Maternal and Neonatal Mortality: Are We Tackling All the Main Causes?

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ISGlobal Instituto de Salud Global Barcelona

cism centro de investigação em saúde de manhiça

Absence of Data

- **Most of the world's population live in areas where vital registration systems are either not functioning or simply do not exist**
  - **People are born and die without having being counted**
  - **There is no attribution to their Cause of Death**

- The lack of **accurate determination of the CoD for most of the world's population**, is being increasingly recognized by international health and funding agencies as a **critical limitation to reduce the burden of mortality** especially in vulnerable populations

Knowing which are the **main causes of death** is invaluable for

- **health planning**
- **priority setting**
- **designing effective health programs**
- **evaluating their impact**

- Global **MNH** programs are designed on the basis of **estimated causes** of mortality and morbidity
  - these estimations are **based on unreliable information**,
    - the programs designed are bound to fail or being at least not as effective as they could be

- Only **less than 3%** of the more than 6 million deaths in children that occur each year, -nearly half of them are neonates-, are medically certified
  - need to make **difficult assumptions** as to the causes of these deaths

Ascertainment of causes of mortality

- In developing countries the two sources of information on the causes of deaths are **Verbal Autopsies** and **Clinical Records**

Verbal autopsies

- Relies on the interpretation by clinicians of data collected by trained health workers
- Subject to **misclassification errors** especially for conditions with poor diagnostic specificity such as **maternal and peri-neonatal deaths**

Clinical records

- Only from patients **who come to HF**
- **High number of clinical errors** even in well equipped tertiary level hospitals

- At Maputo Central hospital
  - Increased in maternal deaths due to malaria

- Descriptive cross-sectional study
- Subjects: Maternal deaths at MCH
- Clinical questionnaire
- **Complete autopsy**
- The study was focussed on **main diseases** causing the death

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PLOS MEDICINE

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

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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% of deaths

56.1% of deaths

84% infectious diseases

Menéndez C et al. PLOS Medicine 2008

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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

Major discrepancies

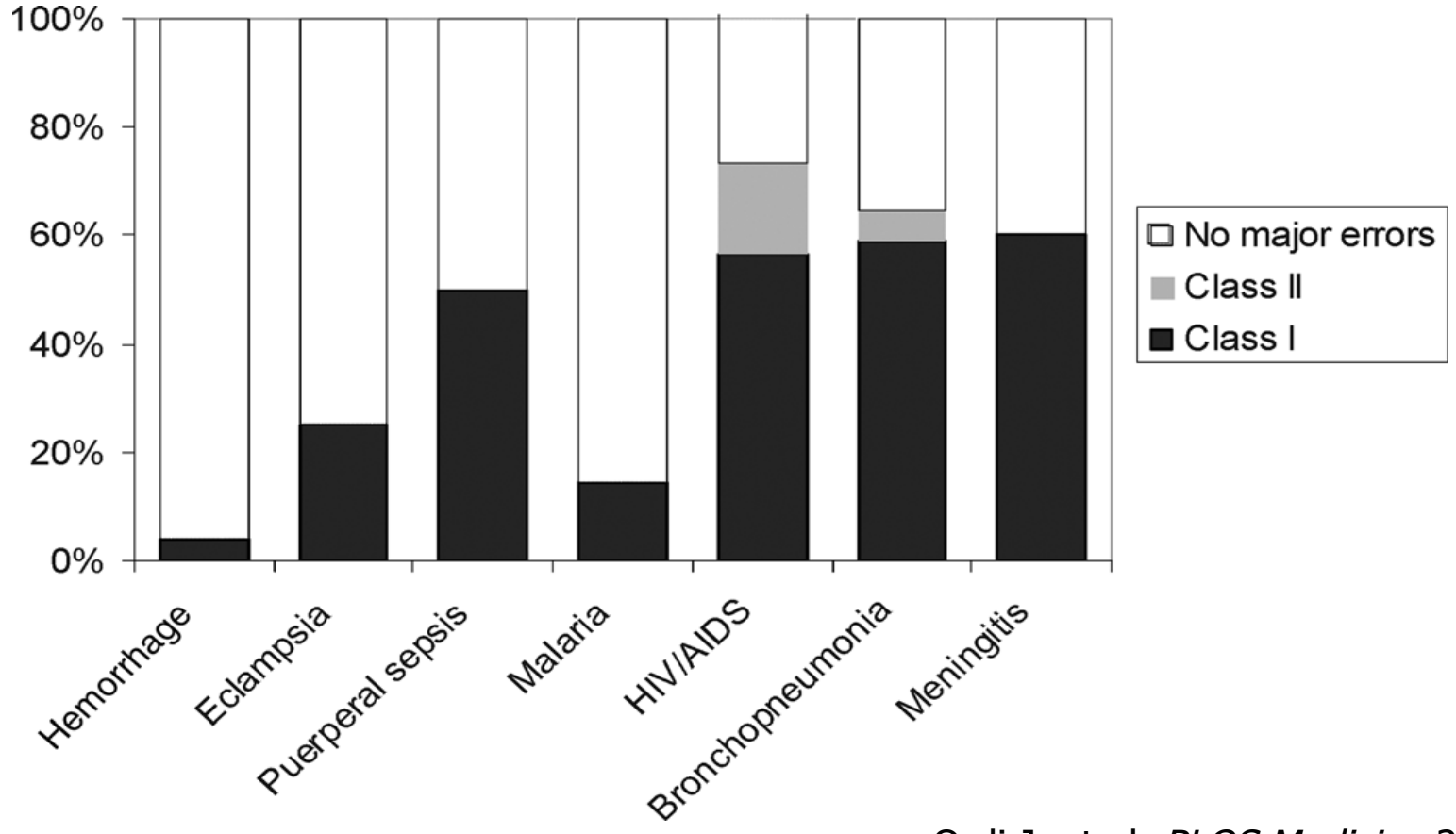
- **Class I ->** **the knowledge of the diagnosis would have led to changes in the management that could have prolonged the survival or cured the patient**
  - **Pyogenic meningitis treated as eclampsia**
- **Class II ->** the survival would have not been modified
  - Fulminant hepatitis treated as septicemia
  - 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

