

## Tackling Public Enemy #2:

### Screening to Prevent Cryptococcal Deaths



NATIONAL HEALTH  
LABORATORY SERVICE

GERMS

## Fighting a deadly fungus

A common, deadly  
and costly disease

Weighing up strategies  
to prevent deaths

Screening to prevent  
deaths in South Africa

Case studies

## Fighting a deadly fungus

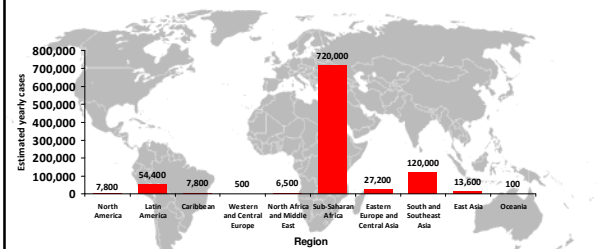
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## Global burden of HIV-associated cryptococcal meningitis

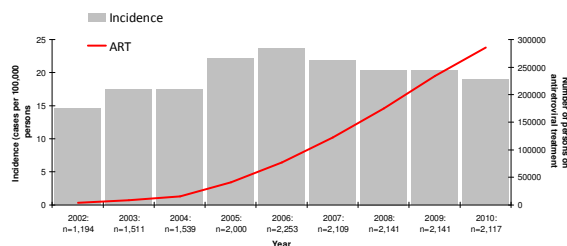


~1 million new cases per year  
and ~ 625,000 deaths per year

Park BJ, et al. AIDS 2009;23:525-30.

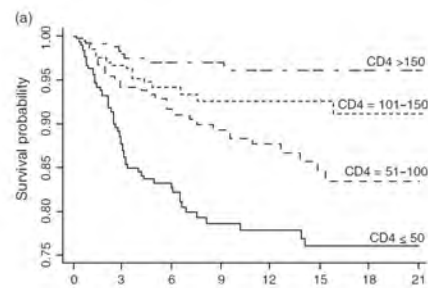
## High burden of cryptococcosis in South Africa

Incidence of cryptococcosis (n=17,005\*) vs. number of persons on antiretroviral treatment (ART)\*\* by year, Gauteng Province, 2002-2010



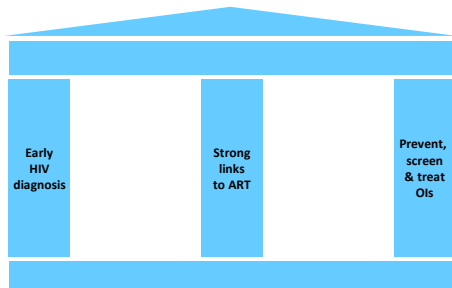
\*Complete surveillance audits were conducted throughout; \*\*ASSA-2003 model

## High, early mortality amongst adults accessing ART in sub-Saharan Africa



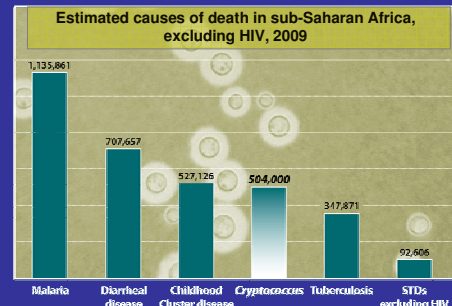
Lawn S, et al. AIDS. 2008

### 3-pillared strategy to reduce early mortality



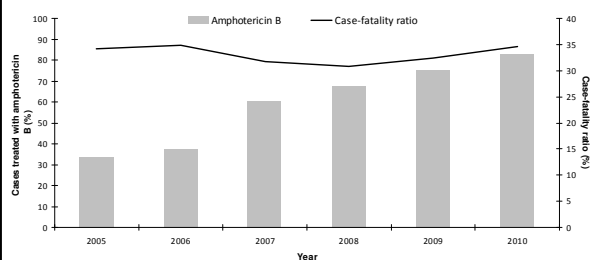
Lawn S, et al. AIDS. 2008

### Death from *Cryptococcus* in sub-Saharan Africa



### High in-hospital mortality

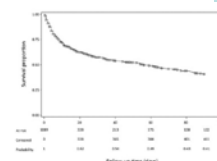
Induction treatment with amphotericin B and in-hospital case-fatality ratio for cases of incident lab-confirmed cryptococcosis (n=9,498\*) diagnosed at GERM-SA enhanced surveillance sites, South Africa, 2005-2010



