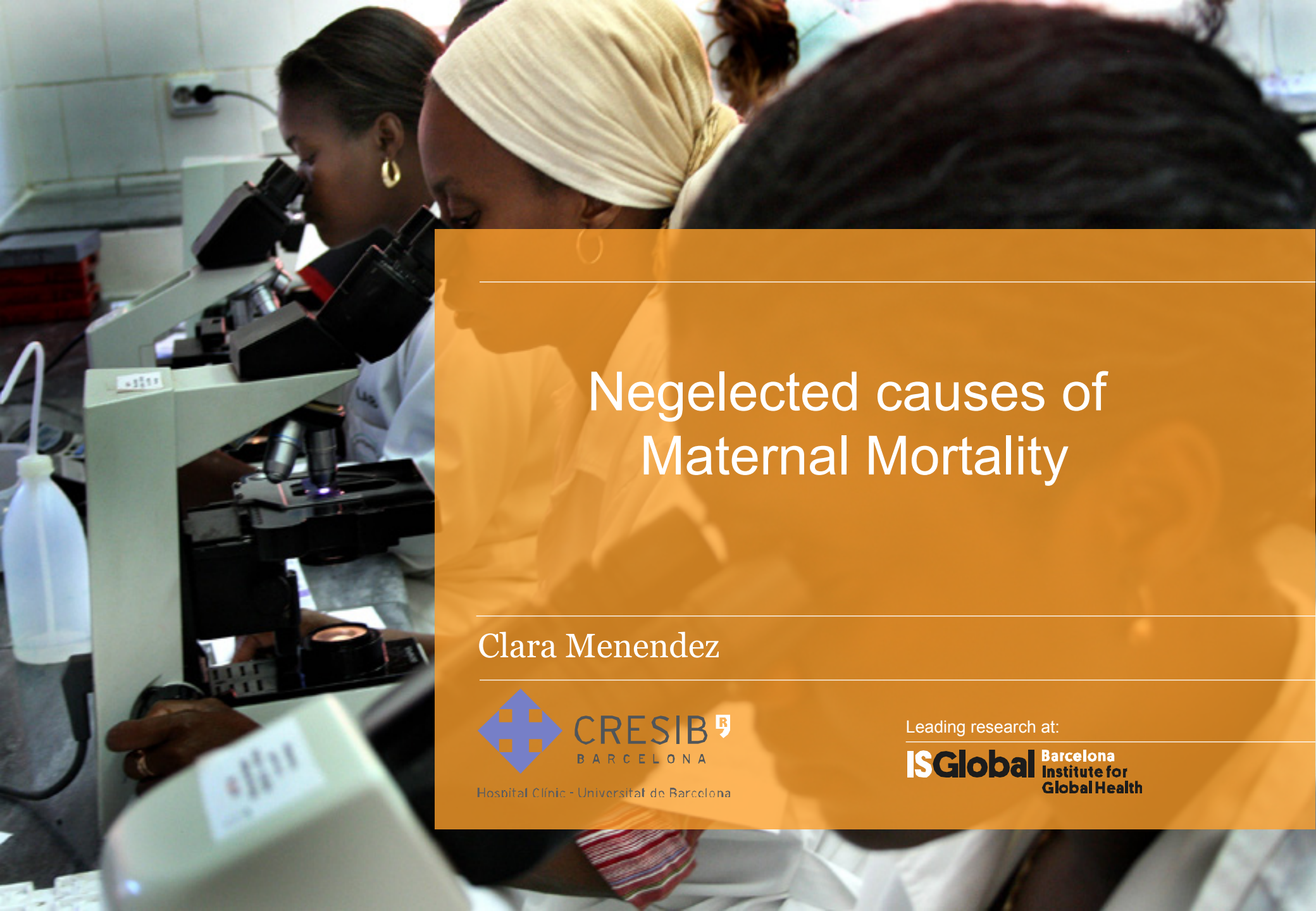

Negelected causes of Maternal Mortality

Clara Menendez

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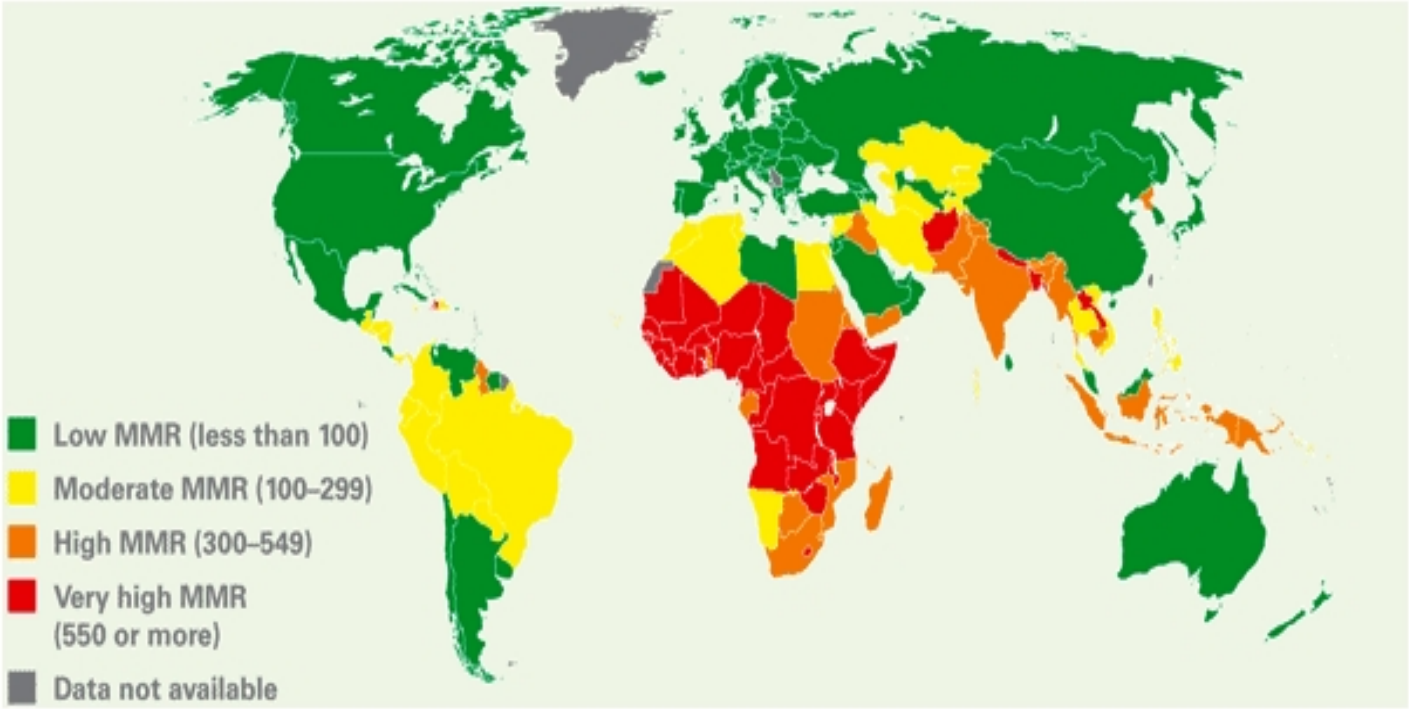
- **Every day ~1000 women die worldwide due to preventable pregancy-related causes**
  - **99% of the nearly 300.000 annual maternal deaths occur in low income countries**
    - **>50% in SSA**