- **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.

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

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Autopsy Diagnosis	Clinical Diagnosis: 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

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Clinical Diagnosis	Autopsy Diagnosis: TB
Bacterial meningitis	•3
Bacterial bronchopneumonia	•2
HIV/AIDS	•1

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

Conclusions

Implications for cause of death determination

- **VA and clinical records may contain substantial inaccuracies**
- Pathology autopsies can only be carried out exceptionally in low income settings
  - new approaches of cause of death determination should be validated with pathology autopsies information

Rigorous knowledge of the causes of MM is critical to guide effective reduction strategies and a crucial resource for health planning and prioritization

What can it be done?

- Although **Complete Autopsies** are the gold standard for CoD determination
  - are difficult to do in low income countries
- Need to develop **simpler** and **feasible** methods
- **Minimally invasive autopsies- MIAs**
  - Based on targeted key organ biopsies
  - They could be done in rural settings by trained health workers

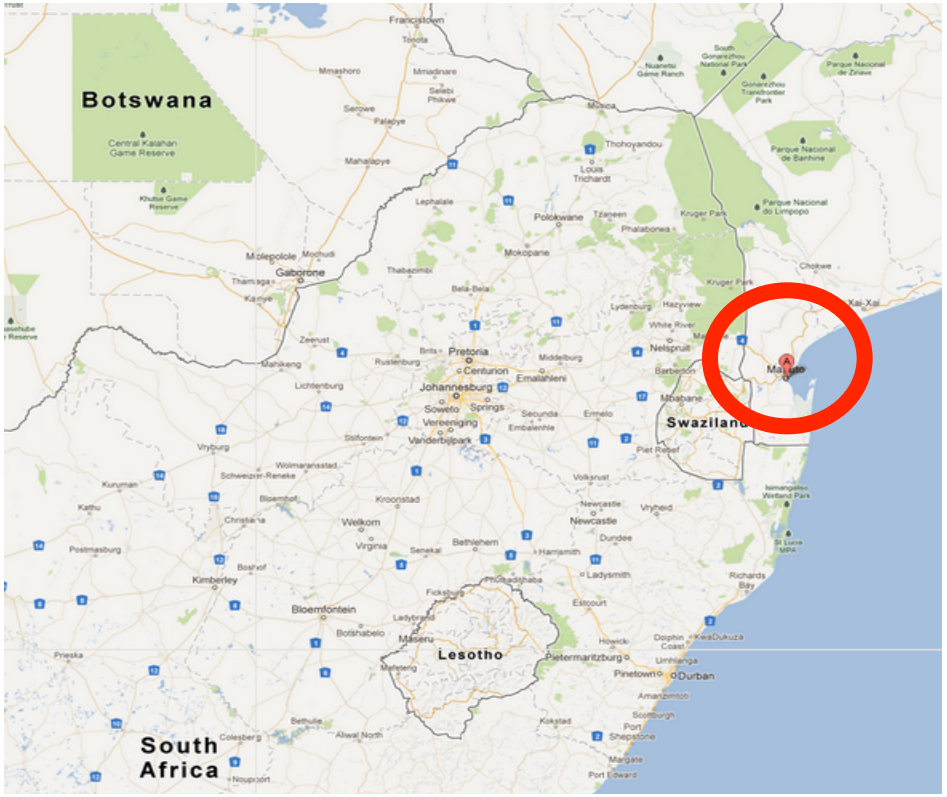
Goal

- To validate the **minimally invasive autopsy (MIA)** procedure for investigation of infectious CoD in all age-groups,

