

**UNDP/UNFPA/WHO/WORLD BANK Special Programme of Research,
Development and Research Training in Human Reproduction
Development of Reproductive Health and Research**

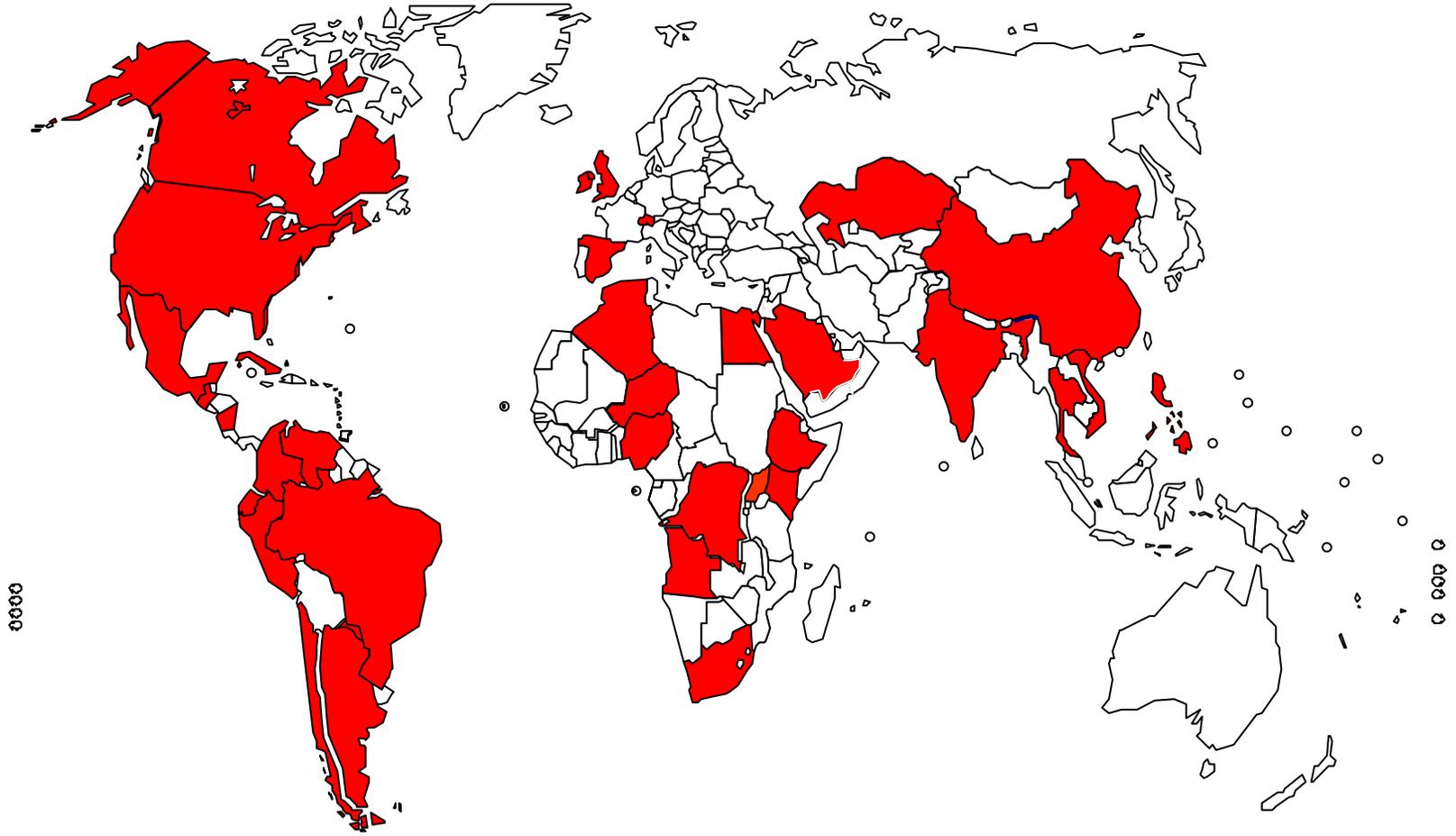


MATERNAL AND PERINATAL RESEARCH

**José Villar, Mariana Widmer, Mario Merialdi, Archana Shah
for the WHO Maternal and Perinatal Research Network**



WHO Maternal and Perinatal Research Network



**UNDP/UNFPA/WHO/WORLD BANK Special Programme of Research,
Development and Research Training in Human Reproduction**

Maternal Health Research
Completed

**Programme of Work
1998 - 2003**

Maternal and perinatal health research completed during 1995-2004 with leading participation of the Programme

	Countries	Women	Status
Antenatal care	5	24 678	Published (2001)
Postpartum haemorrhage	9	18 530	Published (2001)
Treatment of pre-eclampsia (MAGPIE trial*)	28	10 141	Published (2002)
Reduction of unnecessary Caesarean section	5	149 206	Published (2004)
Epidemiology of preterm delivery, IUGR	4	38 319	Published (2005)
Pre-eclampsia			
WHO Reproductive Health Library	2	76 053	Submitted (2005)
Prevention of pre-eclampsia (calcium supplementation)	7	8 300	Submitted (2005)
<u>Long term follow-up mothers and infants</u>			
Calcium trial I	1	591	Published (1997)
Magpie Trial*	19	3 375	Submitted (2005)
Calcium trial II	2	800	Submitted (2005)
Total	25* *	329 993	

