Reproductive health research at WHO

The success story of the Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Paul F.A. Van Look, MD PhD FRCOG

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

7 April 1948

Functions

"In order to achieve its objective, the functions of the Organization shall be:

(a) to act as the directing and co-ordinating authority on international health work;

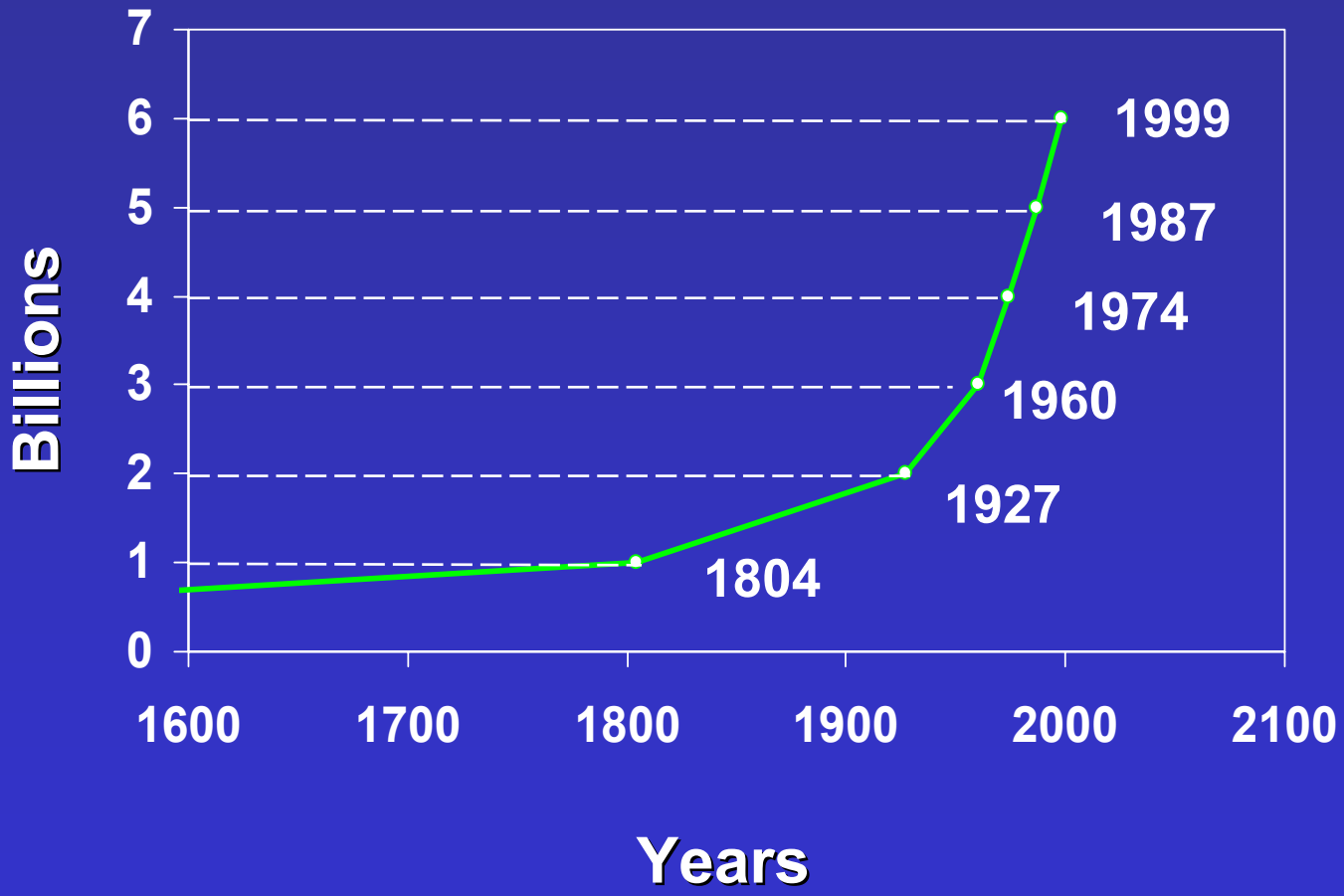
...

(n) to promote and conduct research in the field of health;

..."

(WHO Constitution, Article 2)

Growth of total world population



The Programme's history

"REQUESTS the Director-General to develop further the programme proposed:

(a) in the fields of reference services, studies on medical aspects of sterility and fertility control methods and health aspects of population dynamics; …"

(WHA Resolution 18.49; 1965)

The Programme's history

1965: **WHA18.49**

→ **Human Reproduction Unit within existing Division of Family Health**

1971: **Feasibility study**

→ **Expanded (Special) Programme of Research, Development and Research Training in Human Reproduction (HRP)**