AND

- to evaluate the **acceptability and feasibility** of using such tools in different cultural, religious and geographical backgrounds

Objective 1: Sites



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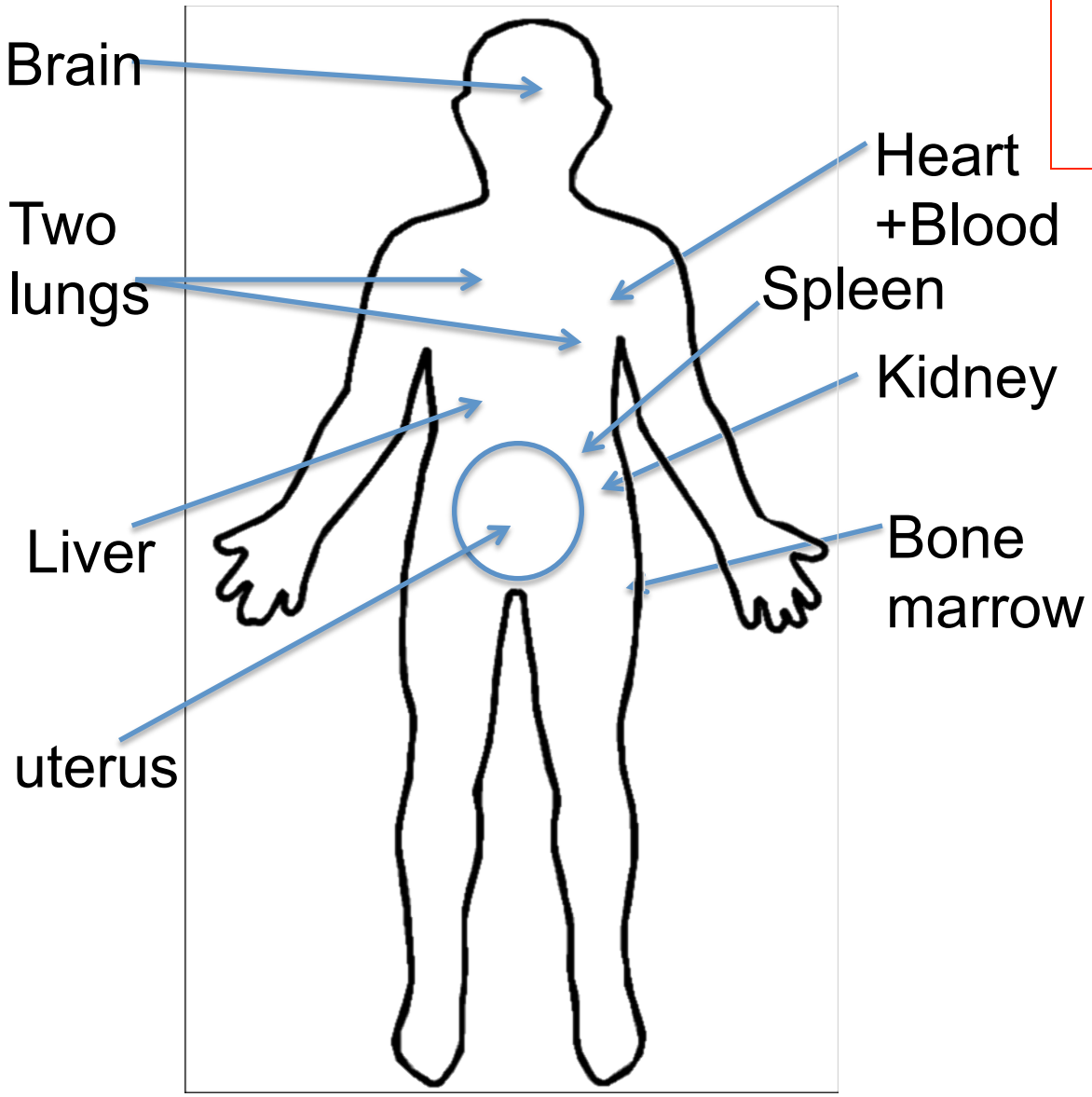
Fundação de Medicina Tropical, Manaus, Brazil