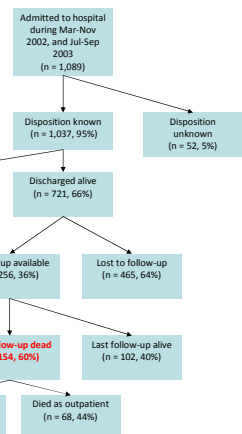
\*Only includes cases with a CRF; missing treatment data for 226 cases and missing outcome data for 85 cases

### Post-discharge survival in the pre-ART era

- Eight hospitals in Gauteng
- Follow-up post-discharge
  - Pharmacy records
  - Outpatient records
  - Interviews

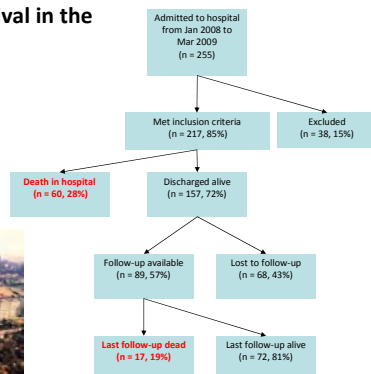


Park BJ, et al. Int J STD AIDS. 2011.



### Post-discharge survival in the post-ART era

- One hospital in Gauteng
- Follow-up post-discharge
  - Pharmacy records
  - Outpatient records
  - Interviews



### What does it cost annually to treat patients in hospital?

Number of cases of cryptococcal meningitis per year  
8,330

Cost of hospitalisation  
R 20,080

Estimated annual cost  
R 167,266,400



GERMS-SA Surveillance 2009;  
Halle et al. APHA Conference Atlanta, 2001

## Fighting a deadly fungus

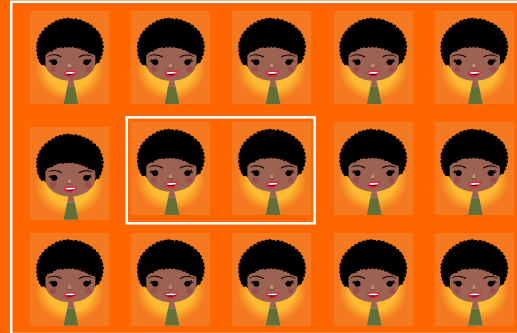
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## Preventing deaths amongst patients with CD4 <100



WHY IS SCREENING AN ATTRACTIVE OPTION?



## 1 - Cryptococcal Antigen

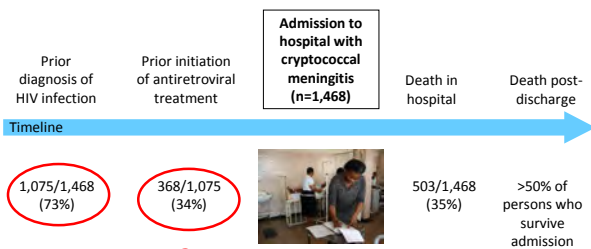
- Detectable in serum, plasma (& urine) before symptoms of meningitis develop
  - Average of 22 days prior to symptom onset<sup>1</sup>
- Highly predictive of who is at risk for developing cryptococcal disease
  - In Cape Town, 13/46 CrAg+ and 0/661 CrAg- patients developed meningitis<sup>2</sup>
- Prevalence of cryptococcal antigenemia ranges from 3% to 21%
  - Highest amongst patients with CD4 <100

<sup>1</sup>French et al. AIDS 2002; <sup>2</sup>Jarvis et al. Clin Infect Dis 2009

