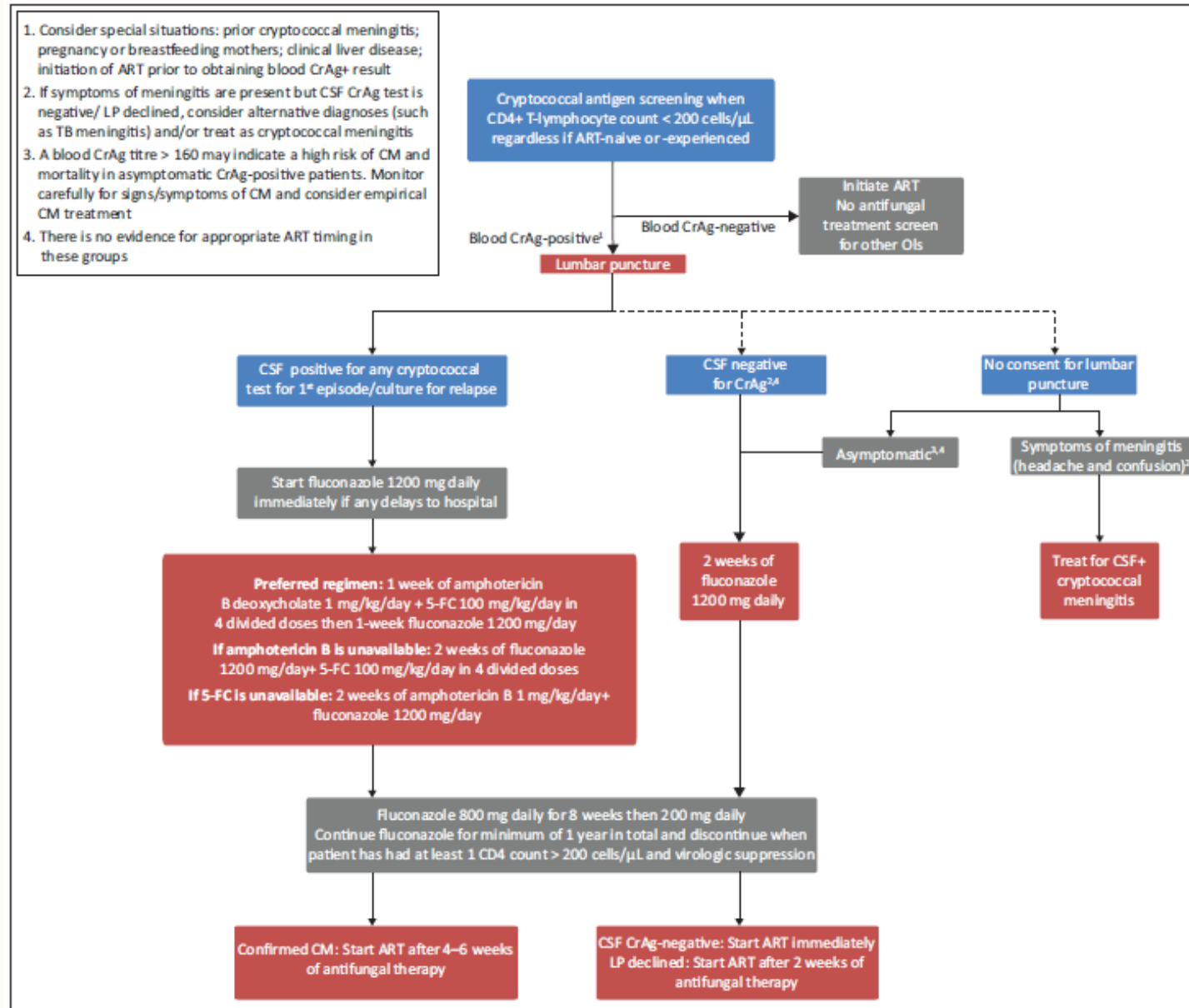