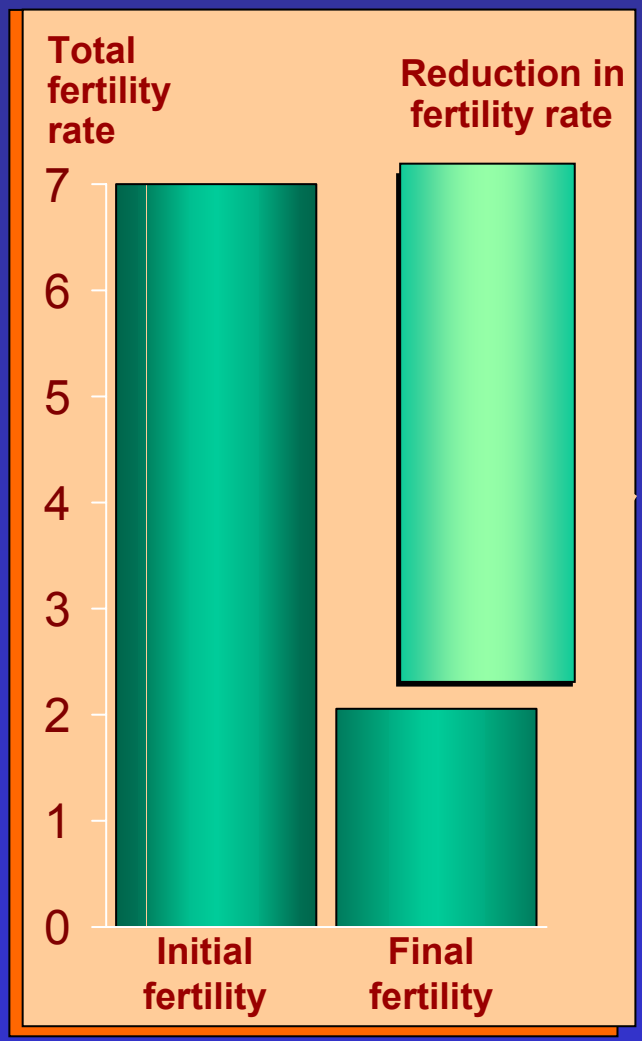
The Programme's history

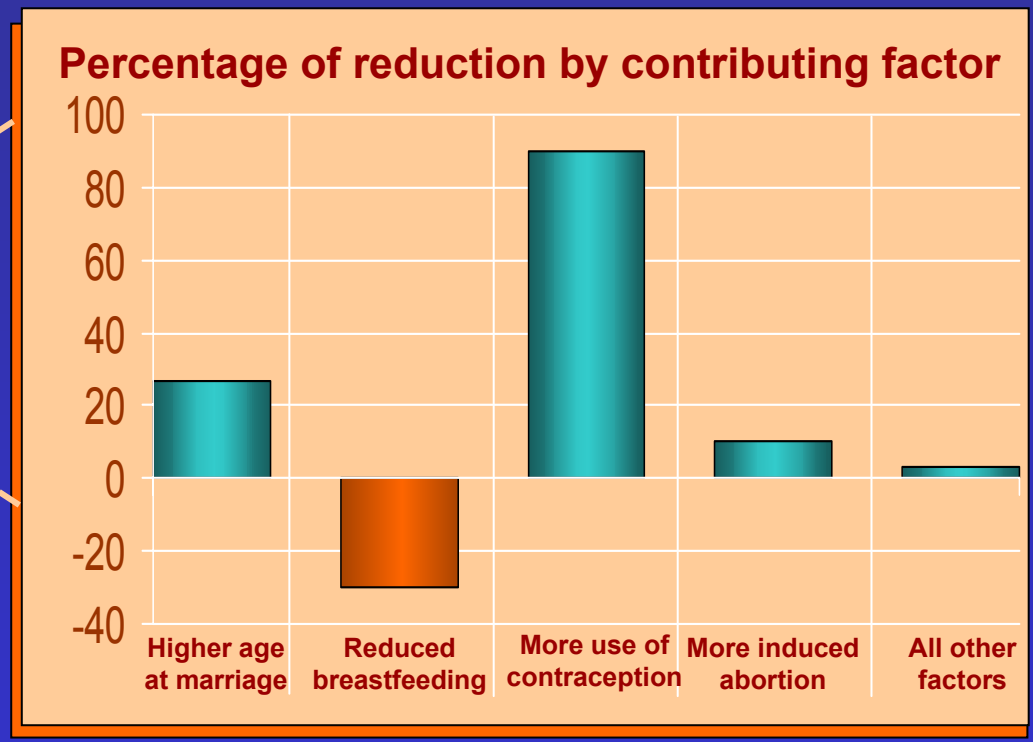
1972-1988: **WHO Special Programme**

1988-present: **UNDP/UNFPA/WHO/World Bank cosponsored Special Programme**
(WHA Resolution 41.9; 1988)

"To coordinate, promote, conduct and evaluate international research in human reproduction."

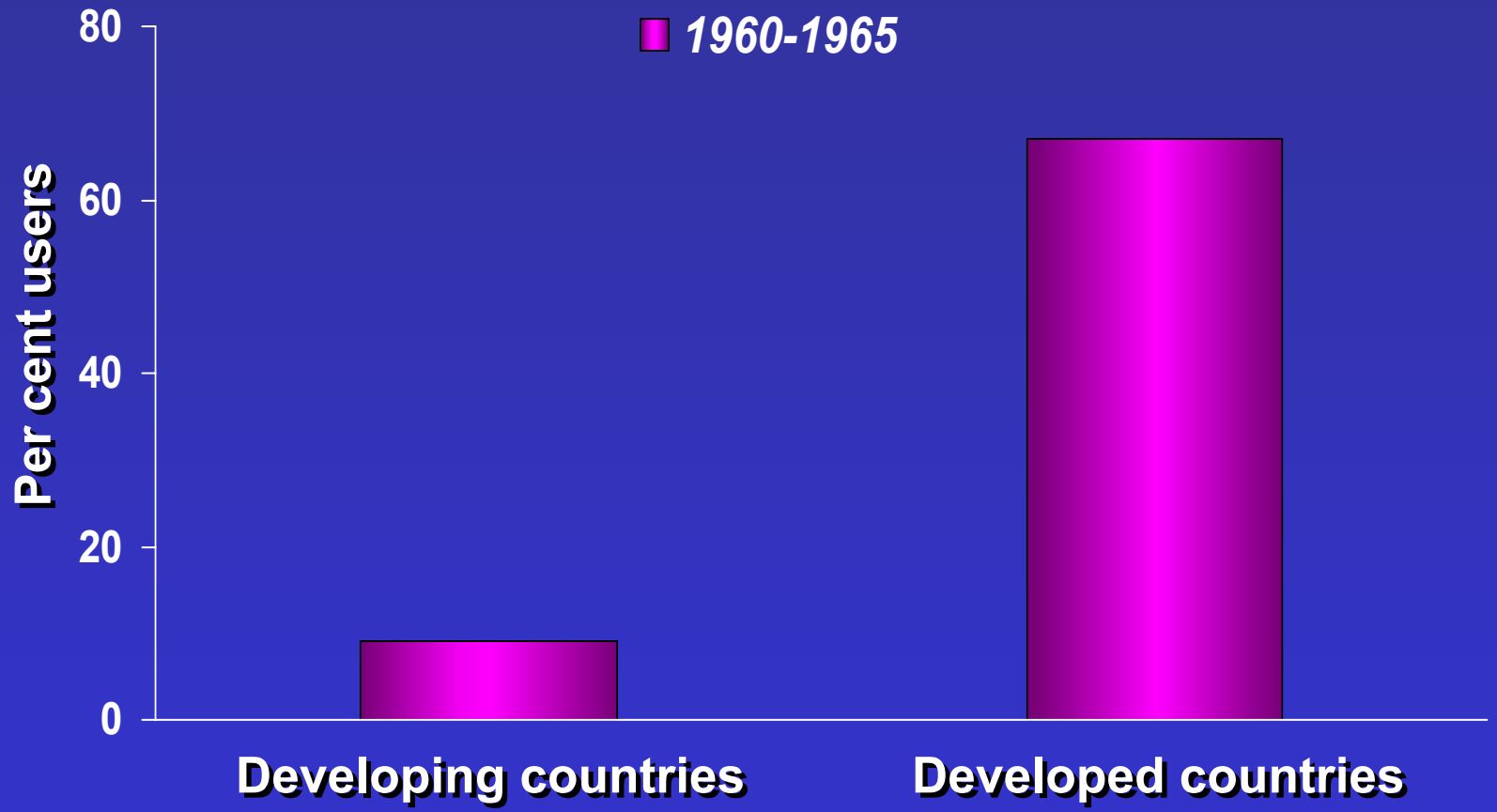
Factors contributing to fertility decline





(Source: World Bank, 1984)

Trends in use of contraception



(Source: United Nations, 1991 and 1999)