* collaboration

** Some countries have been involved in more than one study

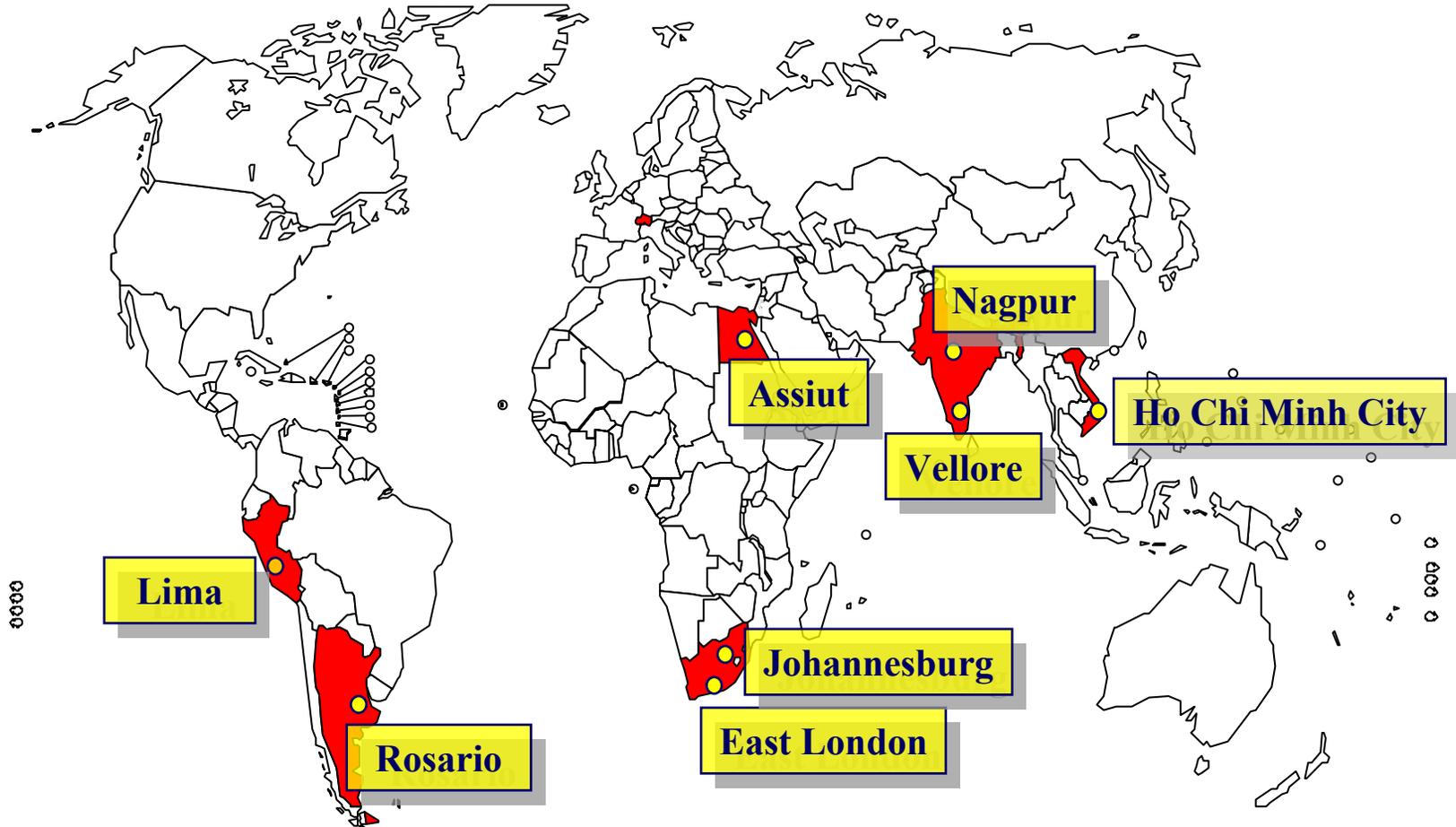
WHO Randomized controlled trial of calcium supplementation for the prevention of pre-eclampsia among low calcium intake women

Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali M, Zavaleta N, Purwar M, Hofmeyr GJ, Ngoc NTN, Campódonico L, Landoulsi S, Carroli G and Lindheimer MD

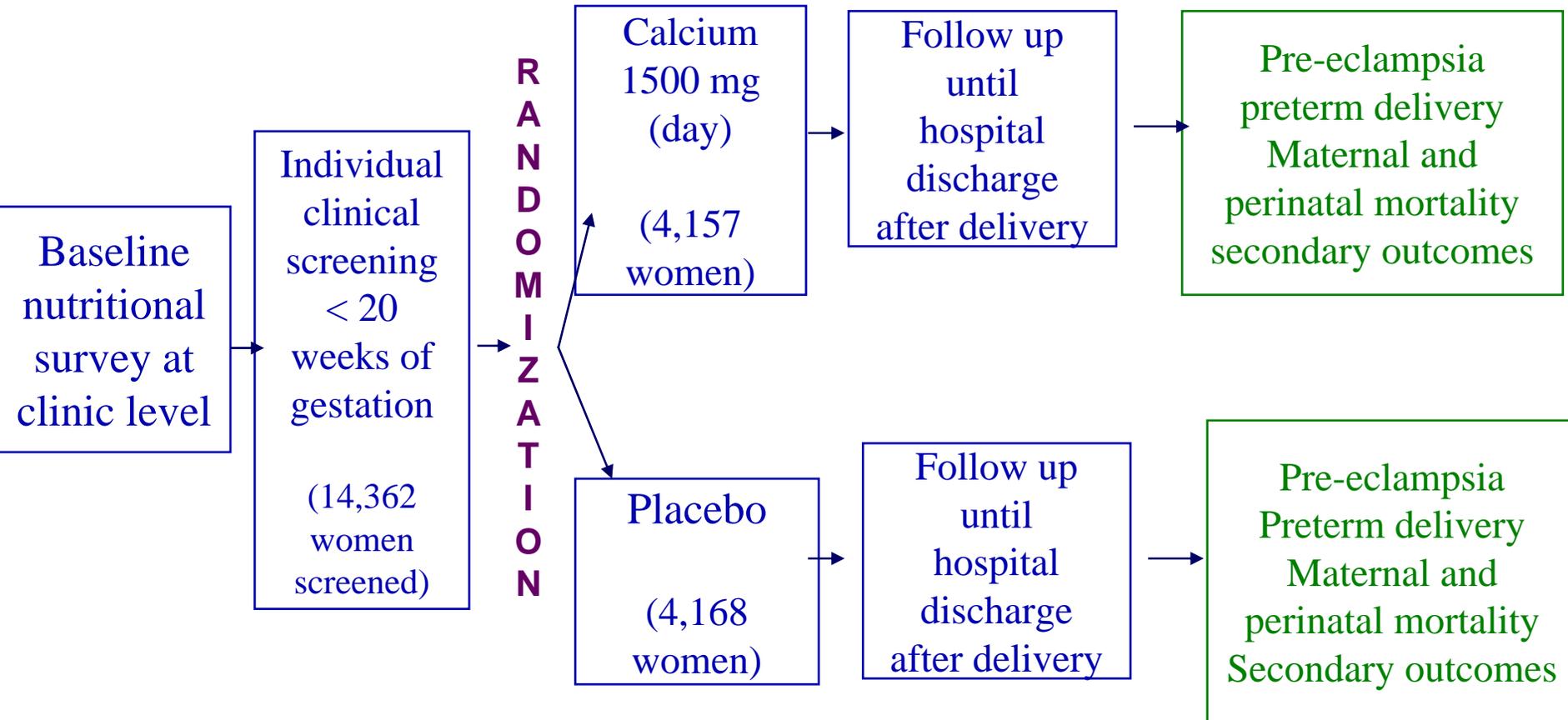
on behalf of the WHO Calcium Supplementation for the Prevention of Pre-eclampsia Trial Group