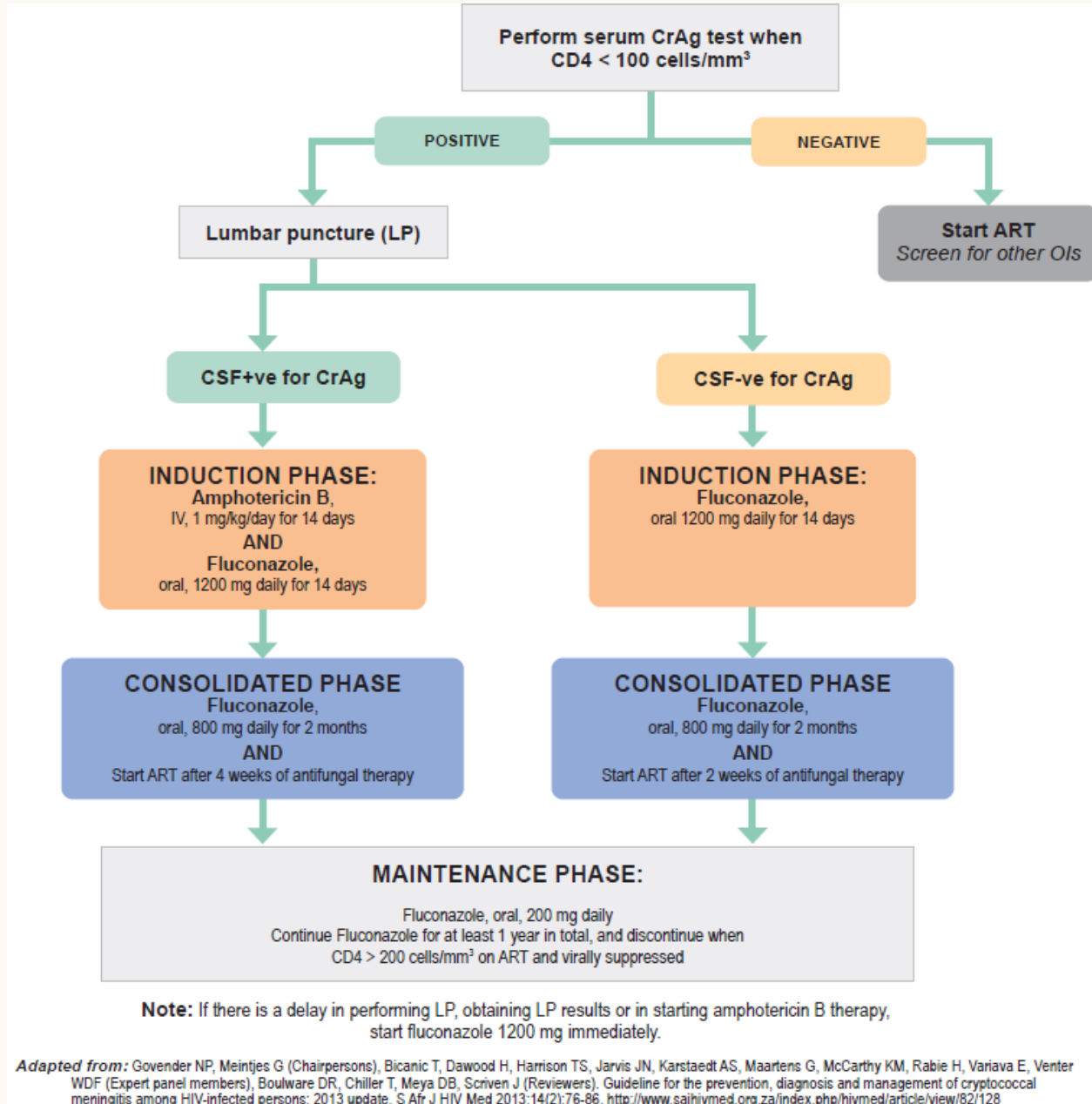