## Cryptococcal Antigenaemia Prevalence in Published Studies

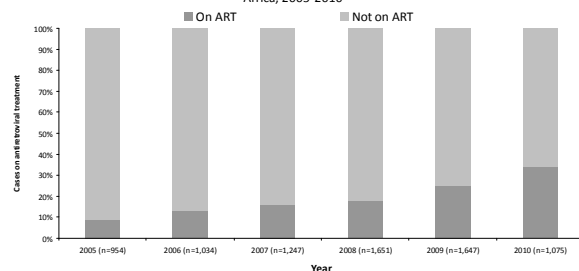
Country	Year	Setting	Serum CrAg Prevalence	Notes
Zaire (Congo)	1989	Newly diagnosed HIV+	12.2% (450)	Includes symptomatic
Rwanda	1990	Laboratory serum tested Cross sectional	4.2% (213)	
South Africa (Soweto)	2011	ART enrollment hospital clinic Prospective	3.0% (1033)	No history of CM CD4 <100
South Africa (Cape Town)	2002-2005	Community clinic Retrospective	7.0% (707)	No history of CM CD4 <100
Uganda	2003-2004	ART clinic Retrospective	5.8% (377)	CD4 < 100
Uganda	2004-2006	ART enrollment Prospective	8.2% (609)	CD4 <200
Uganda	2000	In and out-patients Prospective	10.7% (197)	Stage III or IV
Uganda	1995-1999	Two community clinics Cohort	5.6% (1372)	
Cambodia	2004	ART enrollment Cross-sectional	18.0% (327)	Includes symptomatic CD4 <50
Thailand	2008	Retrospective	9.2% (131)	CD4 <100

## 2 - Missed opportunities for screening



## 2 - Missed opportunities for screening

Antiretroviral treatment at time of diagnosis for cases of incident lab-confirmed cryptococcosis (n=7,397) diagnosed at GERM-SA enhanced surveillance sites, South Africa, 2005-2010



### 3 – development of a new test for *Cryptococcus*

The new test (lateral flow assay) is:

**Simple and quick**

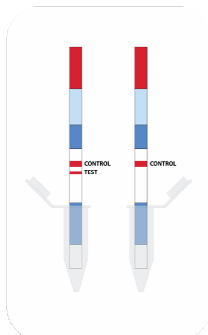
Results available in 10 minutes

**Available and effective**

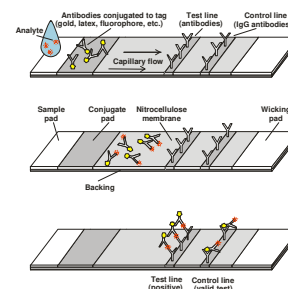
Highly sensitive and accurate (>95%)

**Affordable**

\$2/test



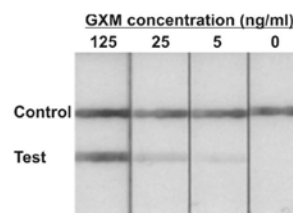
### Lateral flow assay format



### LFA can detect tiny amounts of antigen in body fluids

Immunoassay	Format	Serotype sensitivity (ng Crag/ml)			
		A	B	C	D
IMMY	LA	28	47	380	62
Meridian CALAS	LA	19	37	940	54
Inverness	LA	38	64	1600	50
Meridian Premier	ELISA	28	23	>2000	770
mAbs F12D2 + 339	ELISA	0.6	0.8	5.0	0.6
IMMY	LFA	1	1	9	8

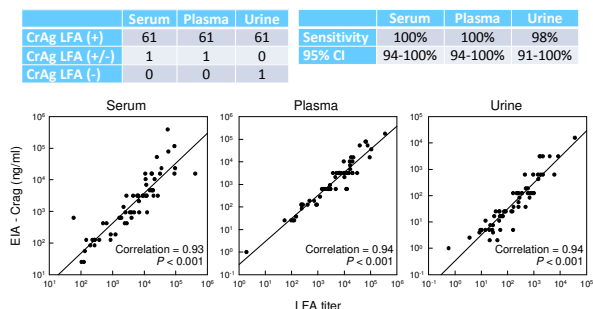
### LFA is very sensitive



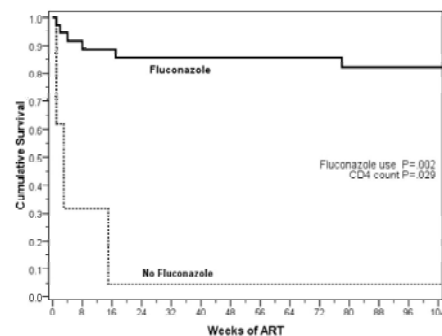
Jarvis, et al. Clin Infect Dis. In press.