MATERNAL MORTALITY IS HIGHEST IN COUNTRIES OF SUB-SAHARAN AFRICA AND SOUTH ASIA Maternal mortality ratios (MMR) per 100,000 live births (2005)



A major handicap in achieving the MDG5 in Africa is that efforts to reduce the MMR in the region are not evidence driven

- Insufficient evidence-based data on the main causes of maternal death

The main sources on cause of death determination – **clinical records and verbal autopsies- have substantial limitations**

- >500 MM /100.000 LB
- Malaria said to be an important cause of maternal mortality at Maputo Central Hospital
- Classicaly malaria not an important cause of MM in Africa

- Descriptive cross-sectional study
- Subjects: Maternal deaths occurring at Maputo Central Hospital
- Period of study: October 2002- December 2006
- 21% HIV prevalence in pregnant women
- Clinical questionnaire
- **Complete autopsy**
  - Macroscopic examination and **Histology**
  - PCR for HIV and *P falciparum*

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PLOS MEDICINE

An Autopsy Study of Maternal Mortality in Mozambique: The Contribution of Infectious Diseases

Clara Menéndez[1,2*], Cleofé Romagosa[1,2], Mamudo R. Ismail[3], Carla Carrilho[3], Francisco Saute[4], Nafissa Osman[5], Fernanda Machungo[5], Azucena Bardaji[1,2], Llorenç Quintó[1], Alfredo Mayor[1], Denise Naniche[1], Carlota Dobaño[1], Pedro L. Alonso[1,2], Jaume Ordi[1]

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Table 1. Demographic Characteristics of the Women in the Study

Category	Group	*n*	(%)
Status of pregnancy	Pregnant	35	(25.2)
	Puerperium	93	(66.9)
	Post-abortion	7	(5.1)
	Ectopic pregnancy	2	(1.4)
	Unknown	2	(1.4)
Age	≤20 y	32	(23.0)
	21–30 y	68	(48.9)
	>30 y	36	(25.9)
	Unknown	3	(2.2)
Parity	Primiparous	29	(20.8)
	Secundiparous	19	(13.7)
	Multiparous (≥3)	41	(29.5)
	Unknown	50	(36.0)
Place and type of delivery	Not applicable[a]	44	(25.2)
	Hospital vaginal	31	(22.3)
	Out-of-hospital vaginal	9	(6.5)
	Caesarean section	34	(24.4)
	Unknown	21	(21.6)
Place of residence	Maputo Centre	16	(11.5)
	Maputo periphery	63	(45.3)
	Rural areas	28	(20.2)
	Unknown	32	(23.0)

[a]Patients who died during pregnancy before delivery or after abortion or ectopic pregnancy.

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	n	%
Obstetrical complications		
Hemorrhage	23	16.6%
Puerperal septicemia	12	8.7%
Eclampsia	12	8.7%
Post-cesarean septicemia	2	1.4%
Ectopic pregnancy	2	1.4%
Acute fatty liver of pregnancy	1	0.7%
Amniotic embolism	1	0.7%
Non Obstetric conditions		
HIV/AIDS related conditions*	18	12.9%
Pyogenous bronchopneumonia	17	12.2%
Severe malaria	14	10.1%
Pyogenous meningitis	10	7.2%
Neoplasia	4	2.9%
Other septicemia	3	2.2%
Fulminant hepatitis	3	2.2%
Mycobacterial disease	2	1.4%
Pulmonary hypertension	2	1.4%
Anemia	2	1.4%
Digestive hemorrhage	2	1.4%
Alveolar proteinosis	1	0.7%
Unknown	8	5.8%
Total	139	100.0%