FIGURE 1: Cryptococcal antigen screening and treatment algorithm.



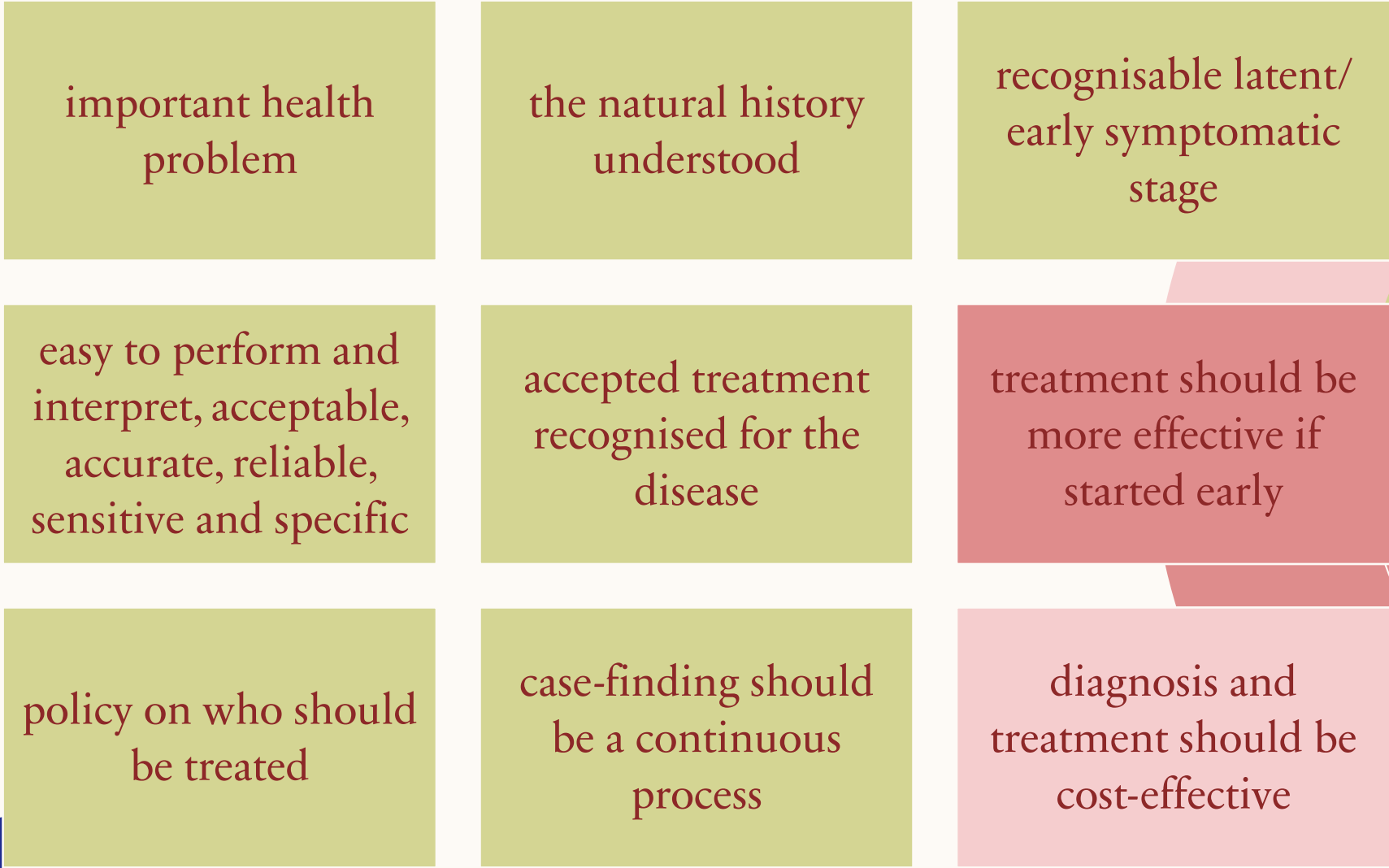




The following baseline laboratory investigations should be performed routinely before a client initiates ART. Clients are not required to wait for the results of the baseline investigations before starting ART, provided the client is asymptomatic. However, the results should be checked at the next visit.