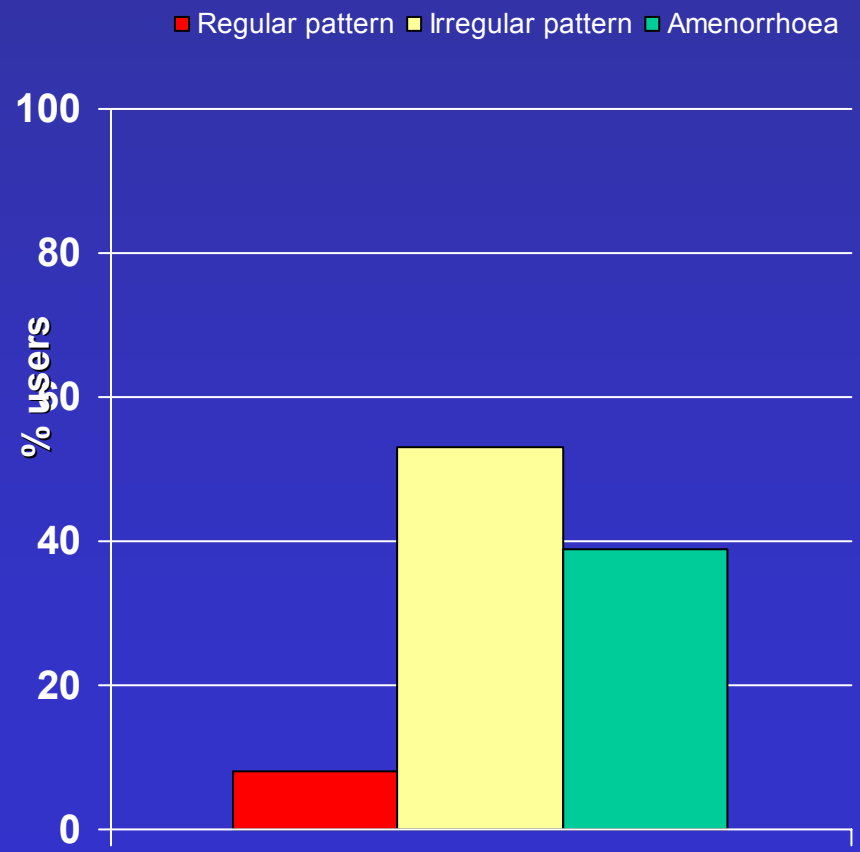
Once-a-month injectables developed by the Programme

Mesigyna® : **50 mg norethisterone enantate + 5 mg estradiol valerate**

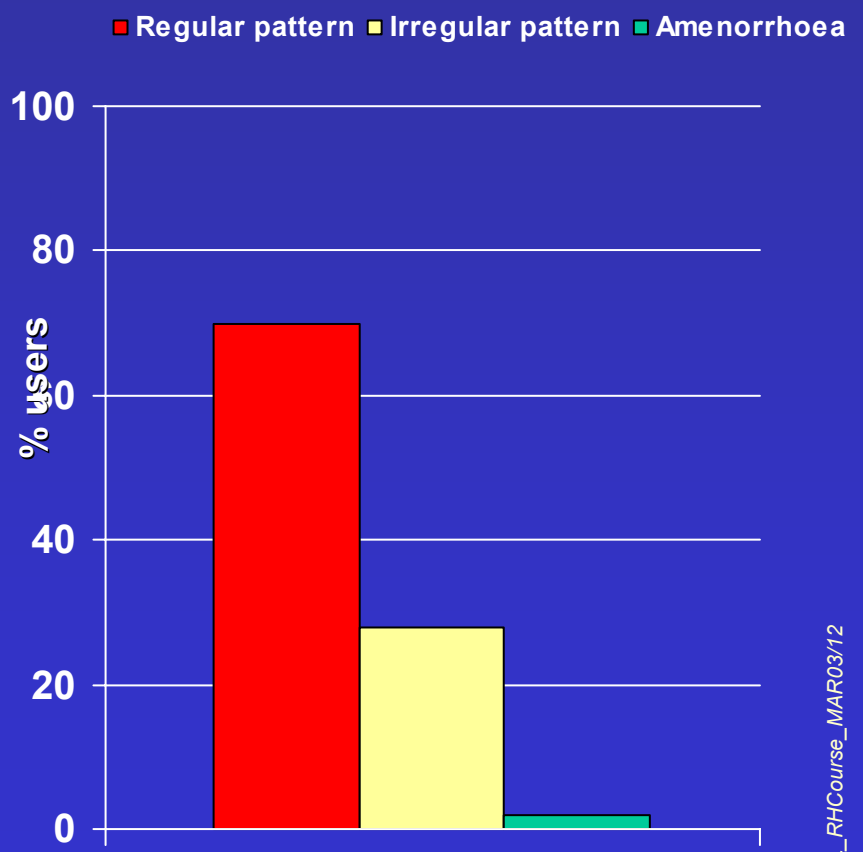
Cyclofem® : **25 mg medroxyprogesterone acetate + 5 mg estradiol cypionate**