38.2% Direct

56.1% Indirect

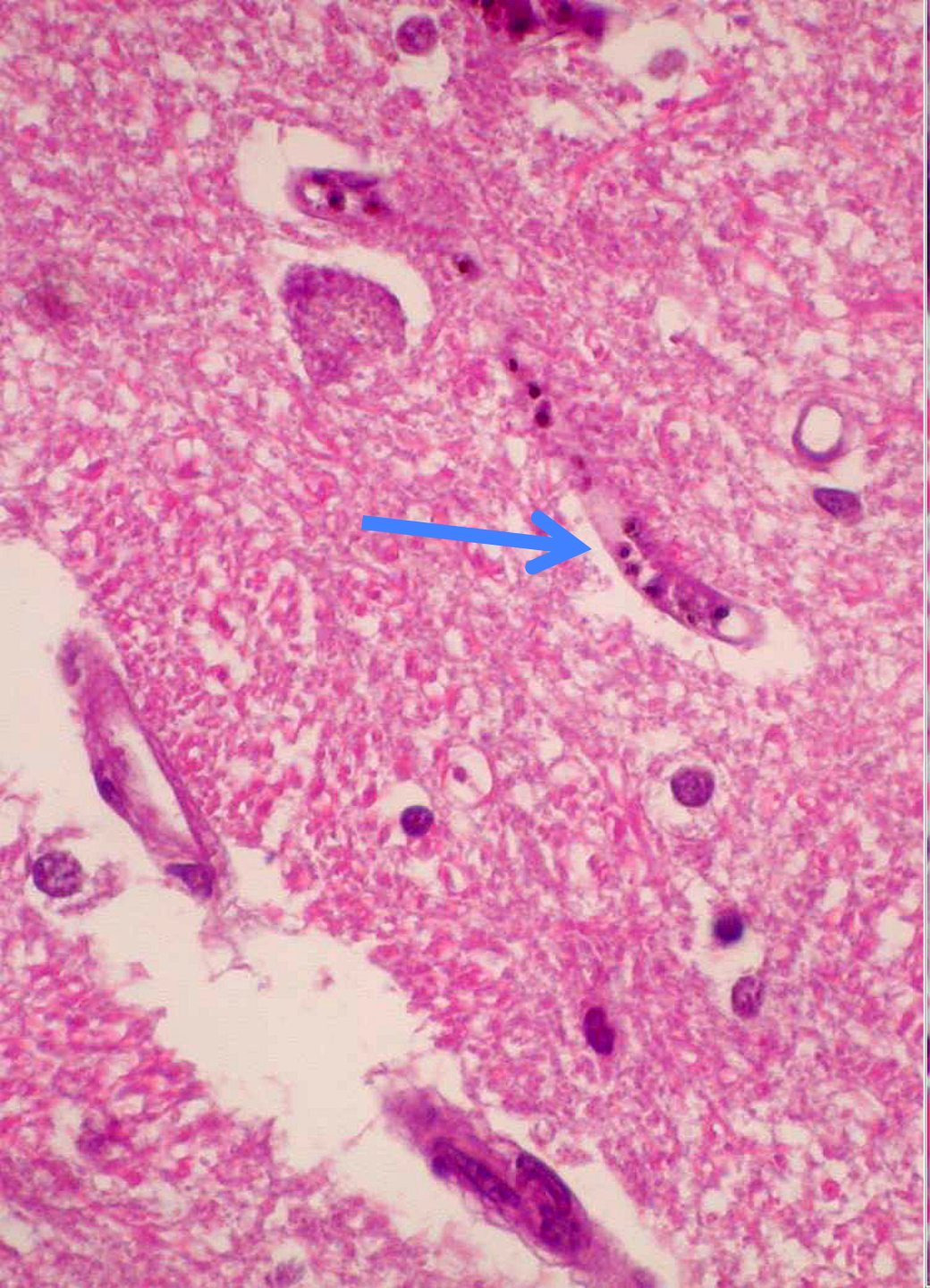
84% infectious diseases

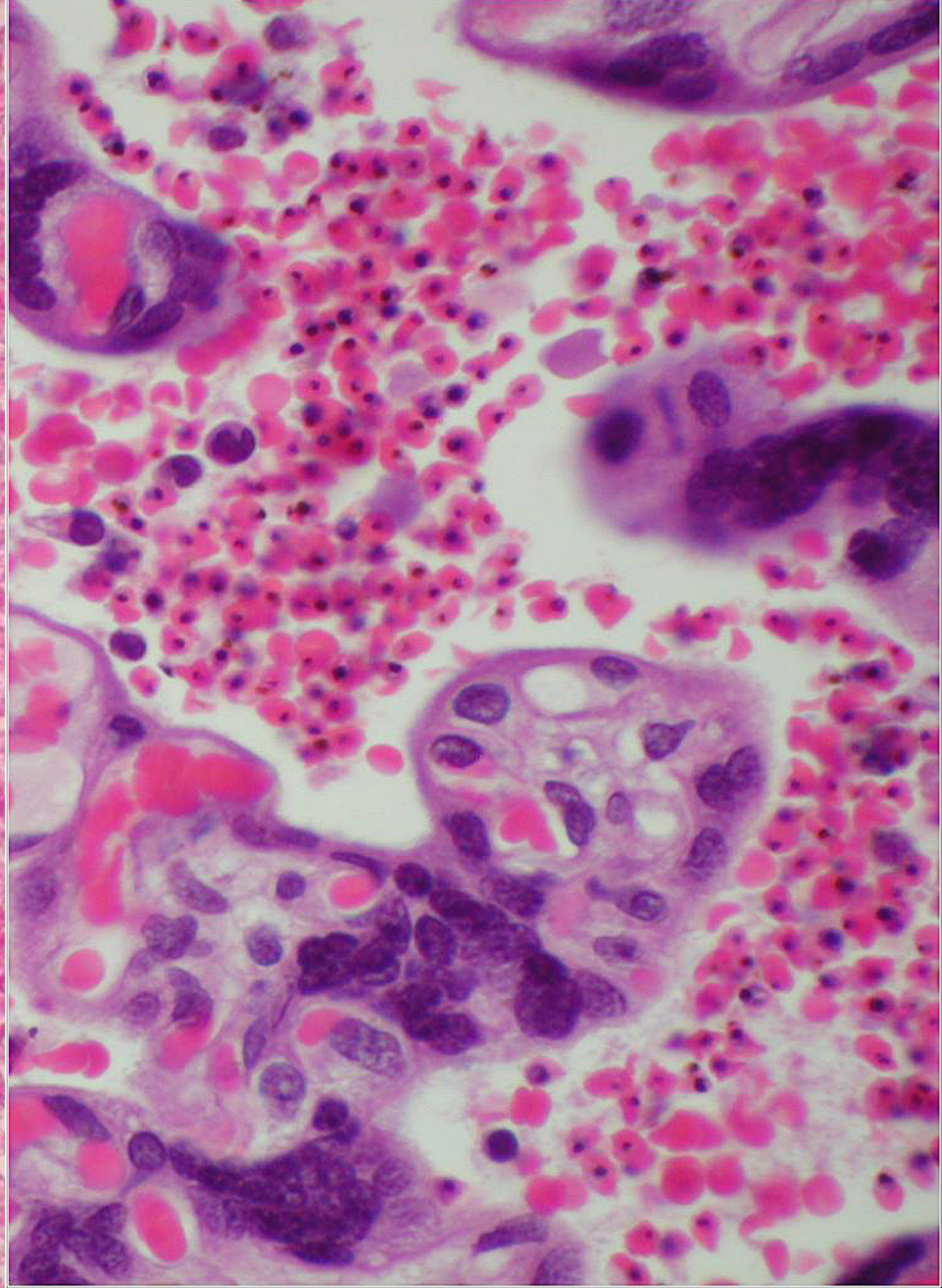