### Comparison of LFA vs. EIA

- Sets of samples from 62 patients with culture-proven cryptococcosis
- Samples assayed by quantitative EIA and by LFA

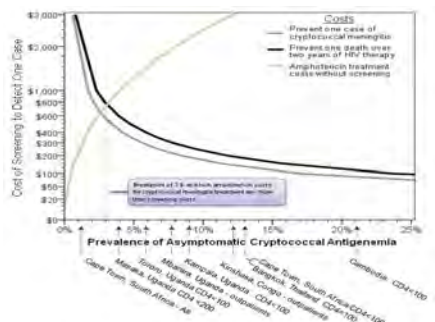


### 4 - An intervention exists...



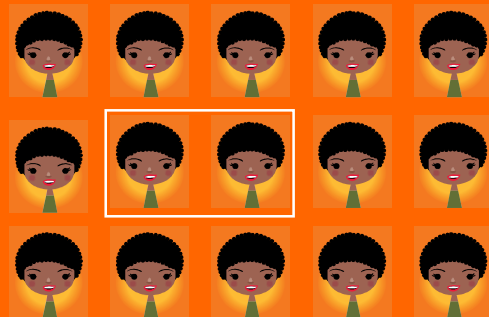
Mehta D, et al. Clin Infect Dis. 2010

## 5 - Screening costs vs. cost of amphotericin B (based on prevalence of cryptococcal antigenemia)



Mehta D, et al. Clin Infect Dis. 2010

## Preventing deaths amongst patients with CD4 <100



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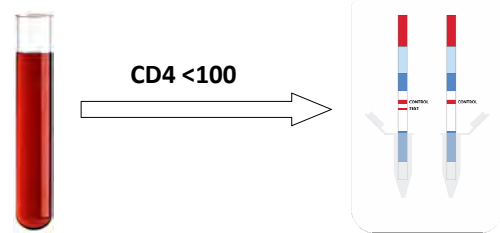
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## Lab-driven screening strategy

Reflex testing of remnant CD4 plasma



## National Screening Programme Cost Evaluation

Number of CD4 specimens <100 per year<sup>1</sup> (636,000)

X

Cost of crypto LFA test<sup>2</sup> (R 21)

=

Estimated annual cost of national screening programme R 13,356,000

Number of CM cases per year<sup>3</sup> (8,330)

X

Cost of hospitalisation for CM<sup>4</sup> (R 20,080)

=

Estimated annual cost of current CM management R 167,266,400

Number of preventable CM cases per year<sup>5</sup> (4800)

X

Cost of hospitalization for CM (R 20,080)

=

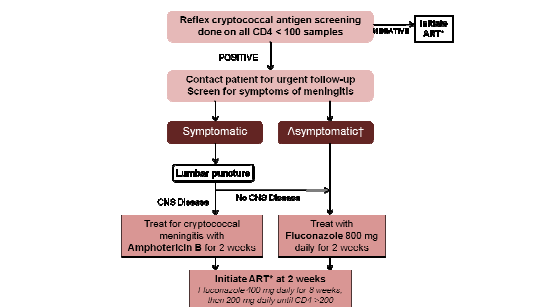
Estimated annual savings from national screening programme R 96,384,000

1. NHLS Data Warehouse  
2. Preliminary NHLS estimate  
3. GEMS Surveillance 2009  
4. Haile et al. APHA Conference Atlanta, 2001  
5. Based on 3% CrAg positivity (Govender et al. unpublished), 28% CM development among CrAg+ (Jarvis et al. Clin Infect Dis 2009), & 10% unpreventable deaths in pts presenting with overt CM (Meintjes, personal communication).