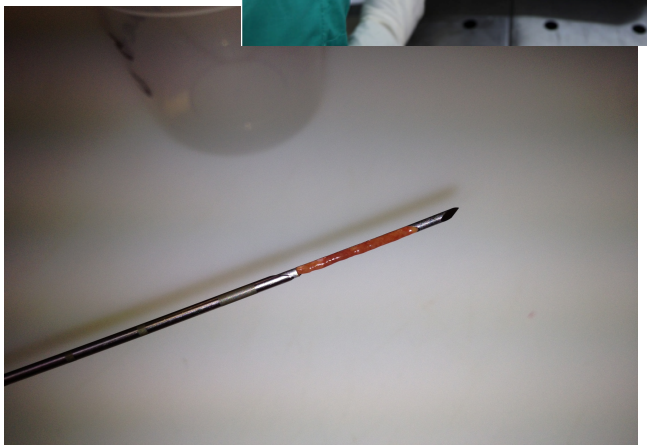
Objective 2: Sites

- Mozambique
- Kenya
- Gabon
- Mali
- Pakistan

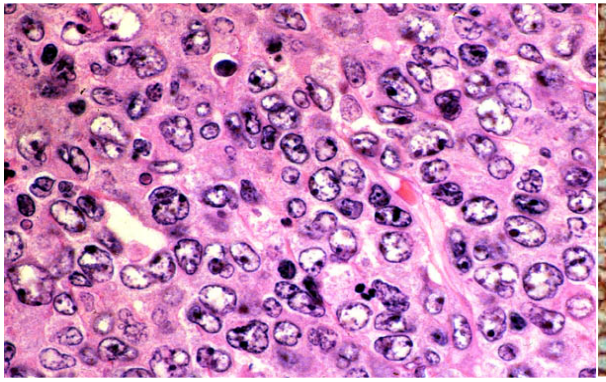
The procedure involves

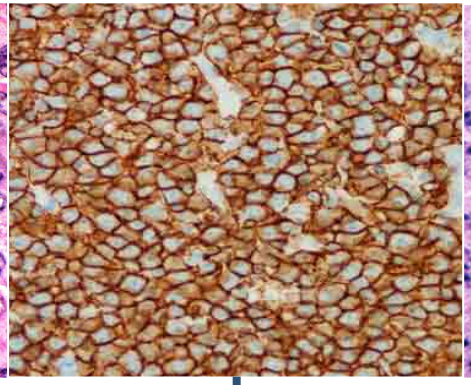
- ultrasound scan examination
- 20 mL of blood
- cerebrospinal fluid
- puncture of key organs

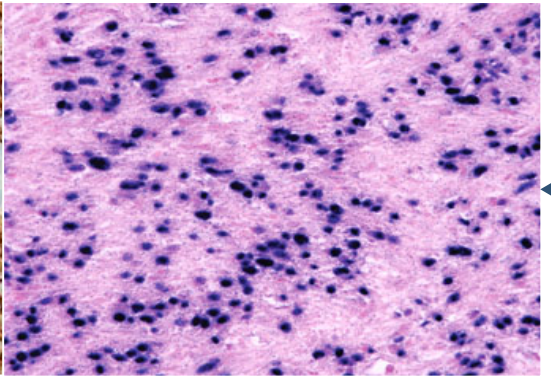




Pathological/histological evaluation







Final diagnosis

Preliminary Results

CoD determination

Cases

- **18** stillbirth
- **41** neonatal deaths
- **54** deaths >28 days <15 yrs of age
  - **31** in >28 days old and <5yrs of age