Menéndez C et al. PLOS Medicine 2008

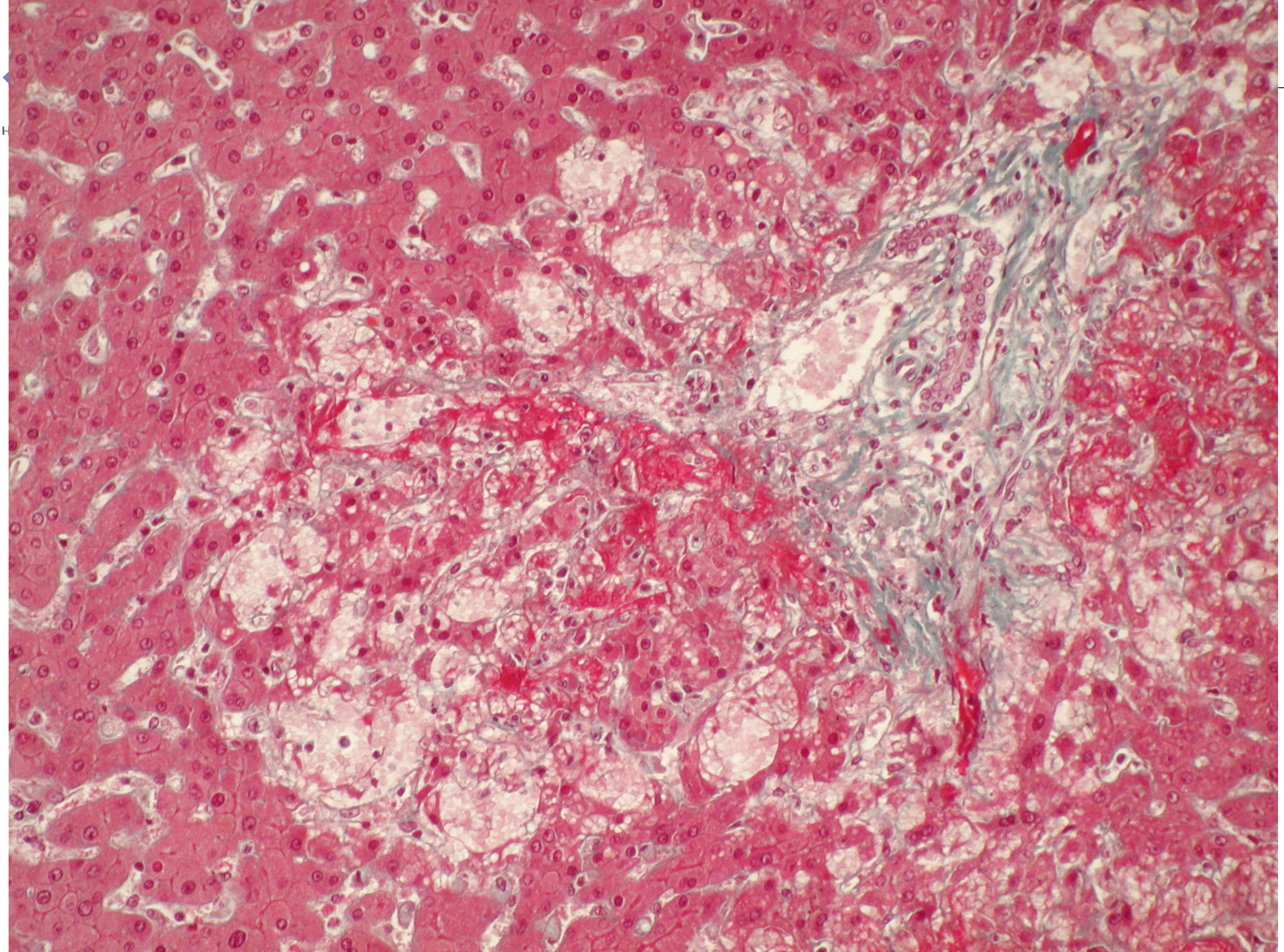
Table 4. Autopsy Diagnoses in HIV-Positive and HIV-Negative Women