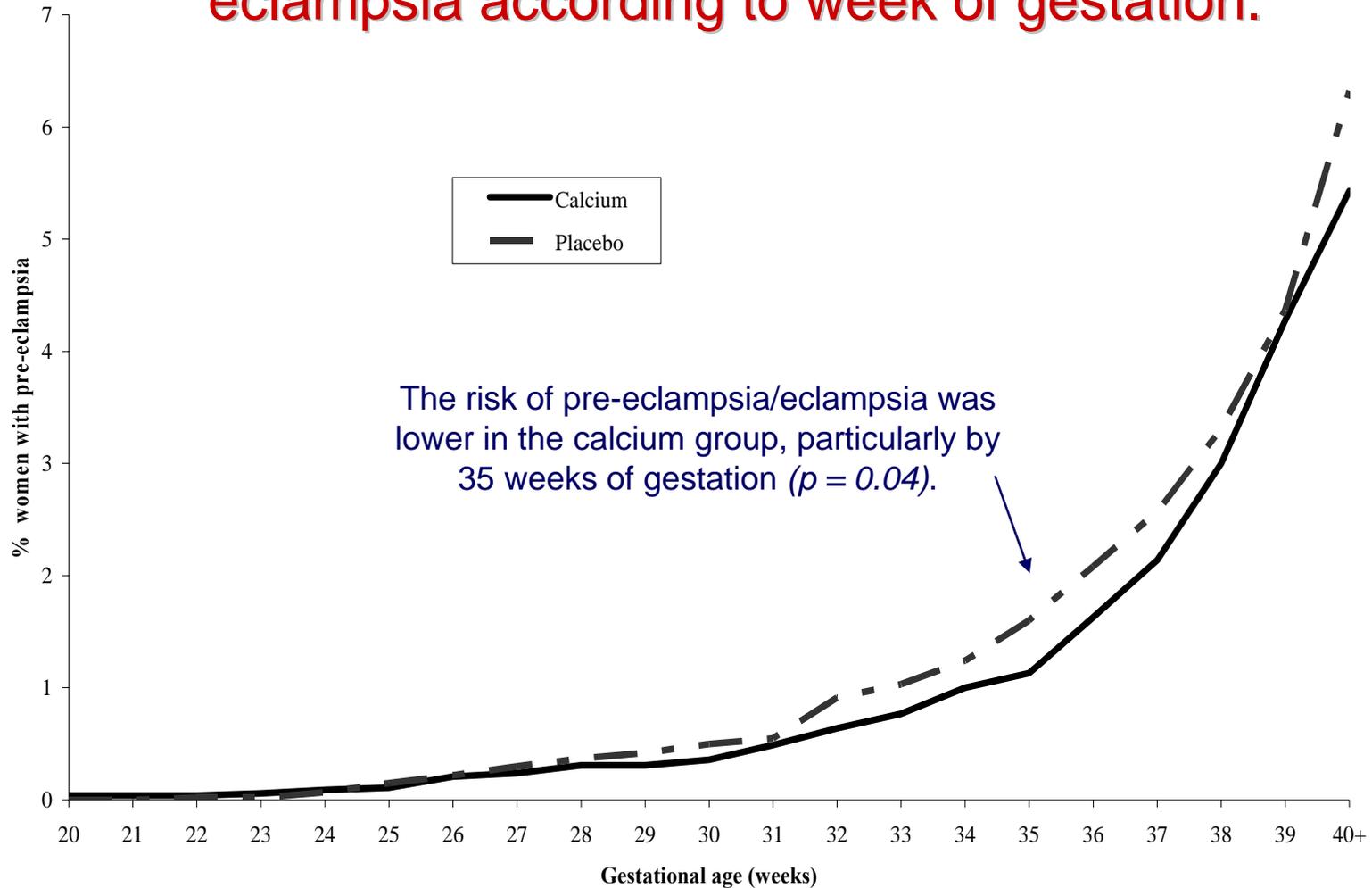
WHO Collaborating Centres participating in the trial