TABLE 8 BASELINE LABORATORY EVALUATIONS

LABORATORY EVALUATION	PURPOSE	ADOLESCENTS (10-19 YEARS) AND ADULTS	PREGNANT WOMEN	CHILDREN (< 10 YEARS)
Confirm HIV test result	To confirm HIV status for those without documented HIV status	✓	✓	✓
CD4 cell count/ %	To identify eligibility for CPT	See "Indications for starting and stopping cotrimoxazole" in table on page 49		
	To identify eligibility for cryptococcal antigen (CrAg) screening	A reflex CrAg test will be done automatically by the laboratory on all CD4 counts < 100 cells/μL		N/A
Creatinine and eGFR if TDF used	To assess renal insufficiency	See table titled "Assessing Renal Function" on page 24		
Haemoglobin (Hb)	To identify and manage anaemia; to determine eligibility for zidovudine (AZT) where necessary	If Hb is low, do a full blood count (FBC). Characterise according to mean corpuscular volume (MCV) as either microcytic, normocytic, or macrocytic and manage accordingly <sup>1</sup>	Treat with ferrous sulphate tds if Hb < 10 g/dL. Refer if < 8 g/dL and symptoms, if anaemia diagnosed at 36 weeks gestation or later, or if no response to treatment	Children < 5 years: Treat with iron supplements and deworm the child <sup>1</sup> Children > 5 years: Do FBC. Characterise according to MCV and manage accordingly <sup>1</sup>
GeneXpert	To diagnose TB	Only for those clients with a <b>positive TB symptom screen</b>	<b>Regardless of TB symptoms</b> , routinely do a TB GeneXpert for all HIV-positive women at first visit in antenatal clinic, due to the lower sensitivity of the TB symptom screen in pregnant women	Only for those with a <b>positive TB symptom screen</b>
Cryptococcal antigen test (CrAg) if CD4 < 100 cells/μL	To identify asymptomatic clients who need pre-emptive fluconazole treatment	A reflex CrAg test will be done automatically by the laboratory on all CD4 counts < 100 cells/μL If CrAg-negative, no fluconazole is required If CrAg-positive, the client will require treatment of the infection All clients with a positive CrAg should be referred for a lumbar puncture	All pregnant women with a positive CrAg should be referred for a lumbar puncture, regardless of symptoms. The results of the lumbar puncture and further management should be discussed with an expert, or one of the helplines provided on page 42	N/A



## Cost Effectiveness of Cryptococcal Antigen Screening as a Strategy to Prevent HIV-Associated Cryptococcal Meningitis in South Africa

Joseph N. Jarvis<sup>1,2,3\*</sup>, Thomas S. Harrison<sup>3</sup>, Stephen D. Lawn<sup>1,2</sup>, Graeme Meintjes<sup>4,5,6</sup>, Robin Wood<sup>2,4</sup>, Susan Cleary<sup>7</sup>