Bleeding patterns experienced by injectable users at 1 year of use

Depo-provera



Cyclofem



Once-a-month injectables for women

Mesigyna

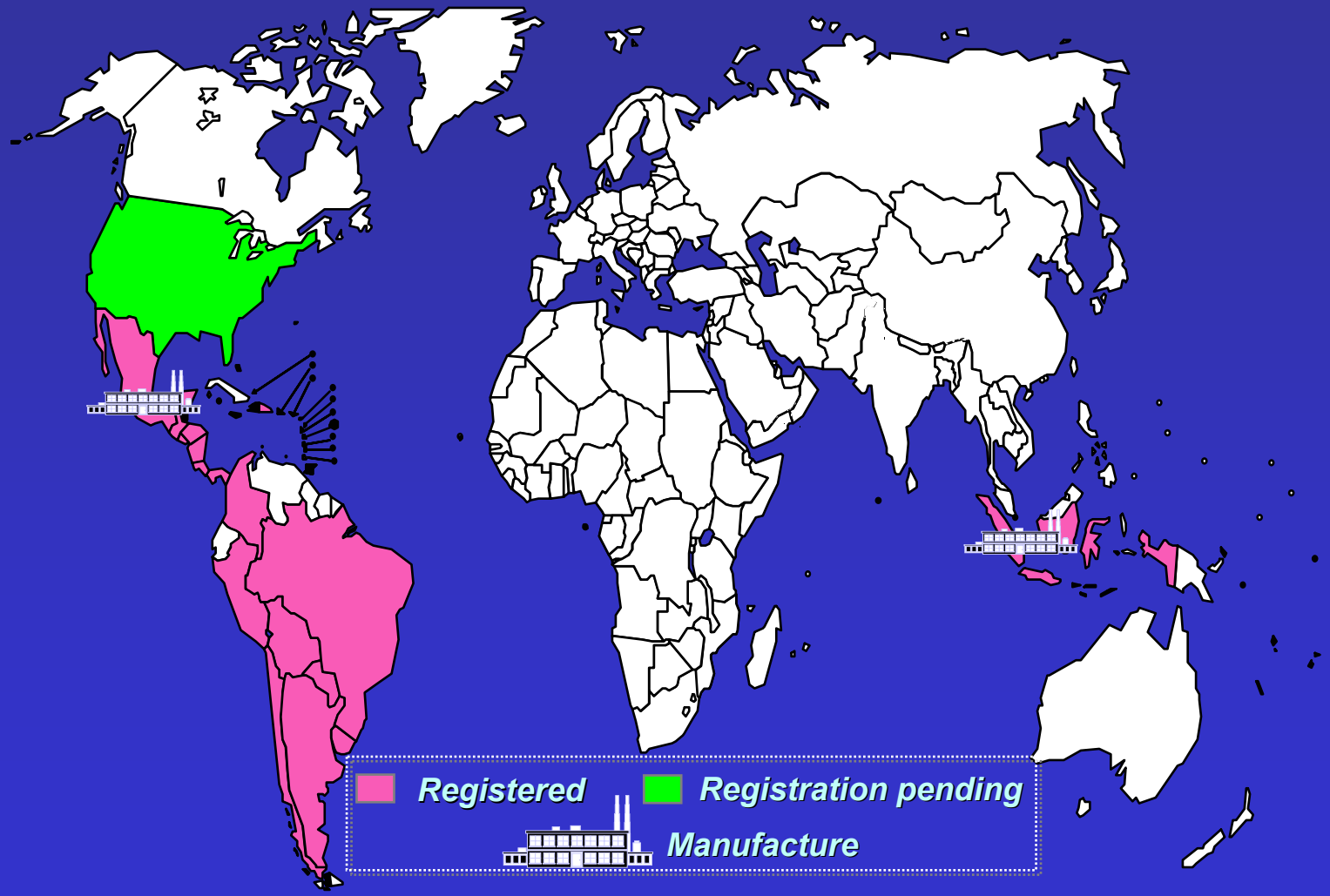
- licensed to **Schering**

  (low public sector price)

- currently registered in
  - *Caribbean and Latin America (44 countries)*
  - *Egypt*
  - *Kenya*
  - *Tanzania*
  - *Turkey*

CYCLOFEM

25 mg medroxyprogesterone acetate + 5 mg estradiol cypionate



What is emergency contraception?

Methods which women can use AFTER intercourse to PREVENT pregnancy

(Consensus Statement, Bellagio, 1995)

Methods of emergency contraception in early 1990s

- Ethinylestradiol/levonorgestrel (Yuzpe regimen) (1974)
  - nausea 50%, vomiting 20%
  - efficacy approx. 75%
- Copper-T intrauterine device (1970s)
  - often unsuitable, requires trained providers
  - painful at insertion, risk of PID
  - efficacy of greater than 90%

Emergency contraception is indicated to prevent pregnancy after intercourse

- When no contraceptive was used
- When there is a contraceptive failure or misuse, including:
  - condom breakage, slippage or misuse
  - 2 or more consecutive missed oral contraceptive pills
  - late for contraceptive injection
  - failed coitus interruptus, etc.
- In cases of sexual assault

Lower pregnancy rate after levonorgestrel

Group	Number of women	Observed pregnancies	Pregnancy rate (95% CI)
Yuzpe	979	31	**3.2%** (2.2, 4.5)
LNG	976	11	**1.1%** (0.6, 2.0)

The difference in pregnancy rate was statistically significant.

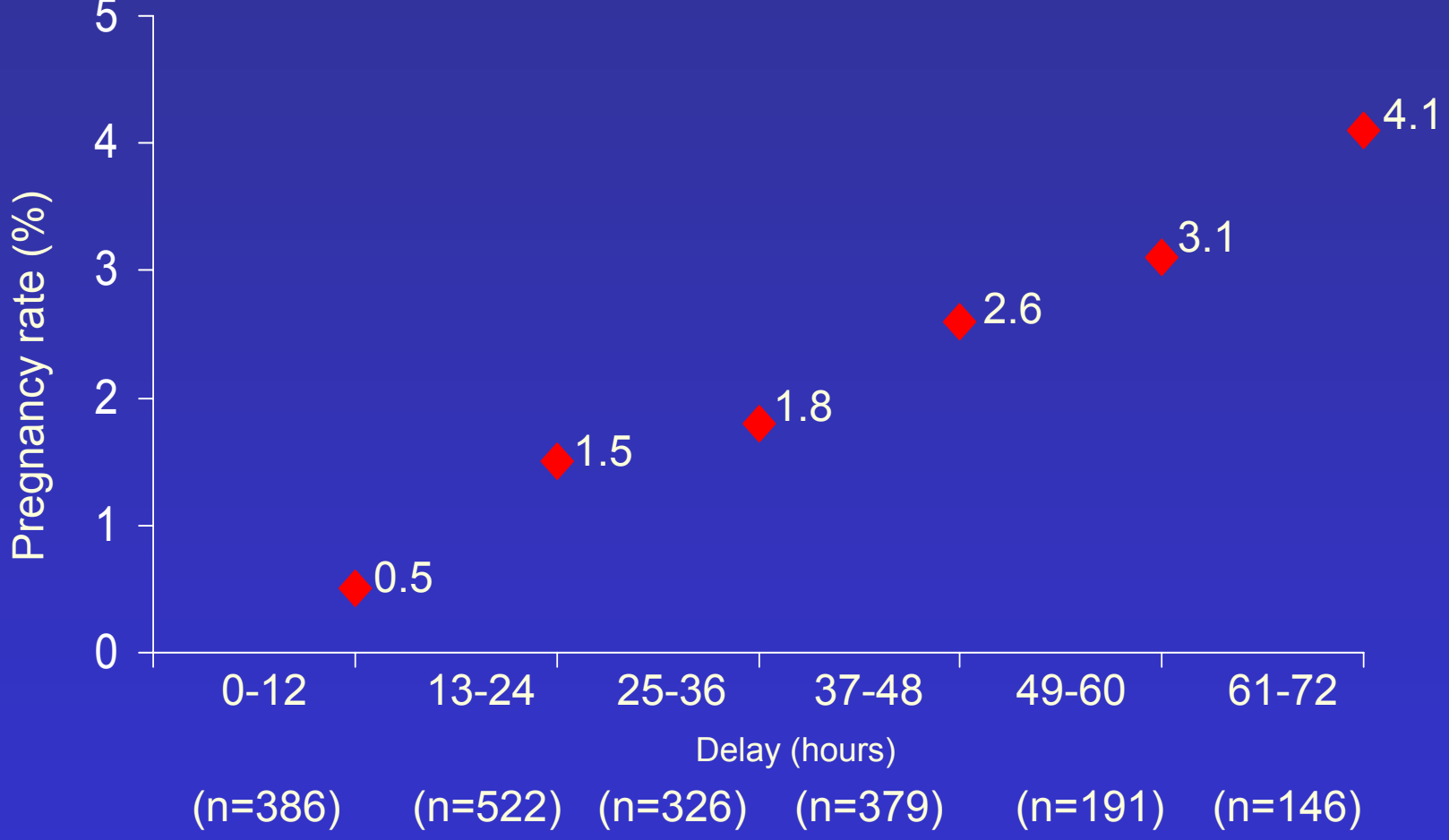
(Source: WHO, Lancet, 1998)