Study design and patient flow

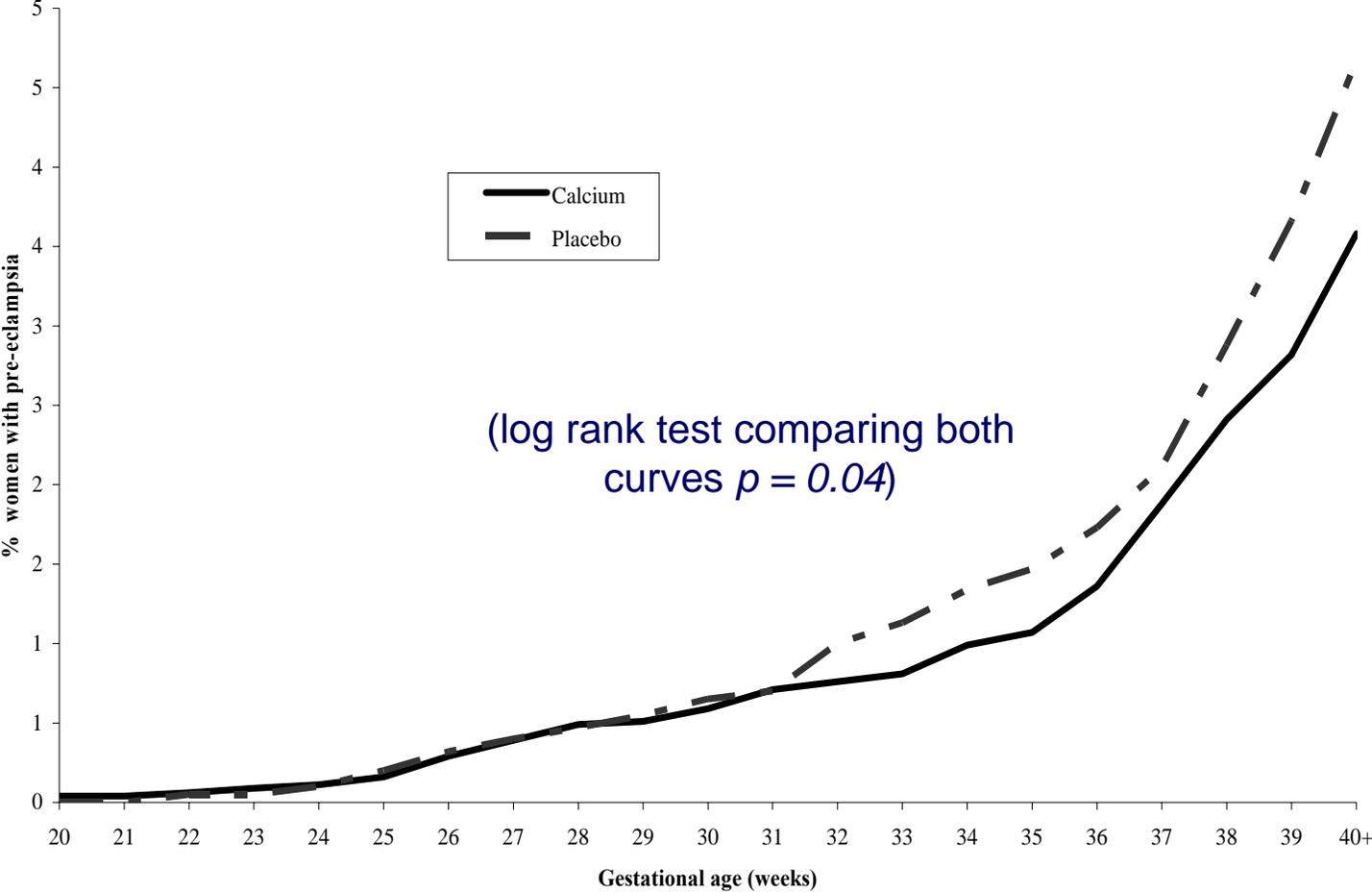


Cumulative risk for women in the calcium and placebo groups for the development of preeclampsia and/or eclampsia according to week of gestation.



The risk of pre-eclampsia/eclampsia was lower in the calcium group, particularly by 35 weeks of gestation ($p = 0.04$).

Cumulative risk for women in the calcium and placebo groups for the severe preeclamptic complications index according to week of gestation.



Preterm delivery according to treatment group and maternal age at trial entry

	Calcium n/N	Placebo n/N	Risk Ratio	95% Confidence Interval
Total population				
Preterm delivery (<37 weeks)	398/4038	436/4042	0.91	0.79 - 1.06
Early preterm delivery (<32 weeks)	106/4038	130/4042	0.82	0.71 - 0.93
Women ≤20 years				
Preterm delivery (<37 weeks)	148/1400	180/1404	0.82	0.67 - 1.01
Early preterm delivery (<32 weeks)	34/1400	53/1404	0.64	0.42 - 0.98
Women >20 years				
Preterm delivery (<37 weeks)	250/2638	256/2638	0.97	0.83 - 1.15
Early preterm delivery (<32 weeks)	72/2638	77/2638	0.93	0.68 - 1.28

All risk ratios and 95% Confidence Intervals are adjusted by centre effect.

The denominators include multiple births.

Severe Maternal Mortality-Morbidity Index

The index was defined as the presence of at least one of the following: maternal admission to intensive care or any special care unit, eclampsia, severe preeclampsia, placental abruption, HELLP, renal failure or death.

Severe morbidity and mortality according to treatment group

	Calcium n/N	Placebo n/N	Risk Ratio	95% Confidence Interval
Maternal admission to intensive care any special care unit	116/4151	138/4161	0.85	0.75 - 0.95
Maternal death	1/4151	6/4161	0.17	0.03 - 0.76
Severe maternal morbidity and mortality index (*)	167/4151	209/4161	0.80	0.70 - 0.91
Stillbirth	105/4181	113/4197	0.93	0.74 - 1.17
Neonatal mortality	37/3953	53/3956	0.70	0.56 - 0.88

(*) At least one of the following: Admission to Intensive Care or any special care unit, eclampsia, severe preeclampsia, placental abruption, HELLP, renal failure or death.

All risk ratios and 95% Confidence Intervals adjusted by centre effect. Maternal outcomes are also adjusted by maternal body mass index.

Strengths of the trial

- Training and standardization of all data acquisition methodology
- Identical treatment and placebo tablets
- Large sample size
- Baseline characteristics evenly distributed
- Limited lost to follow up
- Good treatment compliance
- Effect on preterm delivery among women < 20 years consistent with hypothesis and previous trial

Limitations of the trial

- Power not enough to detect as statistically significant a 10% reduction in pre-eclampsia
- Severe mortality-morbidity index was not identified as primary outcome
- Use of severe composite index for pre-eclampsia only secondary outcome
- Dietary intake obtained from a survey conducted before the study in representative samples of women attending the same antenatal clinics
- Unexplained why there is an effect on severe conditions and mortality without an effect on overall pre-eclampsia

Conclusions

Although supplementation with 1.5 gm Ca/day did not significantly reduce the overall incidence of pre-eclampsia (primary outcome), **it decreased the risk for its more serious complications**, including maternal and neonatal morbidity and mortality (secondary outcomes), as well as preterm delivery among young women (primary outcome but stratified analysis).