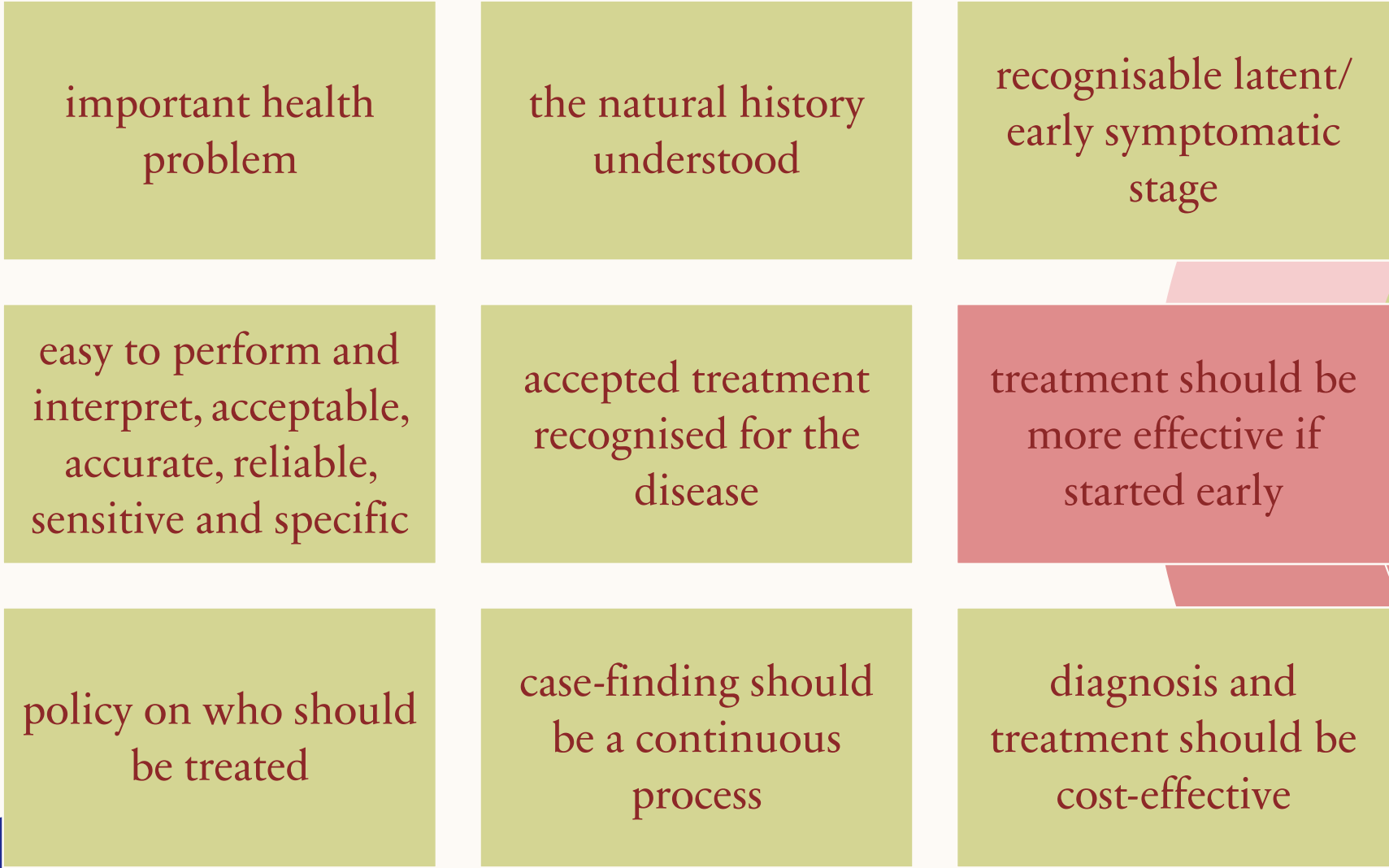
# HEALTH ECONOMICS

Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa

Jacqui Miot<sup>1\*</sup> , Trudy Leong<sup>2</sup>, Simbarashe Takuva<sup>3,4</sup>, Andrew Parrish<sup>5</sup> and Halima Dawood<sup>6,7</sup>