Less side-effects after levonorgestrel

Side-effect	Yuzpe No. (%) of cases	LNG No. (%) of cases	p-value
Nausea	494 (50.5)	226 (23.1)	<0.01
Vomiting	184 (18.8)	55 (5.6)	<0.01
Headache	198 (20.2)	164 (16.8)	0.06
Dizziness	163 (16.7)	109 (11.2)	<0.01
Fatigue	279 (28.5)	165 (16.9)	<0.01

(Source: WHO, Lancet, 1998)

Emergency contraception is more effective the sooner it is started

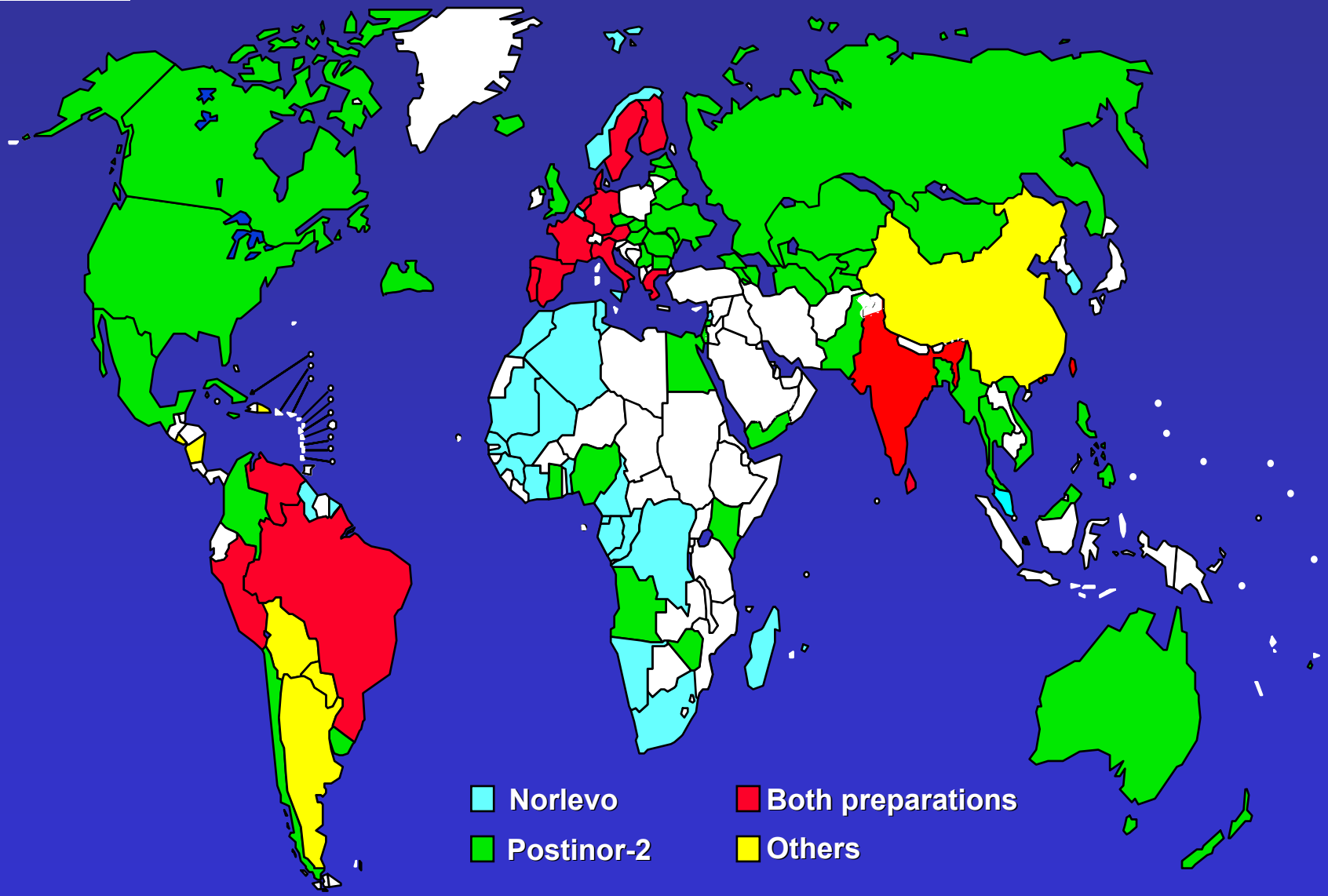


(Source: WHO, Lancet, 1998)


2 Tabl.
POSTINOR-2™
Levonorgestrel


NORLEVO®
750 microgrammes
Lévonorgestrel
2 Comprimés
Voie Orale

Availability of levonorgestrel preparations for emergency contraception (as of November 2002)



Levonorgestrel and mifepristone do not differ in efficacy

Group	Observed pregnancies /total	Rate
LNG 0.75 mg x 2	24/1356	1.77%
LNG 1.5 mg x 1	20/1356	1.47%
Mifepristone 10 mg	21/1359	1.55%
All LNG	**44/2712**	**1.62%**

(Source: WHO, Lancet, 2002)