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Maternal and Perinatal Health Research

**Second Programme of Work
2004 - 2009**

Global Program to Conquer Preeclampsia / Eclampsia



Areas of work

- 1. Systematic Reviews**
- 2. Trials**
- 3. Perinatal Epidemiology (secondary analysis of WHO data set)**
- 4. WHO Global Survey on Maternal and Perinatal Health**

1. Systematic Reviews

- Focussed on aetiology and pathophysiology of maternal and perinatal morbidities (new area for systematic reviews)
 - As background for WHO trials and observational studies

Recent examples

Aetiology and screening:

- Mapping the theories of pre-eclampsia: The role of homocysteine
Mignini L. et al. Obstet-Gynecol 2004
- WHO systematic review of screening for pre-eclampsia
Conde-Agudelo A. et al. Obstet-Gynecol 2004
- WHO systematic review of PIGF for screening for pre-eclampsia (*in preparation*)

Randomized controlled trials:

- Systematic review of RCT of Misoprostol to treat postpartum haemorrhage
Hofmeyr J et al. BJOG 2005
- Systematic review of duration of treatment for ASB in pregnancy
Villar J. et al. Cochrane Library 2004

Epidemiology:

- WHO systematic review and multinational nutritional survey of calcium intake during pregnancy

Meriardi M. et al. Fetal and Maternal Medicine Review 2005

Methodology:

- Mapping the theories of pre-eclampsia: the need for systematic reviews of mechanisms of disease

Mignini L. et al. Am J Obstet & Gyn 2005 (in press)

2. Trials

	Countries	Women	Status
Screening and treatment of UTI	4	18 000 ;900	Ongoing (11780; 300)
Prevention of pre-eclampsia (anti-oxidants)	4	1 700	Ongoing (700)
WHO Global Survey	16	178 000	(completed Africa and Americas)
Treatment of postpartum haemorrhage	5	1 400	Ongoing (1)
Prevention of pre-eclampsia (treatment of hypertension)	6	2 000	In preparation
Screening for pre-eclampsia	7	12 000	In preparation
Caesarean Section techniques	9	4 000	In preparation
Total expected	51*	191 550	

* Some countries have been involved in more than one study



WORLD HEALTH ORGANIZATION

DEPARTMENT OF REPRODUCTIVE HEALTH AND RESEARCH
UNDP/UNFPA/WHO/World Bank
Special Programme of Research, Development and
Research Training in Human Reproduction

CALCIUM SUPPLEMENTATION
FOR THE PREVENTION OF PRE-ECLAMPSIA
AMONG LOW CALCIUM INTAKE WOMEN;

A RANDOMIZED CONTROLLED TRIAL

TRIAL 98295

OPERATIONAL MANUAL

Geneva, Switzerland
October 2001



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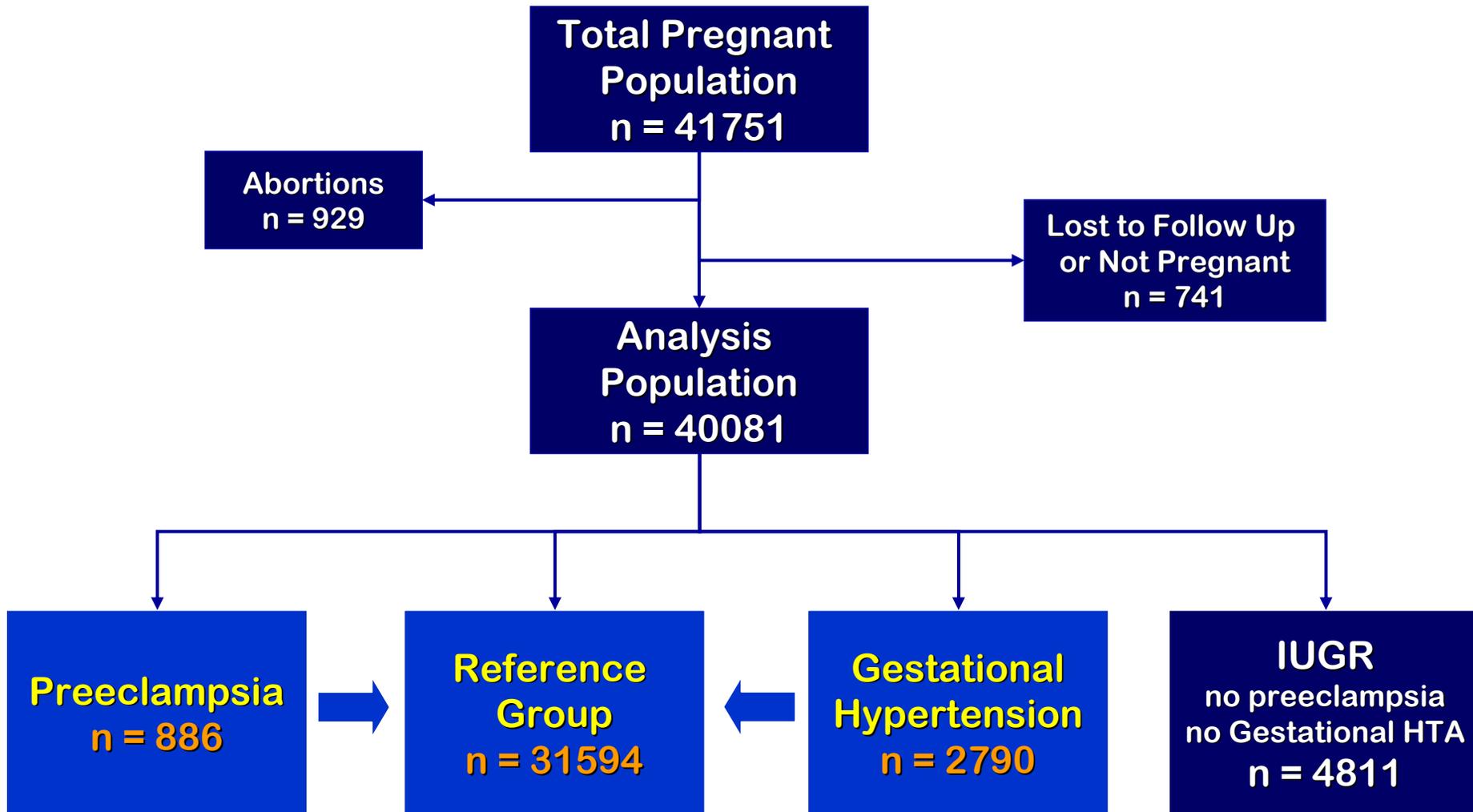
**A practical guide on how to measure
blood pressure and test for proteinuria**

Geneva, Switzerland
December 2001

3. Perinatal Epidemiology

- Small for age, Pre-eclampsia and Hypertension, same or different? (AJOG in-press 2005)
- Determinants of perinatal mortality (submitted for publication 2005)
- Effect of radiations on reproductive health (in collaboration with Institute for Cancer Research, UK) (completed)