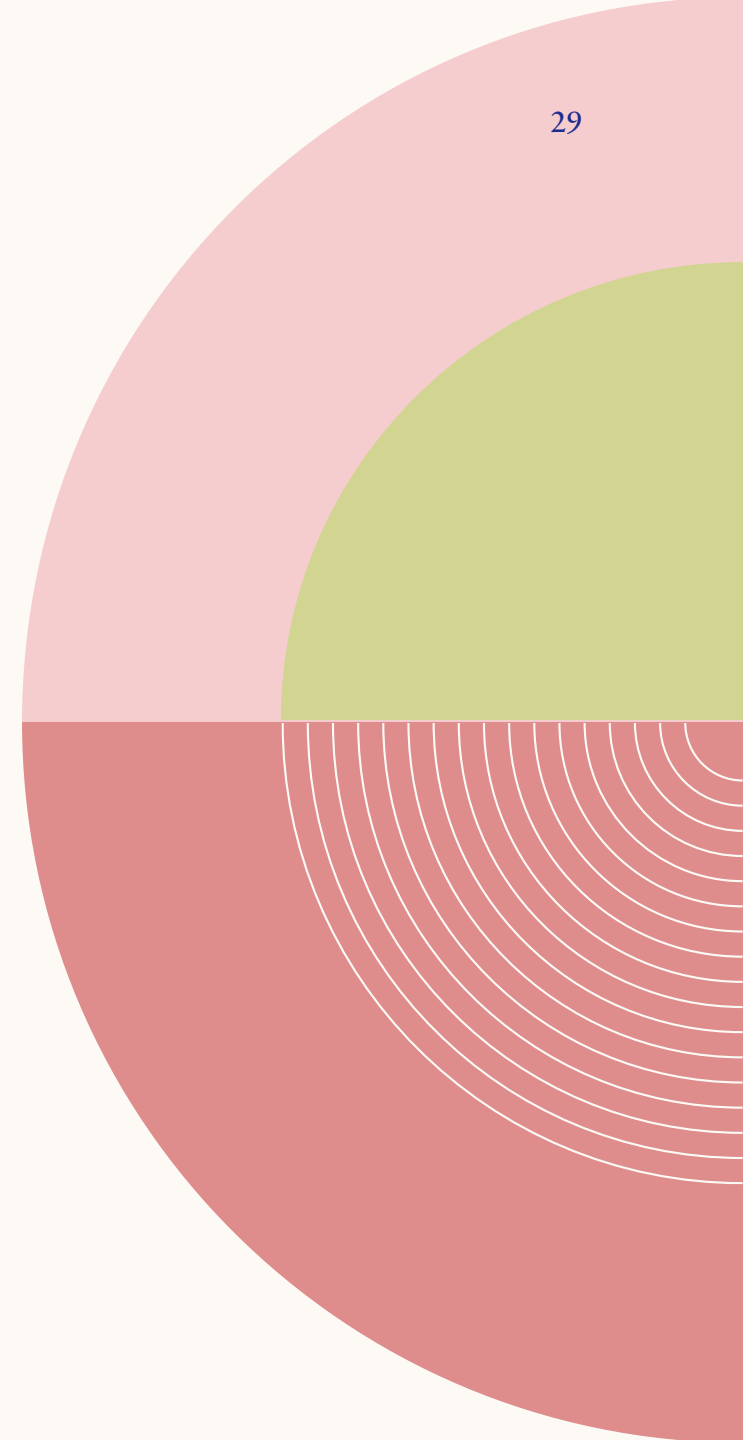
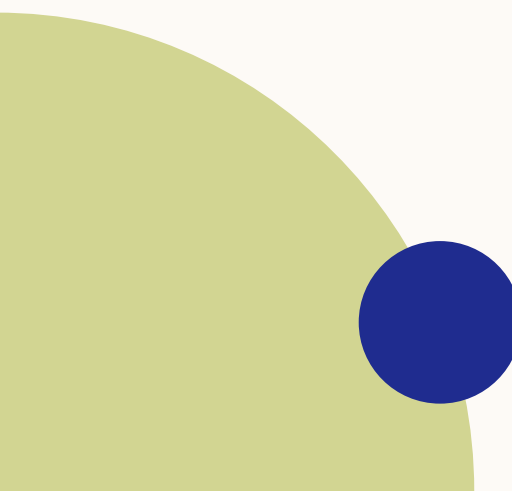
Cost-effectiveness of single, high-dose, liposomal amphotericin regimen for HIV-associated cryptococcal meningitis in five countries in sub-Saharan Africa: an economic analysis of the AMBITION-cm trial

*David S Lawrence\*, Charles Muthoga\*, David B Meya, Lillian Tugume, Darlisha Williams, Radha Rajasingham, David R Boulware, Henry C Mwandumba, Melanie Moyo, Eltas N Dziwani, Hendramoorthy Maheswaran, Cecilia Kanyama, Mina C Hosseinipour, Chimwemwe Chawinga, Graeme Meintjes, Charlotte Schutz, Kyla Comins, Funeka Bango, Conrad Muzoora, Samuel Jjunju, Edwin Nuwagira, Mosepele Mosepele, Tshelo Leeme, Chiratidzo E Ndhlovu, Admire Hlupeni, Shepherd Shamu, Timothée Boyer-Chammard, Sile F Molloy, Nabila Youssouf, Tao Chen, Tinevimbo Shiri, Shabbar Jaffar, Thomas S Harrison\*, Joseph N Jarvis\*, Louis W Niessen\*, on behalf of the AMBITION Study Group*



# **CRYPTOCOCCAL ANTIGEN SCREENING IS IDEAL**

Or at least, it has the potential to be...