Category	Cause	HIV-Positive ($n = 47$)[a]		HIV-Negative ($n = 58$)		*p*-Value[b]
		n	(%)	*n*	(%)	
Obstetric complications	Haemorrhage	5	(10.6)	12	(20.7)	0.19
	Puerperal septicaemia	6	(12.9)	6	(10.3)	0.76
	Eclampsia	6	(12.9)	4	(6.9)	0.33
	Other	1	(2.1)	4	(6.9)	0.38
Nonobstetric conditions	Pyogenic bronchopneumonia	8	(17.0)	9	(15.5)	1
	Severe malaria	5	(10.6)	8	(13.8)	0.77
	Pyogenic meningitis	5	(10.6)	3	(5.2)	0.46
	Neoplasia	1	(2.1)	3	(5.2)	0.63
	Other	5	(10.6)	6	(10.3)	1
	Unknown	5	(10.6)	3	(5.2)	1

[a]No blood for HIV testing was available in 16 cases; and the 18 HIV/AIDS-associated deaths are excluded from this table (see Table 2).
[b]*p*-Values were calculated using Chi-square or Fisher exact test.
doi:10.1371/journal.pmed.0050044.t004







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PLOS MEDICINE

Clinico-Pathological Discrepancies in the Diagnosis of Causes of Maternal Death in Sub-Saharan Africa: Retrospective Analysis

Jaume Ordi[1,2*], Mamudo R. Ismail[3], Carla Carrilho[3], Cleofé Romagosa[1,4], Nafissa Osman[5], Fernanda Machungo[5], Josep A. Bombí[1], Juan Balasch[6], Pedro L. Alonso[2,4], Clara Menéndez[2,4]

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Classification of clinico-pathologic discrepancies

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Major discrepancies

- **Class I ->** **the knowledge of the diagnosis would have led to changes in the management that could have prolonged the survival or cured the patient**
  - **Pyogenic meningitis treated as eclampsia**
- **Class II ->** the survival would have not been modified
  - Fulminant hepatitis treated as septicemia
  - Terminal AIDS with multiple opportunistic infections treated as a bacterial infection

Minor discrepancies

- **Class III ->** symptoms that should have been treated or would have eventually affected the prognosis
  - mild aspirative pneumonia in a patient with eclampsia
- **Class IV ->** Non-diagnosed diseases with possible epidemiological or genetic importance
  - schistosomal infections
- **Class V ->** Correctly diagnosed patients
- **Class VI ->** nonclassifiable cases
  - necropsy unsatisfactory or with no clear diagnosis

Prevalence of major diagnostic errors by pathology at autopsy

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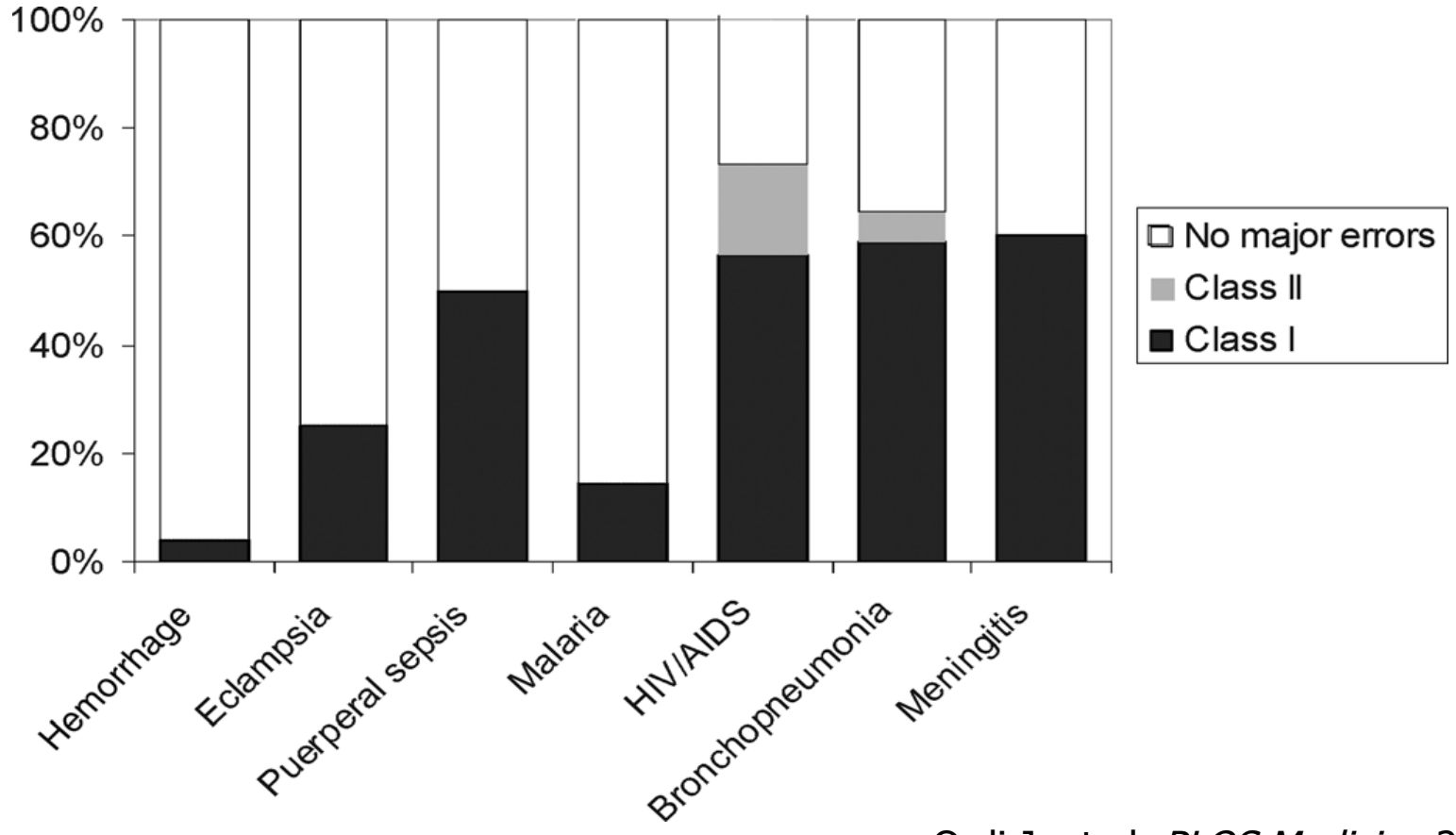
- **Clinical errors present in 62% of maternal deaths**
- **A major clinical error detected in 40.3% maternal deaths**