Preeclampsia versus Gestational Hypertension



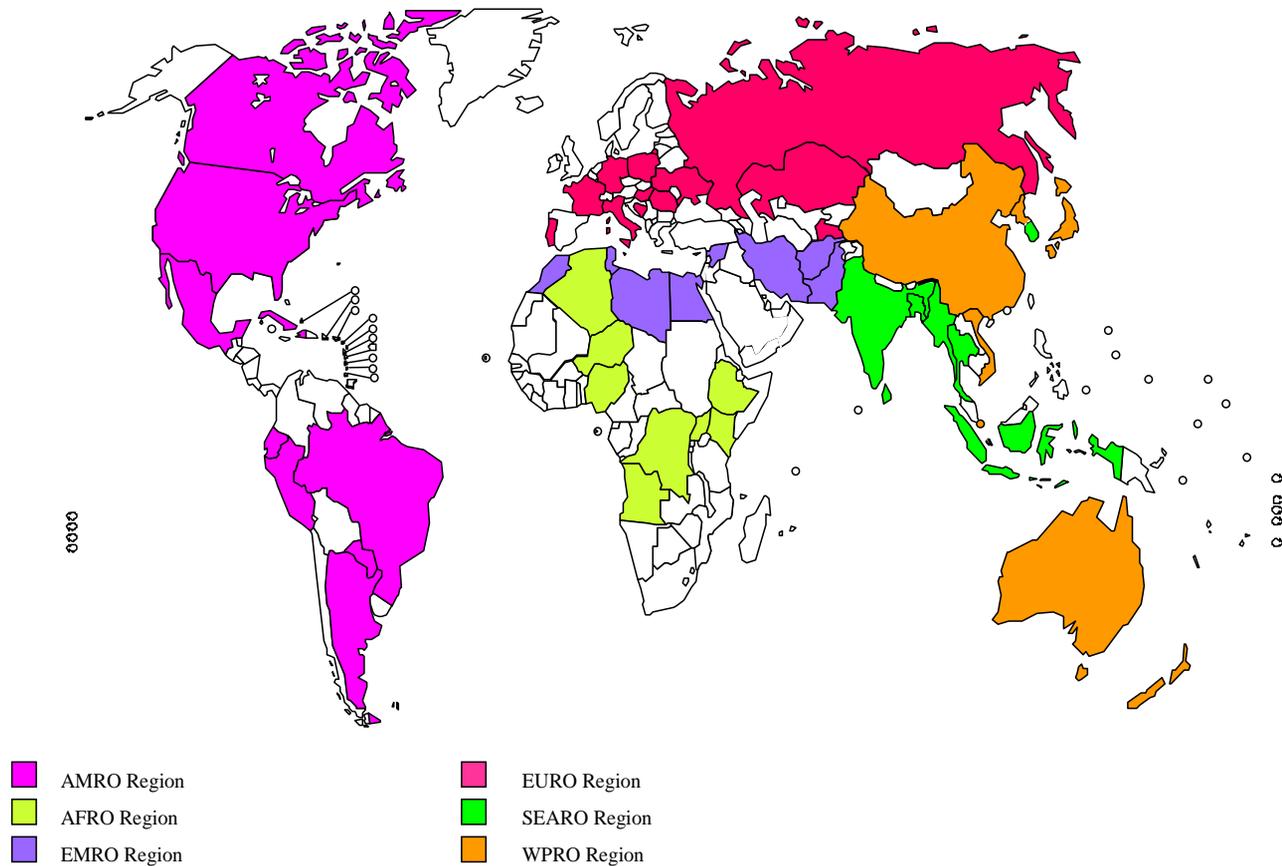
Perinatal Outcomes for Pre-eclampsia and Gestational Hypertension as compared to the Reference Population

	Preeclampsia (n = 886) OR (95% CI)	Gestational HTA (n = 2790) OR (95% CI)
NICU Stay 7 or more days	5.6 (4.7 – 6.8)	2.0 (1.7 – 2.3)
Neonatal Death	4.2 (2.7 – 6.5)	1.5 (1.0 – 2.3)