Mifepristone research

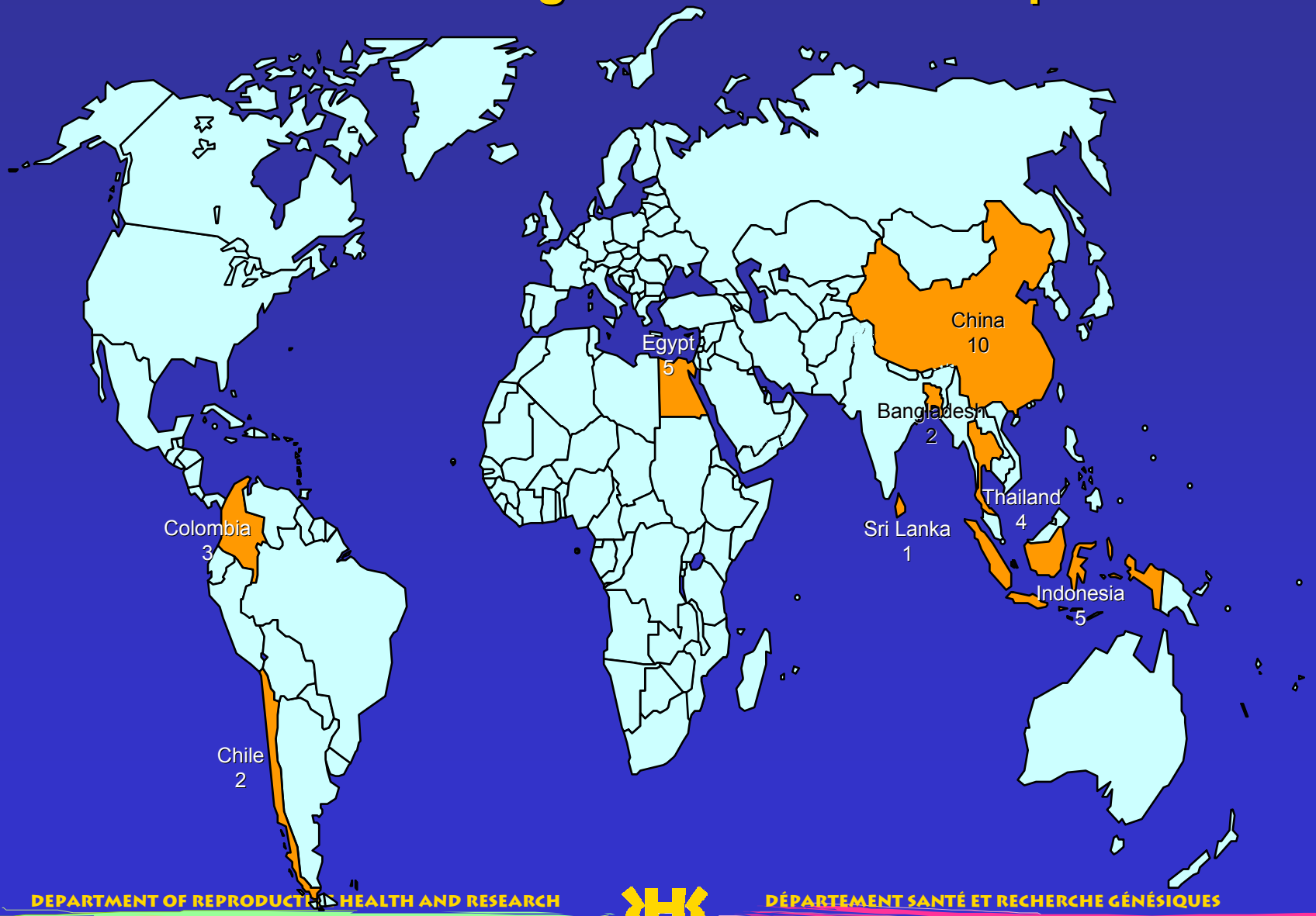
- **pregnancy termination (first and second trimester)**
- **cervical ripening**
- menses induction
- ovulation blocking
- luteal contraception
- **emergency contraception**

Faith Versus Facts

Important new knowledge about safety/efficacy of hormonal fertility-regulating methods

- Oral contraceptives and cancer (benefits and risks)
- Oral contraceptives and cardiovascular disease
- Oral contraceptives and breast cancer
- DMPA and breast cancer
- Safety and efficacy of mifepristone
- Third-generation oral contraceptives and venous thromboembolism
- Long-term safety and efficacy of Norplant®

Countries (number of clinics) participating in Post-marketing surveillance of Norplant®



Post-marketing surveillance of Norplant®

Cumulative pregnancy rate at five years

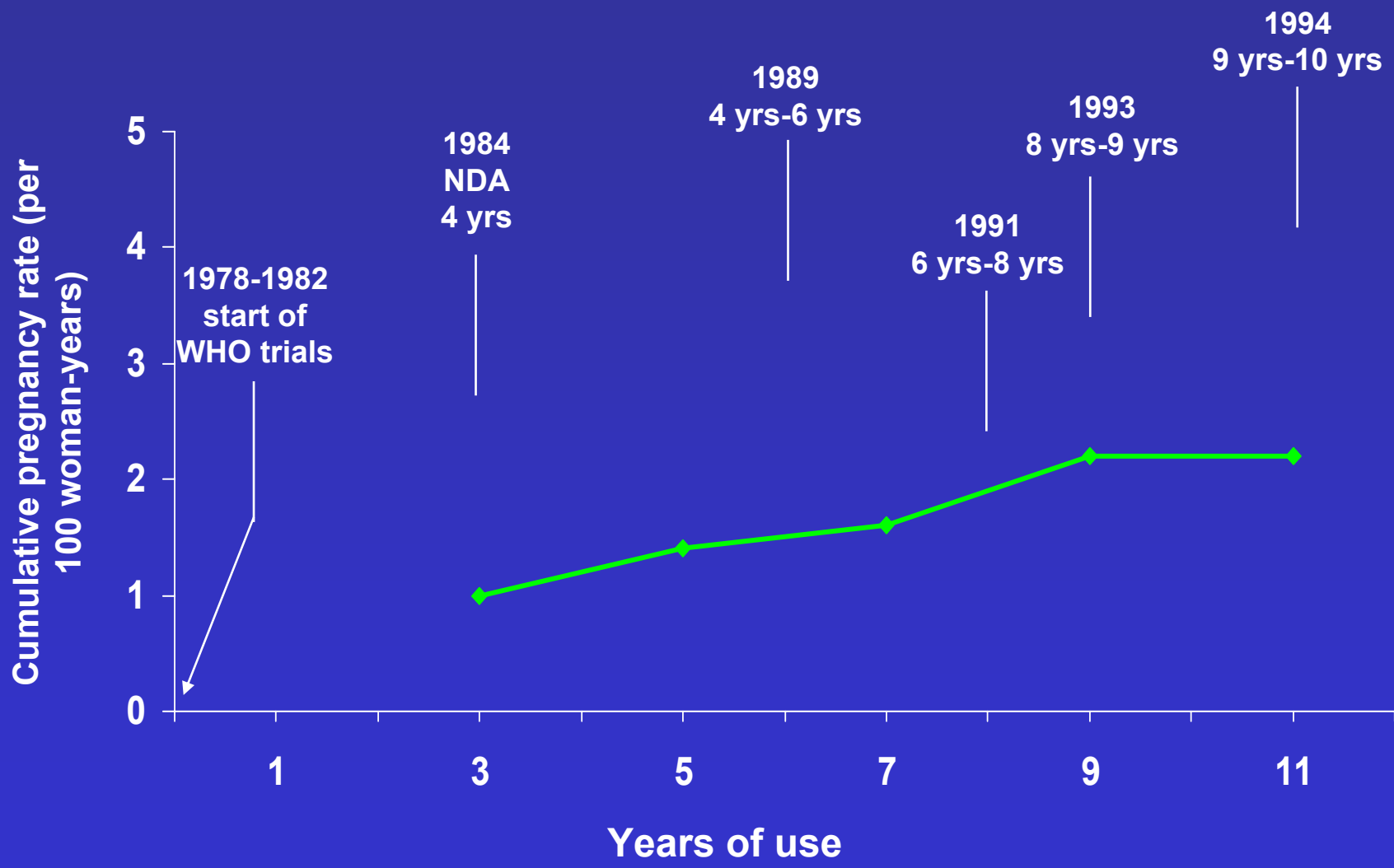
	Norplant®	Copper IUD	Non-Copper IUD	Sterilization
Woman-years	32,977	24,289	2619	6905
Events	88	215	77	10
Rate (SE)	1.46 (0.16)	4.19 (0.28)	13.00 (1.39)	0.72 (0.23)