## Cryptococcal Screening Programme Objectives

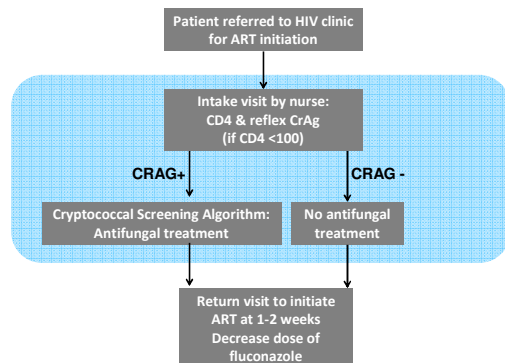
1. Identify patients at risk (CD4 <100)
2. Test for cryptococcal antigen
3. Treat with oral fluconazole
4. Prevent cryptococcal meningitis deaths

### Proposed Cryptococcal Screening Algorithm for HIV+ Patients



\* A lumbar puncture may be considered in asymptomatic patients. Pregnant women, children, and those with liver failure may require special attention.  
\* Initiate ART if not already started

### Screening Fits into Routine HIV Care

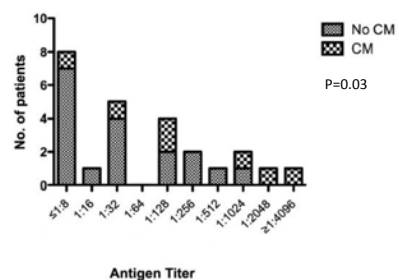


### Role of lumbar puncture



- **Three options for asymptomatic patients**
  - Offer lumbar puncture to all CrAg+ patients
  - Offer lumbar puncture if CrAg titre greater than cutoff value
  - Treat empirically with fluconazole, no lumbar puncture

### Role of lumbar puncture



Jarvis et al. Clin Infect Dis. 2009

### Role of lumbar puncture



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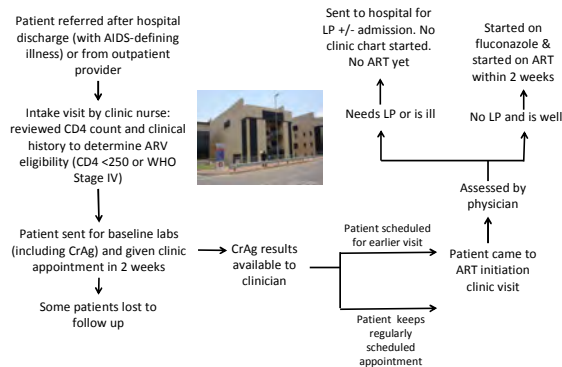
### Timing of ART initiation

- SA HIV Clinicians' Society Guidelines: 2 to 4 weeks post-diagnosis
- IDSA Guidelines: 2 to 10 weeks post-diagnosis
- Zolopa<sup>1</sup>: supportive of 2 weeks
- Makadzange<sup>2</sup>: <3 days not recommended
- Boulware: ongoing, NIH-funded, multicentre RCT

<sup>1</sup>Zolopa et al ACTG A5164 PLOS One; <sup>2</sup>Makadzange et. al. Clin Infect Dis 2010

## Screening in the real world:

Soweto, 2009-2010



## How did screening work in practice?

- CrAg results provided to clinicians within 1 week
- Prevalence of incident antigenaemia = 3%
- Approximately half of CrAg+ patients had previous history of CM
- Median CD4 count of patients with incident CrAg+ was extremely low (19)



## How did screening work in practice?

- Almost one-third (30%) of incident CrAg+ patients never returned to ART clinic for follow-up
- Almost half (45%) refused an LP when offered
- Only three-quarters (73%) were prescribed an antifungal drug
- Three incident antigenaemic patients developed meningitis post-screening (no fluconazole)



## Programme Implementation

- **Three initial implementation sites, 2011**
  - 3 NHLS CD4 testing labs in Gauteng and Free State
  - Chosen for convenience
- **Intensive laboratory and clinician training**
- **Monitoring and programme evaluation**
  - Identify operational issues
  - Define magnitude of benefit of screening strategy
- **Long-term goal: Nationwide implementation**

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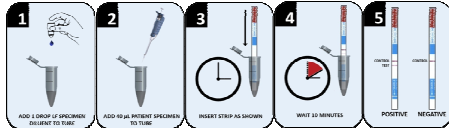
## Case 1

- 40-year old man was seen at primary health care clinic in Cape Town
  - New diagnosis of HIV infection, CD4 count = 9
  - Diarrhoea for 1 month and significant weight loss
  - No headache, fever, photophobia or vomiting
- Unkempt, lived alone in an informal settlement
- Significant alcohol history