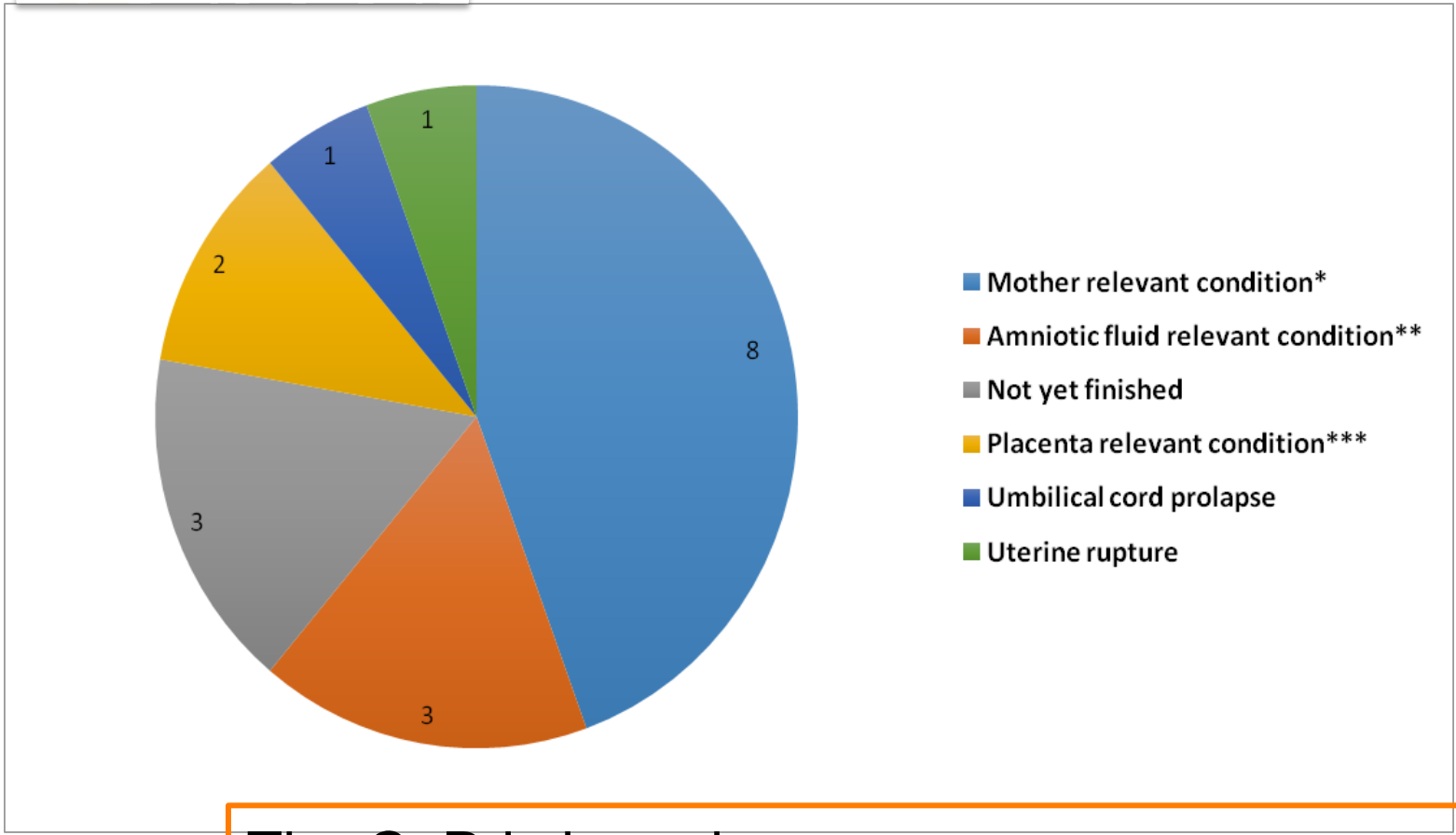
- **Coupled MIA and CDA**
- Universal screening depending on the age group and histological findings
- Microbiological analysis pending completion

SCREENING Stilbirths/neonates	plasma	CSF	Lungs	Brain	Liver
S agalactiae	x	x		(x)	
Sífilis	x	x		(x)	
Pneumococo	x	x		(x)	
TORCH Toxoplasma, Rubeola, CMV, HSV-2, Parvovirus B19, LCMV	x	(x)	x	(x)	x

SCREENING children (>28days- <5 years)	plasma	LCR	pulmón	SNC	Hígado
Pneumococo	x	x	x		
PCR multiplex respiratory virus			x		

SCREENING Universal	plasma	LCR	pulmón	SNC	Hígado
HIV antibodies	x				
HVB surface Ag	x				
HVC antibodies	x				
TB			x		
P. falciparum	x				
bacterial and fungi culture	x	x	x	x	x
HIV+	**plasma**	**LCR**	**pulmón**	**SNC**	**Hígado**
Viral load	x				
Toxoplasma		x	x	x	
Criptococcus		x	x	x	
TB		x		x	