(Source: WHO, 2001)

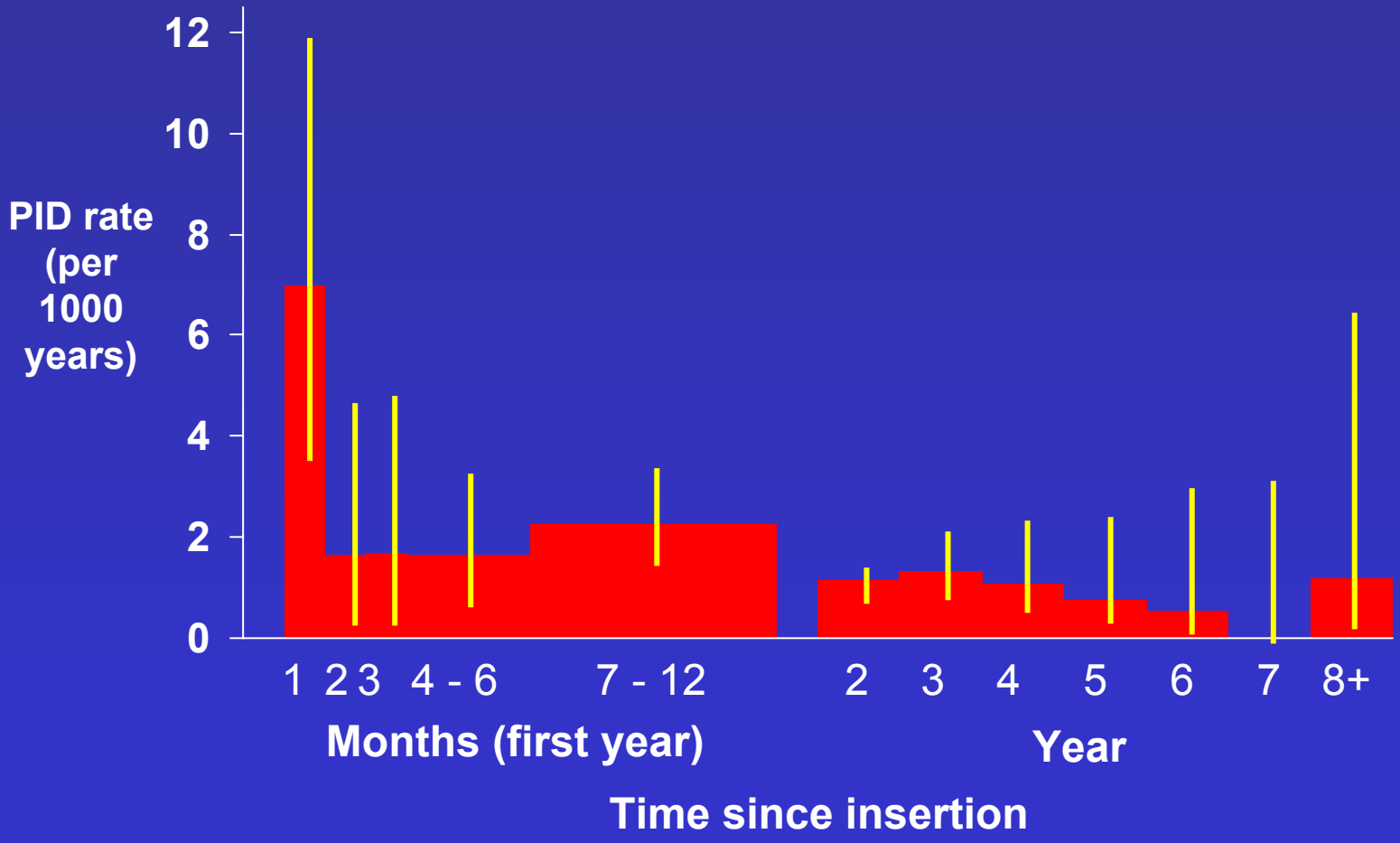
Post-Marketing Surveillance of Norplant®
Selected Side-effects
(Rate ratios Norplant/Controls adjusted for clinic and age)

Bleeding disturbances				
- excessive /irregular, hospitalised	Norplant			
	IUD	1.14	(0.39, 3.31)	0.82
	Sterilization	2.33	(0.28, 19.7)	0.44
- excessive/irregular	Norplant			
	IUD	2.72	(2.49, 2.97)	P<0.001
	Sterilization	11.39	(8.49, 15.3)	P<0.001
- amenorrhoea	Norplant			
	IUD	4.80	(3.88, 5.95)	P<0.001
	Sterilization	6.69	(4.07, 11.0)	P<0.001
Anaemia				
Haemoglobin <10g/dl	Norplant			
	IUD	0.78	(0.53, 1.13)	0.19
	Sterilization	1.10	(0.40, 3.02)	0.85