All cases courtesy of Nicky Longley, Cape Town

## Case 1

- CRAG screening test was performed
- Urgently worked up for initiation of ARVs and asked to return for ARVs in 2 weeks
- Patient defaulted - did not return to clinic and could not be contacted
- CrAg screening test done at clinic was positive



## Case 1

- 3 months later
  - Admitted to GF Jooste Hospital with a 2-week history of headache, neck stiffness and confusion
  - Still not on ARVs
  - LP: India ink positive, serum CrAg positive, opening pressure 45cm water
  - Had therapeutic tap and subsequent daily LPs
  - Started on amphotericin B 1 mg/kg/day
- Patient died on day 5 post-admission

## Discussion points

- Delay in presentation → severe disease
- Early detection of antigenaemia and pre-emptive treatment could have averted fatal disease
- Role of point-of-care testing

## Case 2

- 40-year old man
- Referred to primary health care clinic for ARVs from GF Jooste Hospital
  - New HIV diagnosis, CD4 count = 11
  - Recent admission with PCP: treated with cotrimoxazole & steroids → good recovery
- At clinic
  - Well-looking man
  - No headache, fever, confusion or neck stiffness
  - Severe oral candidiasis
  - Single KS lesion on back
  - Peripheral neuropathy
- Urgently worked up for ART

## Case 2

- CrAg test positive
- Patient called back to clinic
  - Still well, no CNS symptoms
  - Agreed to have an LP
    - 3 attempts at LP failed - very large man (98kg)
    - As patient apparently well, did not persist.
  - Blood culture sent instead
  - Patient started on fluconazole 800 mg per day
  - Plan to follow up in 2 weeks to start ART
  - Given phone numbers if problems

## Case 2

- Day 10 of fluconazole (Thursday)
  - Lab called - *Cryptococcus neoformans* cultured from blood.
  - Spoke to patient - still felt well, taking fluconazole, no headache,
  - Did not want to come to hospital until next Monday but was convinced to go to GF Jooste the next day
- GF Jooste
  - New small umbilicated lesion on left forearm - cutaneous cryptococcosis
  - LP: CrAg positive, India ink positive, opening pressure 21 cm H<sub>2</sub>O
  - Patient started on amphotericin B 1 mg/kg/day with pre-hydration

## Case 2

- GF Jooste
  - Day 4 amphotericin B - creatinine increased from 84 to 176
  - Fluids increased and amphotericin B dose reduced to 0.7mg/kg
  - Completed 16 days amphotericin B
  - Had one subsequent LP with normal opening pressure
  - Developed amphotericin B-induced thrombophlebitis
- Post-discharge follow-up at clinic
  - Fluconazole 400 mg/day, doing well
  - Started on ART (AZT, 3TC, EFZ) in view of high creatinine and peripheral neuropathy, Hb = 9.6

## Discussion points


- If patient had been screened when diagnosed with PCP at GF Jooste, he may have been diagnosed before developing meningitis and been successfully treated with fluconazole
- Insidious onset of cryptococcosis - if he had not been screened, he would not have presented to hospital for some time
- Toxicity of amphotericin B and benefits of detecting cryptococcal disease early
- Late-stage patients often have multiple pathologies – need high index of suspicion

## Case 3


- 35-year old man
- Referred for ARVs from TB clinic
  - Diagnosed with sputum smear-positive TB 4 weeks prior to clinic appointment
  - Started on regimen 1
  - Pulmonary symptoms improving
  - Patient felt well otherwise, no headache, fever and neck stiffness
  - CD4 count = 50; other screening bloods normal.
- CrAg positive
- Started on fluconazole 1200 mg per day for 2 weeks
- Reviewed at 2 weeks to start ART: EFZ, 3TC, TDF

## Discussion points

- 30% of patients with CD4 count <100 will have concomitant TB
- Rifampicin induces cytochrome p450 enzymes → need to increase dose of fluconazole by 50%
- Fluconazole and rifampicin are both hepatotoxic → watch out for signs of liver toxicity
- High-dose fluconazole & TB meds can often cause nausea/GI disturbance
  - May help to split fluconazole dose to twice daily
  - If severe nausea, give antiemetic 30 minutes before



Thank you to all participating patients, laboratory, clinical and administrative staff for submitting case reports and isolates



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