Ordi J, et al. *PLOS Medicine* 2009

Table 1. Causes of Death Detected in the Autopsies

Category	Subcategory	Necropsy Diagnosis	Clinical Diagnosis	False Negative Diagnosis		False Positive Diagnosis	
				n	(%)	*n*	(%)
Obstetrical complications	Hemorrhage	23	24	1	(4.3)	2	(8.3)
	Puerperal septicemia	12	11	6	(50.0)	5	(45.5)
	Eclampsia	12	21	3	(25.0)	12	(57.1)
	Postcesarean septicemia	2	4	0	(0.0)	2	(50.0)
	Ectopic pregnancy	2	2	0	(0.0)	0	(0.0)
	Acute fatty liver of pregnancy	1	0	1	(100.0)	0	(0.0)
	Amniotic embolism	1	0	1	(100.0)	0	(0.0)
Nonobstetric conditions	HIV/AIDS-related conditions	18	10	12	(66.6)	4	(40.0)
	Pyogenic bronchopneumonia	17	11	11	(64.7)	5	(45.5)
	Severe malaria	14	18	2	(14.3)	6	(33.3)
	Pyogenic meningitis	10	7	6	(60.0)	3	(42.9)
	Neoplasia	4	2	4	(100.0)	2	(100.0)
	Other septicemia	3	3	1	(33.3)	1	(33.3)
	Fulminant hepatitis	3	2	1	(33.3)	0	(0.0)
	Decompensated cirrhosis	2	1	1	(50.0)	0	(0.0)
	Mycobacterial disease	2	0	2	(100.0)	0	(0.0)
	Pulmonary hypertension	2	0	2	(100.0)	0	(0.0)
	Anemia[a]	1	6	0	(0.0)	5	(83.3)
	Digestive hemorrhage	1	0	1	(100.0)	0	(0.0)
	Alveolar proteinosis	1	0	1	(100.0)	0	(0.0)
	Other[b]	0	9	0	(0.0)	9	(100.0)
	Unknown	8	8	NA	NA	NA	NA
	Total	139	139	56	—	56	—

The number of clinically suspected diagnoses for each final autopsy diagnosis and the number and percentage of major diagnostic errors separated into false negative and false positive diagnoses.

[a]Clinically severe anemia with no other cause of death and signs of cardiac failure in the autopsy.

[b]Clinical diagnoses in this group were: coma of unknown origin (three cases), cardiomyopathy, diabetes mellitus, pulmonary edema, endocarditis, gastroenteritis, drug toxicity.

NA, nonapplicable.

doi:10.1371/journal.pmed.1000036.t001

Autopsy diagnosis in maternal deaths with false positive clinical diagnosis of eclampsia

Pyogenic meningitis	• 4
Meningioma	• 2
Puerperal sepsis	• 2
Pyogenic bronchopneumonia	• 2
Tuberculosis	• 1
Postpartum hemorrhage	• 1

No pathological lesions related to eclampsia were detected in any of these women

Clinical diagnosis in cases with false negative major errors in patients with TB

Bacterial meningitis	•3
Bacterial bronchopneumonia	•2
HIV/AIDS	•1

The diagnosis of TB had a sensitivity of 25% (0.5-49-5)

ORIGINAL ARTICLE 10.1111/1469-0691.12068

Massive *Plasmodium falciparum* visceral sequestration: a cause of maternal death in Africa

P. Castillo[1], C. Menéndez[1,2], A. Mayor[1,2], C. Carrilho[3], M. R. Ismail[3], C. Lorenzoni[3], F. Machungo[4,5], N. Osman[4,5], L. Quintó[1], C. Romagosa[1,2], C. Dobaño[1,2], P. L. Alonso[1,2] and J. Ordi[1]

1) *Barcelona Centre for International Health Research (CRESIB), Department of Pathology, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain,* 2) *Centro de Investigaçao em Saude de Manhiça, (CISM),* 3) *Department of Pathology, Maputo Central Hospital, Maputo,* 4) *National Malaria Control Programme, Ministry of Health, Maputo, and* 5) *Department of Gynaecology, Maputo Central Hospital, Universidad Eduardo Mondlane, Maputo, Mozambique*