Causes of death among 18 cases of stillbirth



The CoD is based on

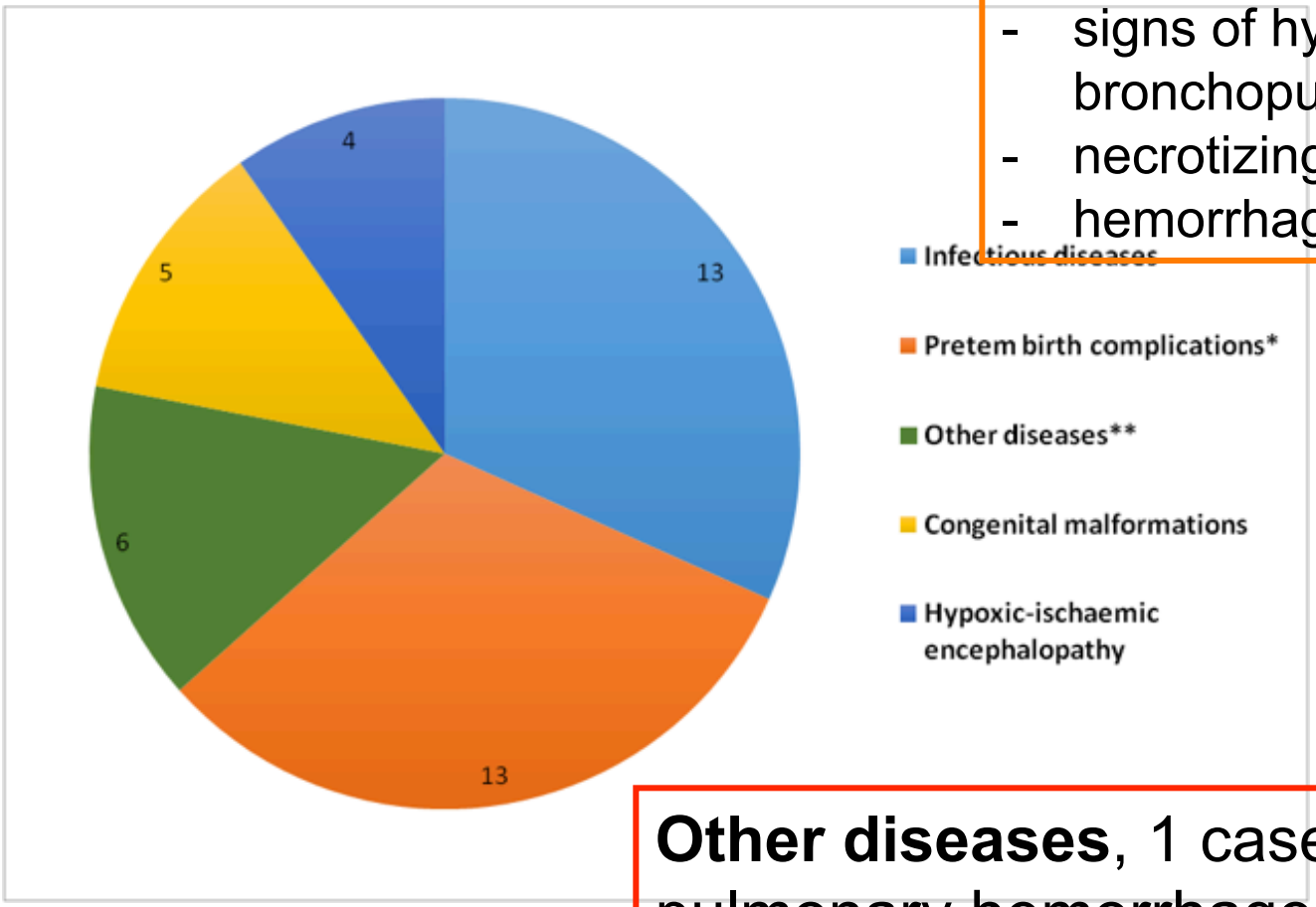
- **clinical data**: gestational age, birth weight and pregnancy clinical record
- **histological analyses** of the autopsy

Agreement CDA-MIA in 18 cases of stillbirth

General CoD Stillbirths	CDA	MIA
Mother relevant condition	8	8
Amniotic fluid relevant condition	3	3
Not yet finished	3	3
Placenta relevant condition	2	2
Umbilical cord prolapse	1	1
Uterine rupture	1	1
Total	**18**	**18**

Causes of death in 41 cases of neonatal deaths

- **Preterm birth complications**
- signs of hyaline membrane and/or bronchopulmonary dysplasia
- necrotizing enterocolitis
- hemorrhages (lungs and CNS)