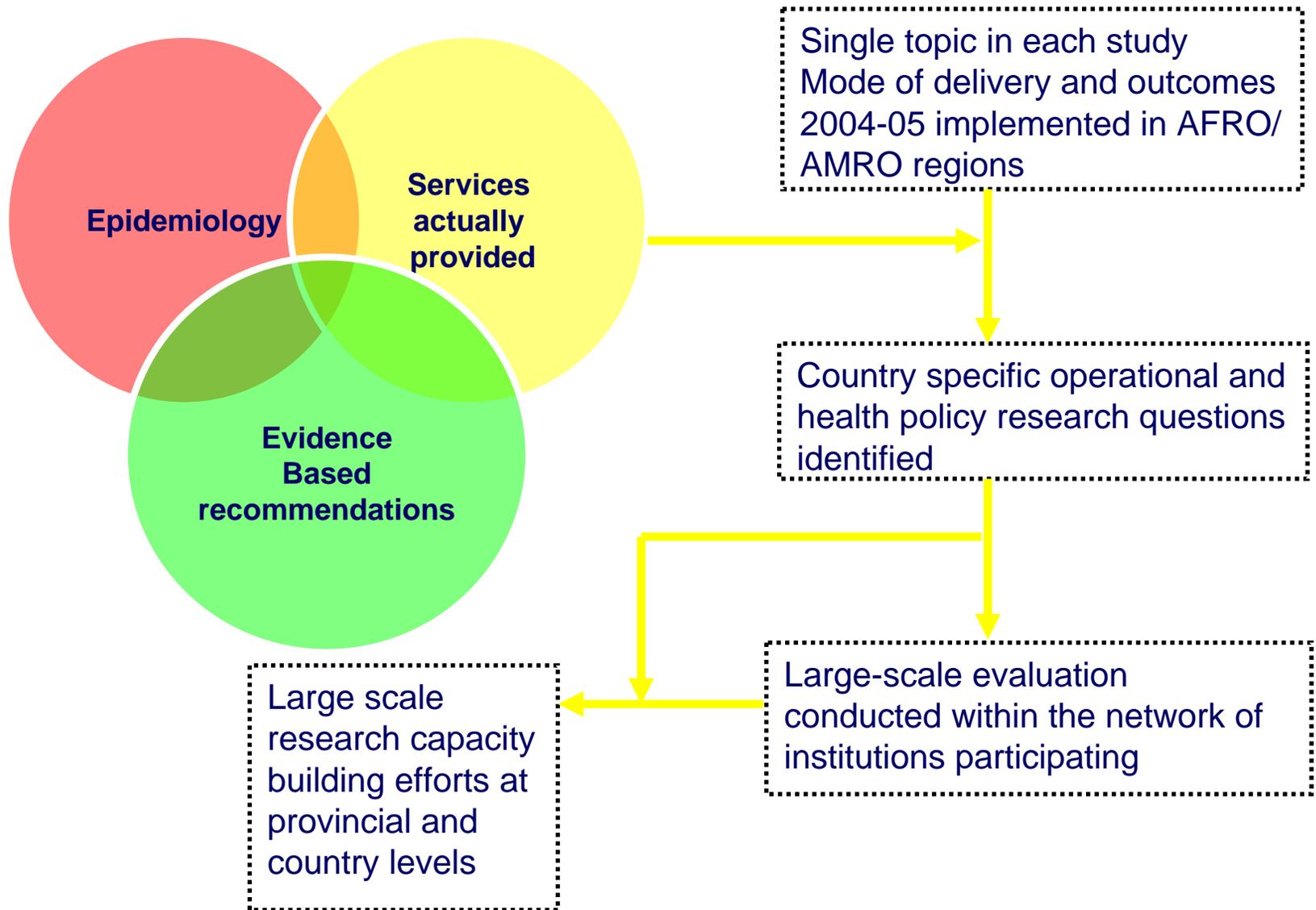
4. Global Survey

Objective: To collect up to date, focused information on the epidemiology, the services actually provided and how the evidence based recommendations are being implemented.

Countries selected per region



WHO Global Survey for Maternal and Perinatal Health



Global Survey 2004-05 (Africa & Americas)

- Countries randomly selected: 15
- Health facilities randomly selected : 245
- Women enrolled between
Sep 2004 – March 2005: 178,055
- Staff collaborating in America : 525
- Completed: August 2005

Data analysis on-going:

- Caesarean rates and outcomes
- Congenital malformations
- Gynaecological fistula (Africa)
- Pre-eclampsia morbidity

Dissemination

Publications in Medical Journals and RHL

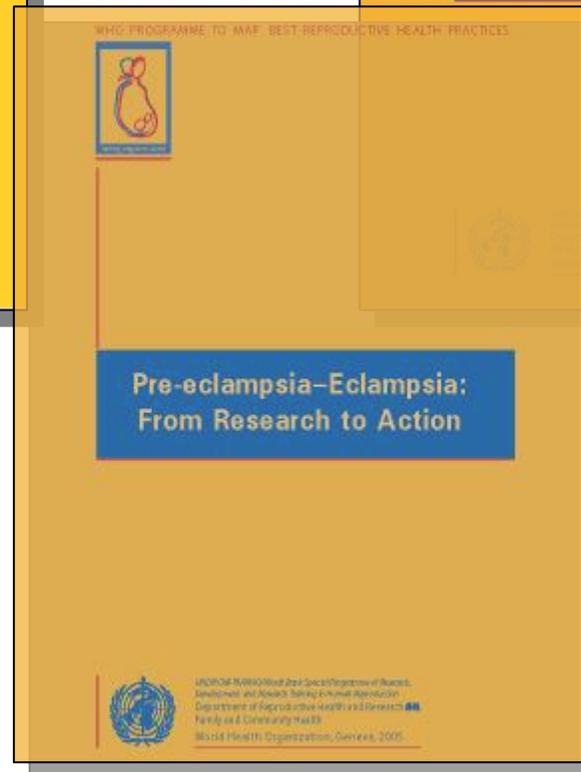
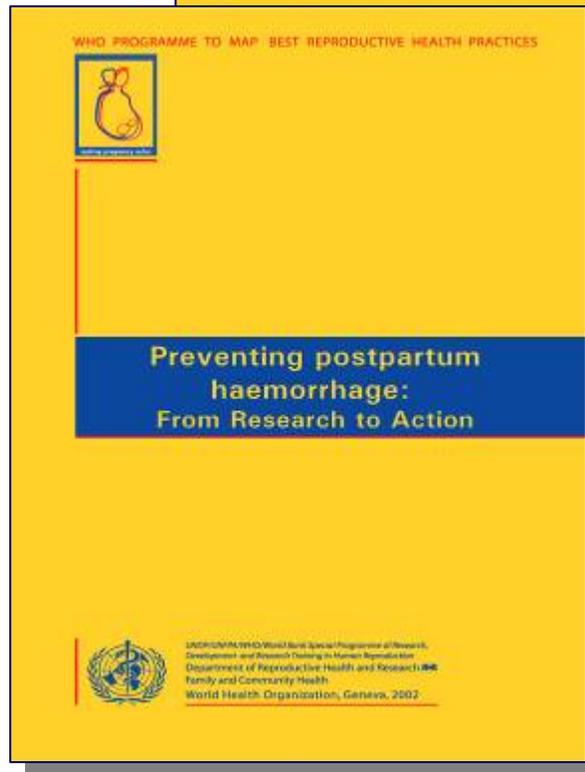
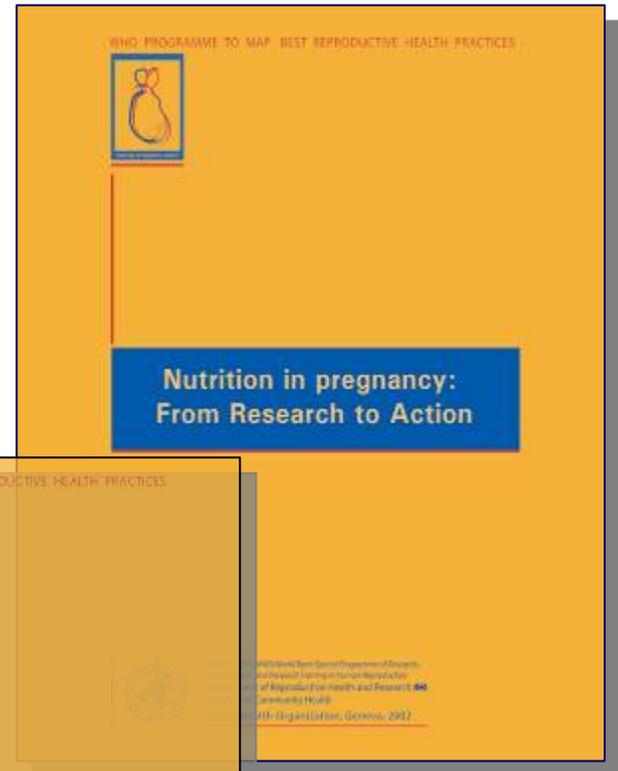
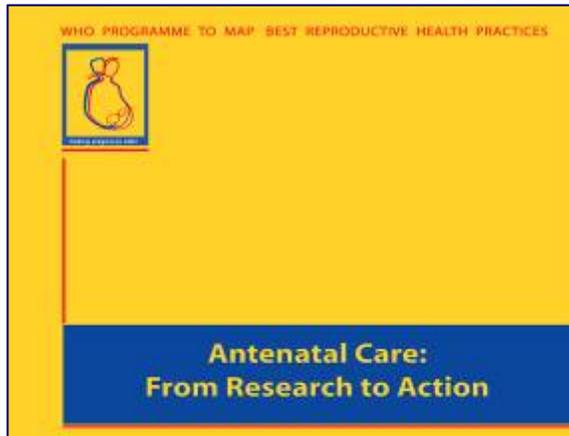
From Research to Action Binders