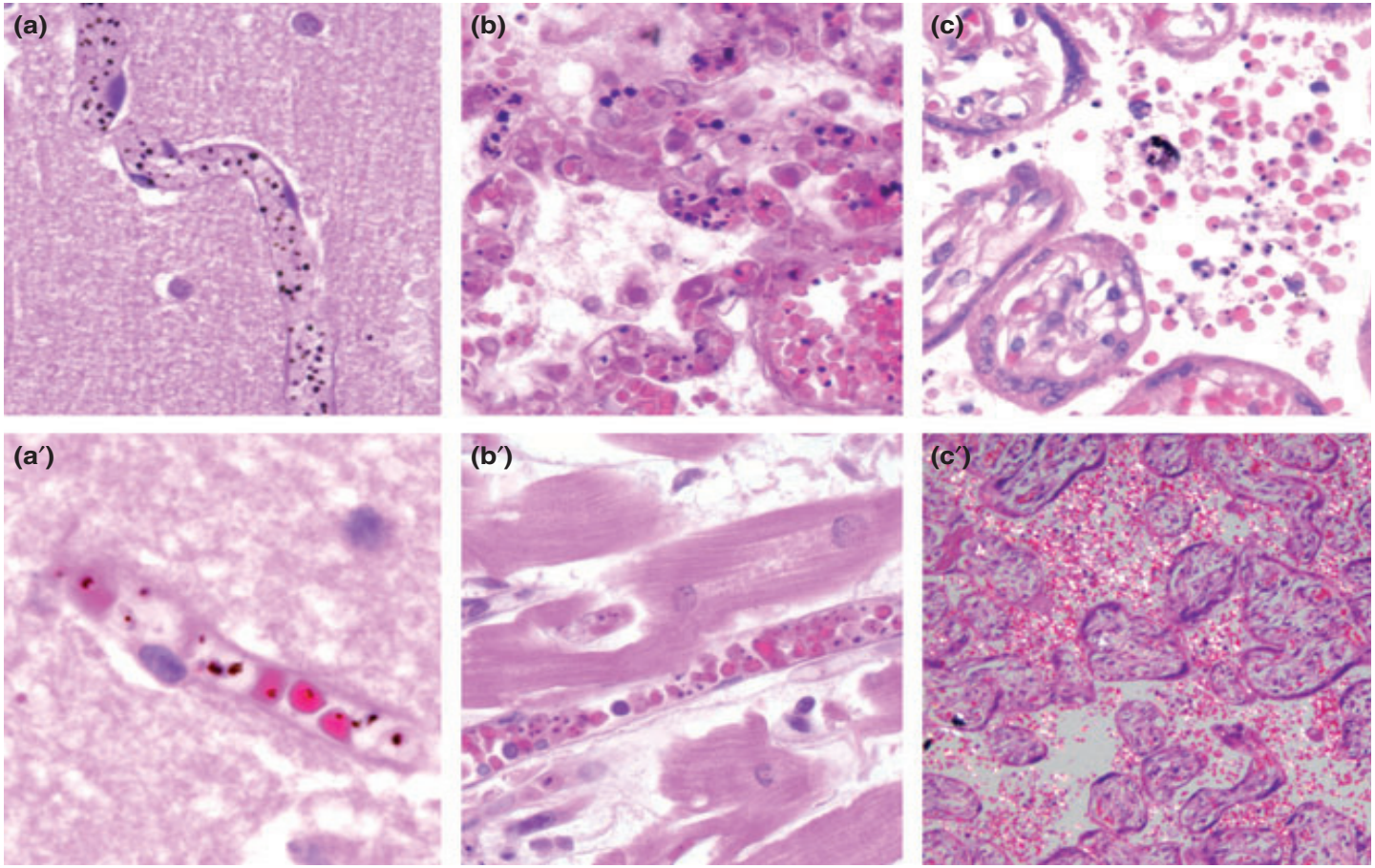


FIG. 1. Massive sequestration of *Plasmodium falciparum*-infected erythrocytes (PfIE) in the capillaries of the central nervous system; (a) cortical vessel showing many parasitized erythrocytes (haematoxylin & eosin, 400×); (a′) high power field (1000×) of a single vessel; (b) lung (200×) and (b′) heart (400×); showing massive accumulation of PfIE in the capillaries. Placenta of the same patient showing massive accumulation of infected maternal erythrocytes in the intervillous space (c) haematoxylin & eosin, 400×; (c′) haematoxylin & eosin, 100×, polarized light.

Conclusions

- Although obstetric causes remain a significant cause of Maternal Mortality, to achieve a major impact in reducing MM **it is crucial to also tackle non-obstetric causes, mainly infectious**, whose contribution may be at least as important as that of direct obstetric causes in many settings

Conclusions

High rate of clinico-pathological discrepancies

- Impact on maternal mortality– a change in clinical management could have modified the prognosis
- High rate of false negative diagnosis for infectious diseases
  - Underestimation of prevalence
  - Low sensitivities (<40%) for frequent infectious categories (HIV/AIDS; pyogenic bronchopneumonia, meningitis, TB)
  - **Significant reductions in MM could be reached through improvements in their diagnosis**

Eclampsia main source of false positive diagnosis (57.1%)

- Can not ruled out that it was a true diagnosis
- A different cause of death was found
- Overestimation of prevalence
- **No pathological lesions related to eclampsia were found**

Implications for Cause of Death Determination

- In developing countries CoD investigation is restricted to **verbal autopsies**
  - Identification of CoD by **analysis of data derived from structured interviews** of family, friends, and caretakers, and available medical records
  - Interpreted by clinicians: large demands on limited resources
  - High degree of misclassification errors, specially for conditions with poor diagnostic specificity such as maternal and peri-neonatal deaths
- Clinical records
  - Many deaths occur outside health facilities
  - They may contain substantial inaccuracies

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Complete Diagnostic Autopsies: gold standard for CoD determination

- Complete diagnostic autopsies (CDA) are challenging in rural areas of the developing world
  - Lack of technical expertise and required facilities
  - **Problems with cultural and/or religious acceptance**
  - **Many deaths occur at the community**
  - **Urgent need to validate newer approaches that could substitute CDA** using a more acceptable, less invasive procedure