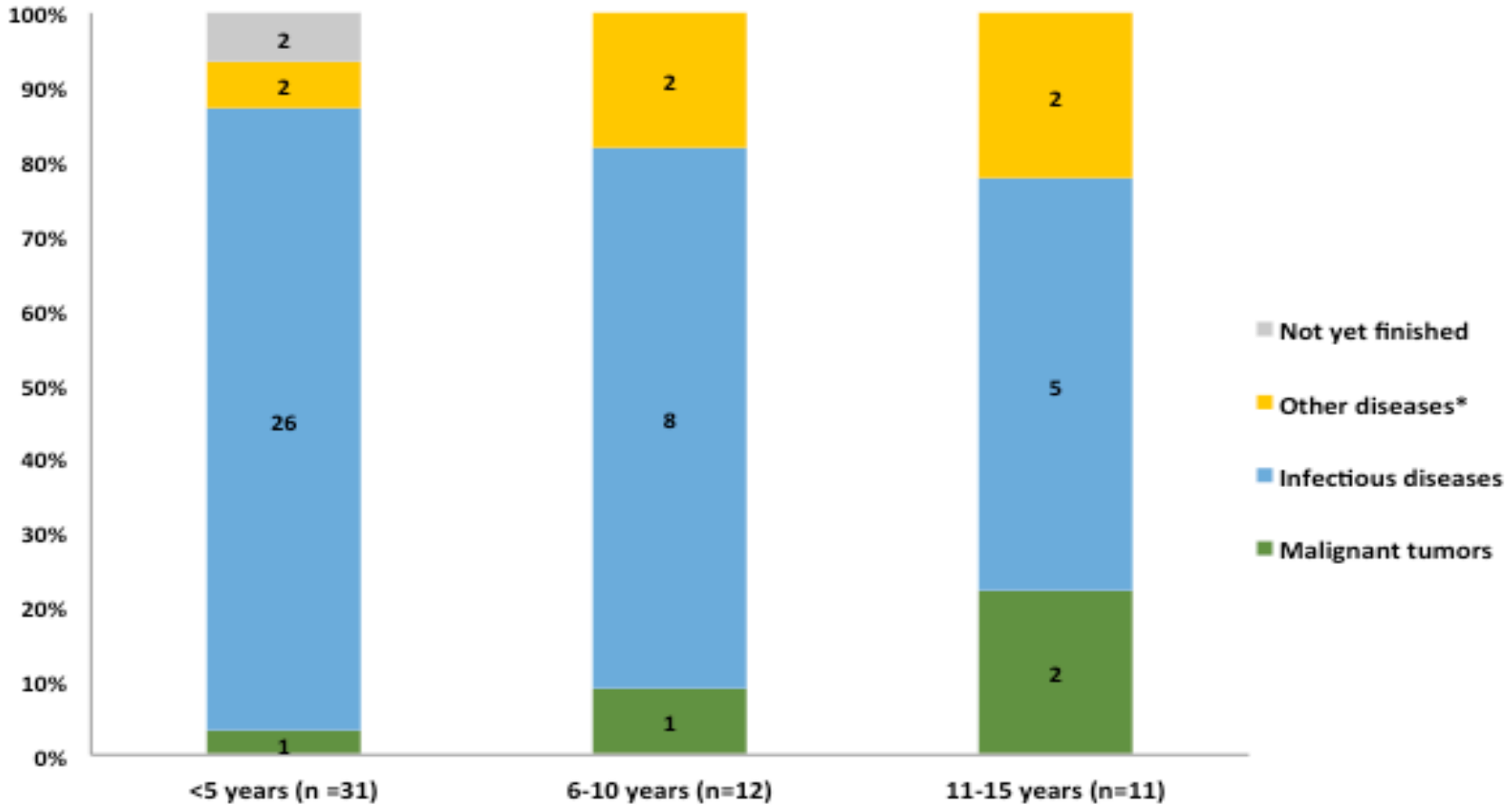


Other diseases, 1 case each of: pulmonary hemorrhage, CNS hemorrhage, intestinal occlusion, severe anemia, kernicterus and hemolytic disease of the newborn

Agreement CDA-MIA in 41 cases of neonatal deaths

CoD Neonates	CDA	MIA	False negative		False positive		% Agreement
			n	(%)	n	(%)	
Infectious diseases	13	14	2	15	3	21	85
Pretem birth complications	13	9	4	31	0	0	69
Other diseases	6	4	5	83	3	75	17
Congenital malformations	5	0	5	100	0	0	0
encephalopathy	4	0	4	100	0	0	1
Not yet finished	0	14	0	0	14	100	NA
Total	41	41	20	0	20	0	51

Causes of death in 54 children between 28 days and 15 years of age



Agreement CDA-MIA in 31 cases of children's deaths >28 days < 5 yrs of age

CoD Children > 28 days and < 5 yrs	CDA	MIA	False negative		False positive		% Agreement
			n	(%)	n	(%)	
Infectious diseases	26	19	8	31	1	5	69
Malignat tumors	1	1	0		0	0	0
Other diseases	2	0	2	100	0	0	0
Not yet finished	2	11	0	0	9	82	NA
Total	**31**	**31**	**10**		**10**		**68**