# WHY NO REAL CHANGE IN MORTALITY?\*

- Challenges in implementation
- Are guidelines adhered to? CD4 testing?
- RfA
- How to actively follow up abnormal results incl. positive CrAg
  - Especially when done by reflex
- Test and treat
  - How soon are patients followed up?
- EFFECT trial highlighting some of the screening programme gaps
  - Situational analysis underway

**“ ON MY SIDE, I CALL THEM, FROM MY OWN CELL PHONE. I WOULD’VE ASKED FOR THEIR NUMBERS– NOT RELYING ON THE INFORMATION IN THE FILE ”**

Dr E, clinic in Gauteng

*Speaking about patient follow-up for flagged abnormal lab results*

# EFFECT

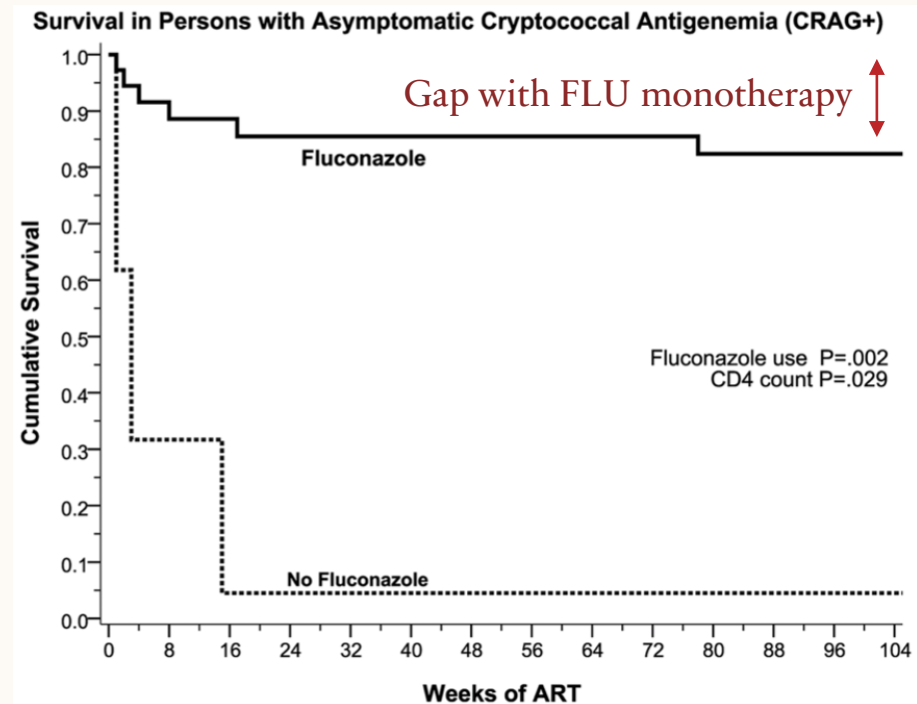
Clinical Trial for Crypto Treatment



## EFFECT OF FLUCONAZOLE PLUS FLUCYTOSINE FOR EARLY CRYPTOCOCCAL TREATMENT

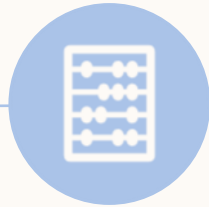
- Phase 3 open-label randomized control trial
- Patients identified through CrAg screening
- CD4 <100, serum CrAg positive
- CSF negative or LP declined and asymptomatic for meningitis
- No previous CM or treated antigenaemia
- Any ART status
- Randomised to current SOC, or to dual therapy with FLU plus 5FC

## RATIONALE





# HOW CAN WE GET THERE?



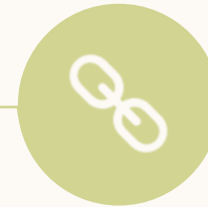
## TRAINING AND IMPLEMENTATION

- Of current local guidelines
- CD4 testing and reflex CrAg screening
- Maintaining up-to-date contact info for patients to recall if positive
- Timely referral for LP if CrAg positive



## THE EFFECT TRIAL

- Optimise treatment of CrAgaemia
- Reduce progression to meningitis and death
- Identify further areas of research



## LINK ALL STAKEHOLDERS

- Ensure guidelines are appropriate and applicable
- Advocate for patients' rights and wellbeing
- Access to essential medicines