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Minimally invasive autopsy

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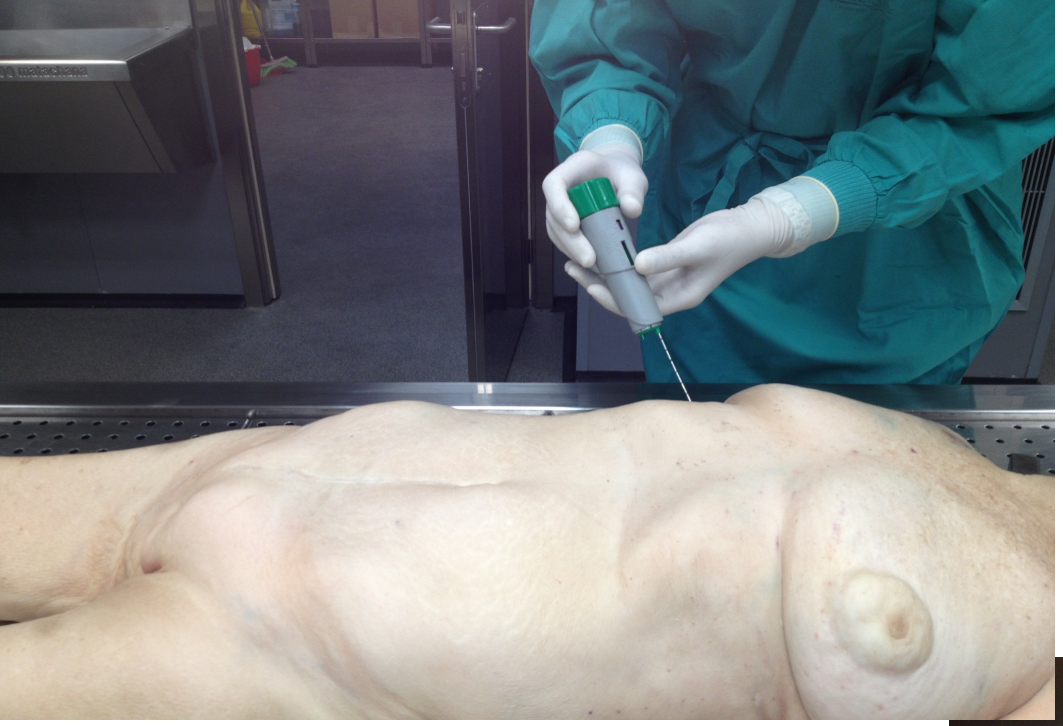
- Use of **imaging techniques** (MRI, CT scan) plus **targeted small needle biopsies** of key organs

- It may produce **reliable and comparable results to the CDA**

- MIA could be performed **guided by low-cost ultrasound** machines or even **without imaging guidance**, based exclusively in targeted key organ biopsies



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Objectives

1. To **assess the performance of MIA compared to CDA**

2. To assess the **feasibility and acceptability** of MIA **in different cultural, religious and geographical backgrounds**

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Objective 1: Sites

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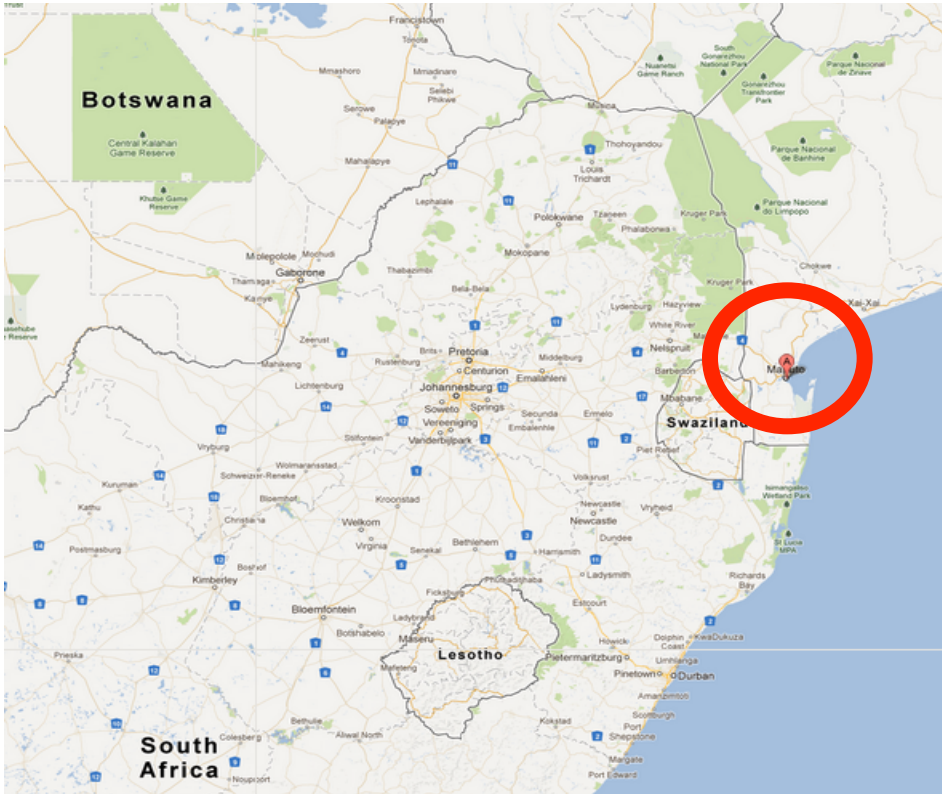

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Objective 2: Sites

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- Mozambique
- Kenya
- Gabon
- Mali
- Pakistan

- **More precise estimates of cause-specific maternal mortality are urgently needed**
  - Global health estimates help to determine the destiny of billions of dollars spent in health funding
  - To plan and prioritize the resources
  - To track disease patterns and changes over time
  - To evaluate the impact of specific interventions targeting specific diseases

To reduce maternal mortality