Agreement CDA-MIA in 23 cases of children's deaths between 5 and 15 yrs of age

CoD children between 5 and < 15 yrs	CDA	MIA	False negative		False positive		% Agreement
			n	(%)	n	(%)	
Infectious diseases	13	13	2	15	2	15	85
Malignat tumors	6	3	3	50	0	0	50
Other diseases	4	1	3	75	0	0	25
Not yet finished	0	6	0		6	NA	
Total	**23**	**23**	**8**	**35**	**8**	**35**	**74**

Causes of mortality in 56 maternal deaths

General CoD Maternal	CDA
Obstetric	**26**
Hemorrhage	13
Puerperal sepsis	8
Eclampsia	4
Ectopic pregnancy	1
Non obstetric	**30**
Infectious diseases	20
Other diseases	8
Malignant tumor	2
Total	**56**

Other diseases

- 1 case of rheumatic valvular heart disease
- 4 cases of hepatic massive necrosis
- 1 case of severe anemia and
- 2 cases with histological findings suggestive of cardiovascular disease

- Haemorraghe: 8 cases post-partum, 2 intra-partum, 1 ante-partum
1 case post abortion

Agreement CDA – MIA in 56 maternal deaths

Categories Maternal deaths	Subcategories	CDA	MIA	False negative		False positive		%
				n	(%)	n	(%)	Agreement
Obstetric complications	Hemorrhages	13	2	11	85	0	0	15
	Puerperal sepsis	8	4	4	50	0	0	50
	Eclampsia	4	2	2	50	0	0	50
	Ectopic pregnancy	1	0	1	100	0	0	0
Non obstetric conditions	Infectious diseases	20	19	5	25	4	21	75
	Other diseases	8	11	4	50	7	64	50
	Malignant tumor	2	1	1	50	0	0	50
	Not yet finished	0	17	0		17	100	NA
	Total	**56**	**56**	**28**		**28**		**50**

Agreement CDA –MIA in 56 maternal deaths

Categories	Subcategories	CDA	MIA	False negative		False positive		Agreement (%)
				n	(%)	n	(%)	**31**
Obstetric complications	Hemorrhage	13	2	11	(85)	0	(0)	18
	Puerperal sepsis	8	4	4	(50)	0	(0)	50
	Eclampsia	4	2	2	(50)	0	(0)	33
	Ectopic pregnancy	1	0	1	(100)	0	(0)	0
Non obstetric conditions								**57**
	Infectious diseases	20	19	5	(25)	4	(21)	**67**
	Other diseases	8	11	4	(50)	7	(64)	29
	Malignant tumor	2	1	1	(50)	0	(0)	50
	Not yet finished	**0**	17	-	-	17	-	-
	Total	**56**	**56**	**28**		**28**		**45**

Clinical errors in 56 maternal deaths

Categories Maternal deaths	Subcategories	CDA	Clinical diagnosis	False negative		False positive		% Agreement
				n	(%)	n	(%)	
Obstetric complications	Hemorrhages	13	12	3	23	2	17	77
	Puerperal sepsis	8	3	5	63	0	0	38
	Eclampsia	4	9	2	50	7	78	50
	Ectopic pregnancy	1	1	0	0	0	0	100
Non obstetric conditions	Infectious diseases	20	19	6	30	5	26	70
	Other diseases	8	9	3	38	4	44	63
	Malignant tumor	2	1	1	50	0	0	50
	Anemia	0	2	0		2	100	1
	Total	**56**	**56**	**20**		**20**		**64**

Preliminary Conclusions

- **Infectious diseases** were an important cause of death in children and pregnant women
- Biological samples **can be obtained adequatley** for pathological and microbiological analysis **through MIA**
- The agreement between CDA and MIA ranged from **moderate to high** depending on
  - the **age** group
    - Higher in **stillbirths** and lower in children over 1 month
  - the **cause of death**
    - Higher for **infectious diseases**

ISGlobal Preliminary conclusions (cont)

- The contribution of **non-obstetric** CoD was higher (53.6%) than that of obstetric ones (46.4%)
  - Specially for infectious diseases (35.7% of the total)
- Agreement CDA-MIA was
  - lowest for **haemorraghe** and highest for **infectious diseases**
  - there was a **high rate of clinical errors** (>35%)
  - Eclampsia was the condition with the **highest percentage of false positive diagnosis** compared to CDA (nearly 80%)

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Preliminary conclusions (cont)

- **Minimally invasive autopsies** could potentially be used as a tool to improve CoD determination in low income settings
- Evaluation of its implementation **in "real world"** situation is needed

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In conclusion

- **“All human deaths count but not all count the same”**
- **“One of the best ways to help the living is to understand what they die of”**
- **This is an inequity between low and high income countries that needs to be resolved**

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