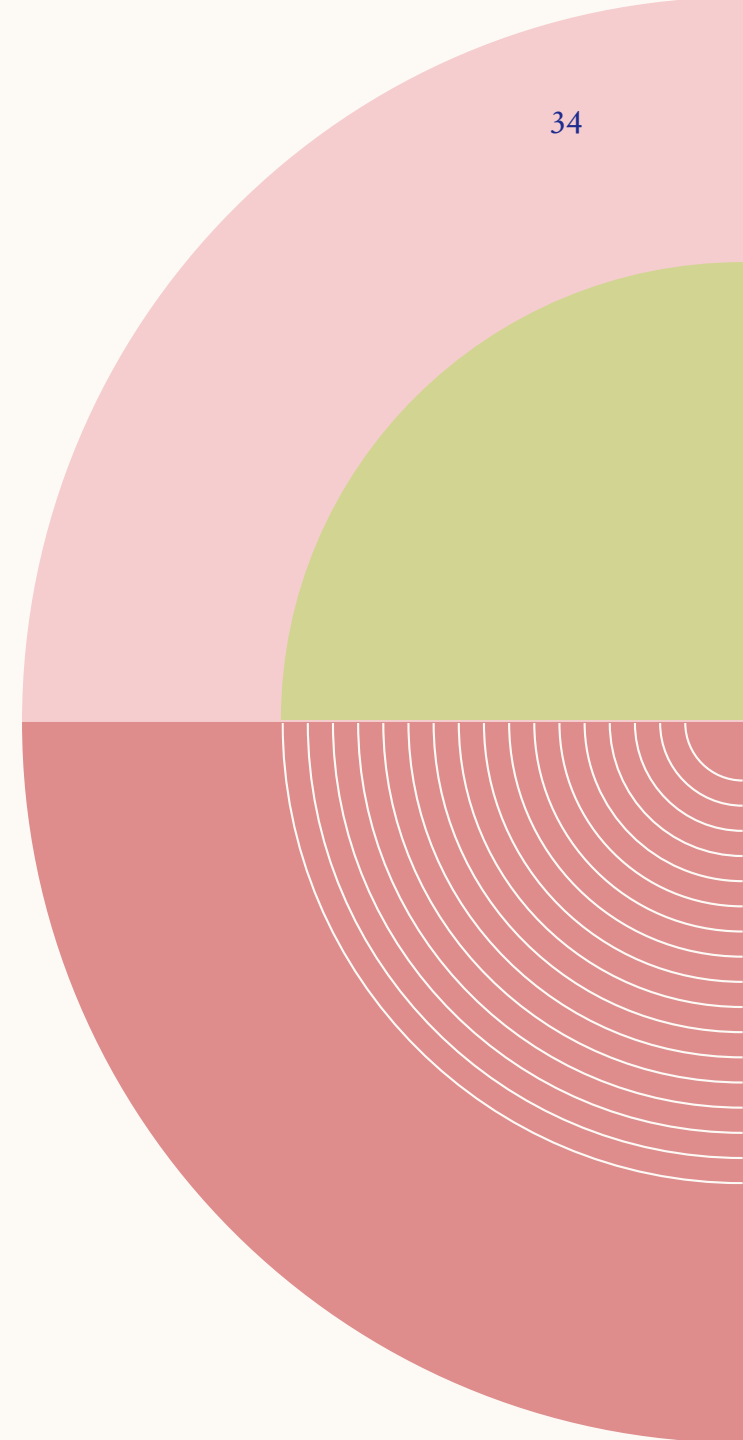
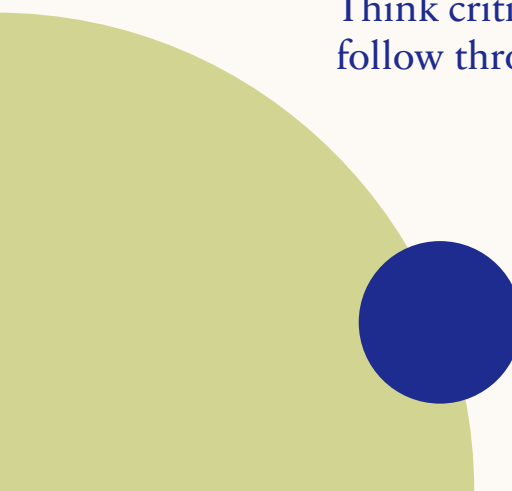
# SUMMARY

Screening programmes rely on adequate implementation at all levels

When done well, meaningful difference can be made

As providers, onus on us to advocate for patients and enhance systems

Think critically about WHY you are doing something for/ to the patient, and follow through to ensure it was not in vain



# THANK YOU

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