Antenatal care e-course
(2004-2005-2006)

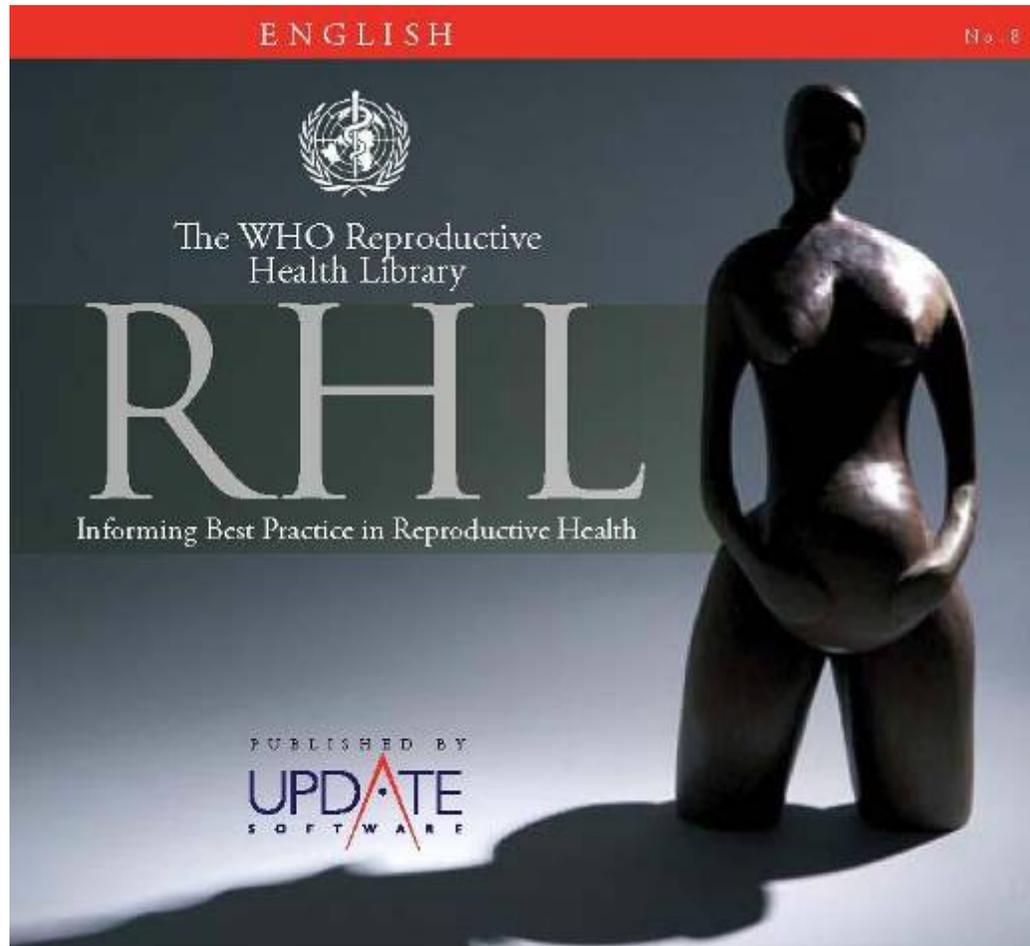
Research and clinical training at country level

Country Programmes

From Research to Action



The WHO Reproductive Health Library

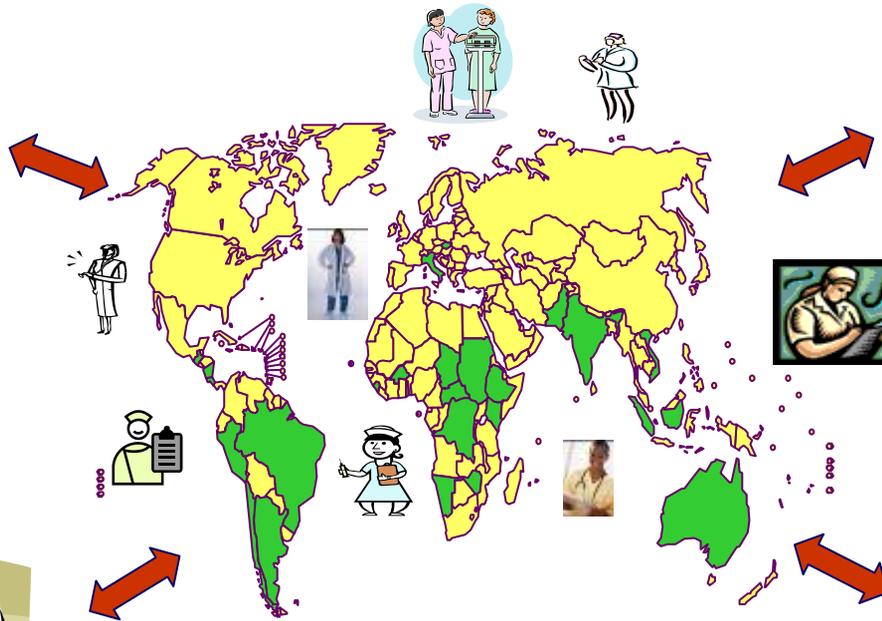


2005 WHO–Boston University e-Course

From research to action: Introduction of WHO new ANC model



WHO e-Professor



WHO e-Professor



WHO e-Professor



WHO e-Professor

British Journal of Obstetrics and Gynaecology
December 1998, Vol. 105, pp. 1244–1247

Randomised trials in maternal and perinatal medicine: global partnerships are the way forward

In 2005, we still believe that Global Partnerships are the way forward