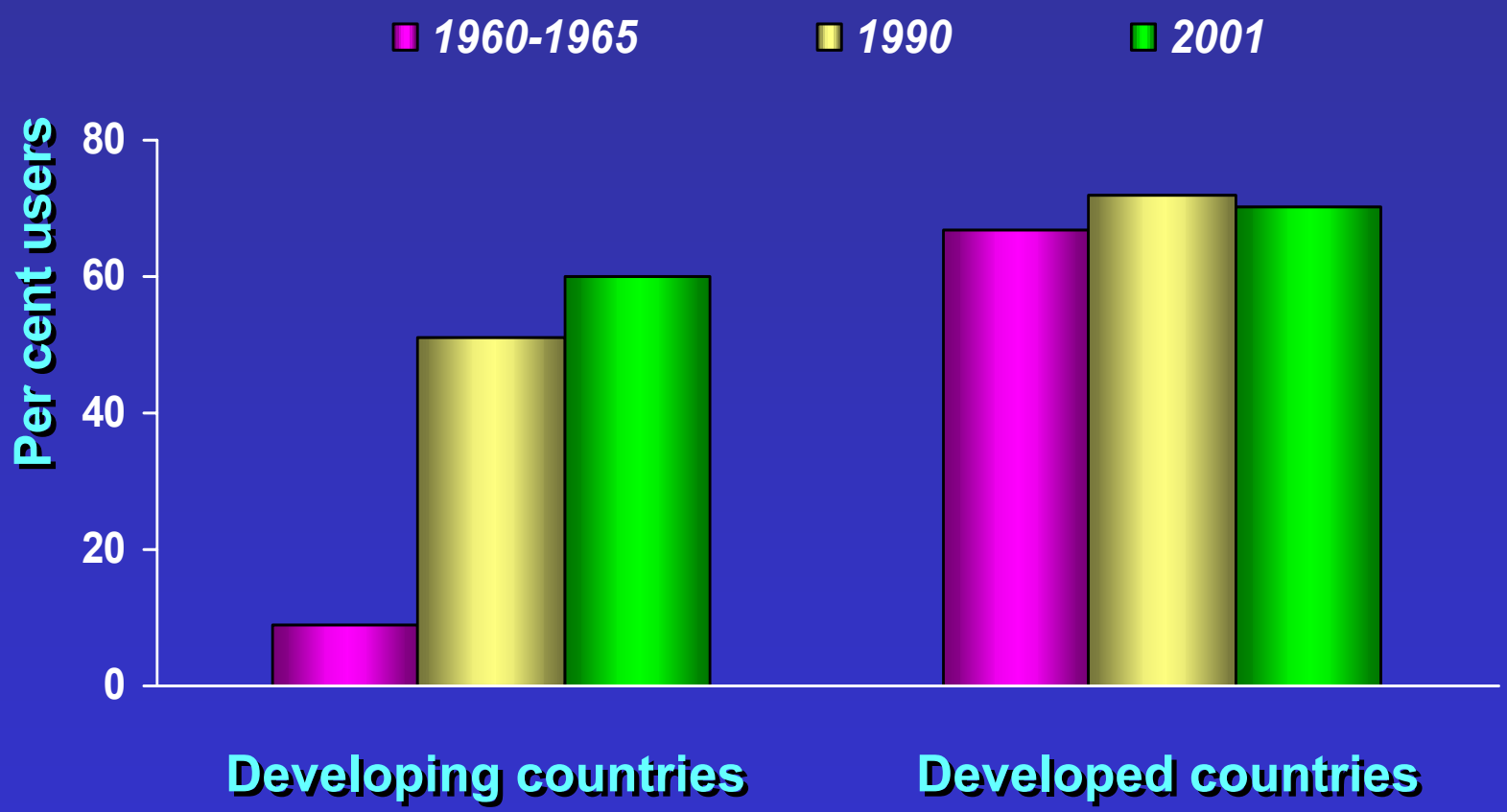
TCu 380A IUD : US FDA APPROVALS



PID INCIDENCE RATE
(95% confidence interval)



Trends in use of contraception



(Source: United Nations, 1991 and 1999)

Emphasis on research capability strengthening

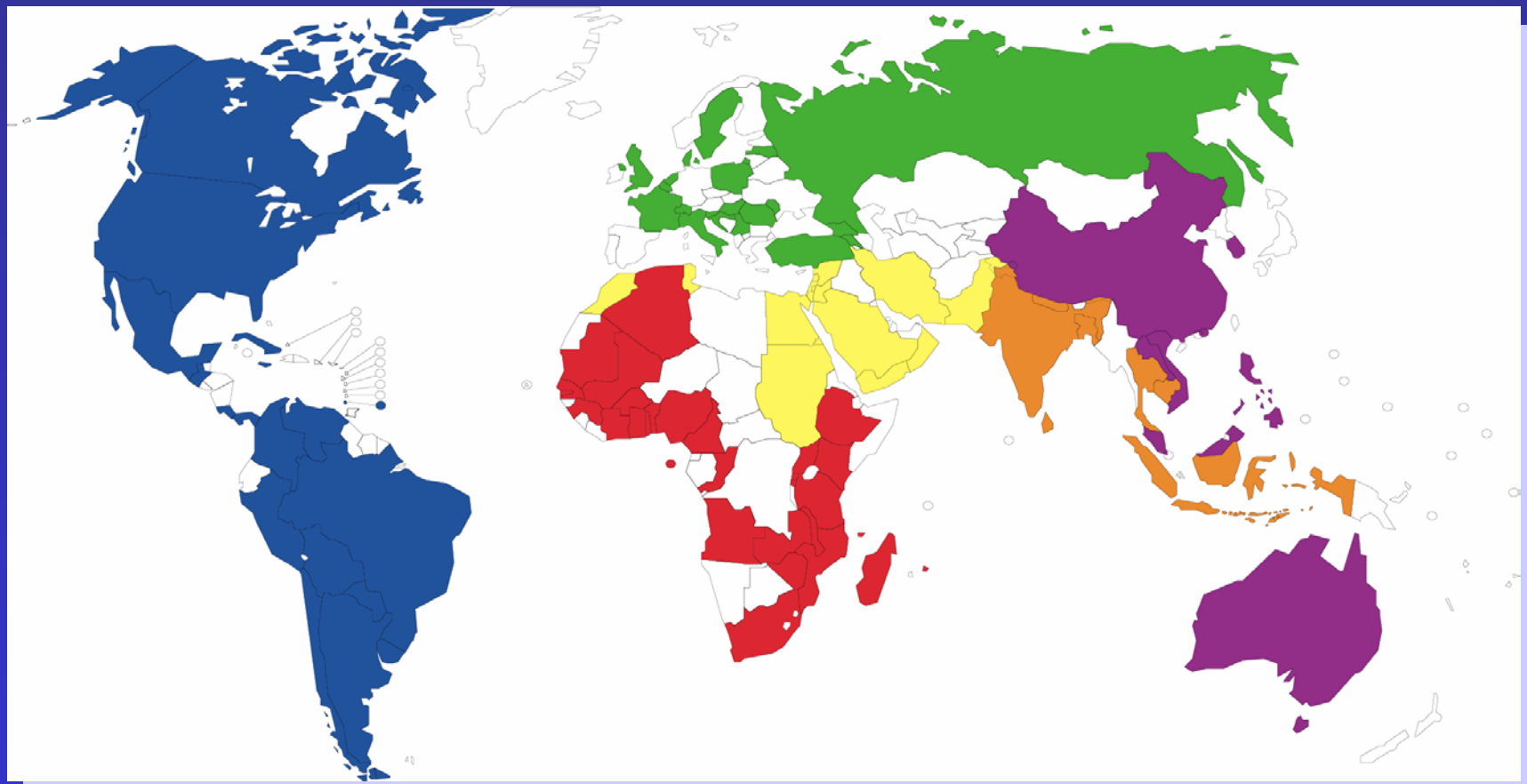
US$ 2

Research and development

US$ 1

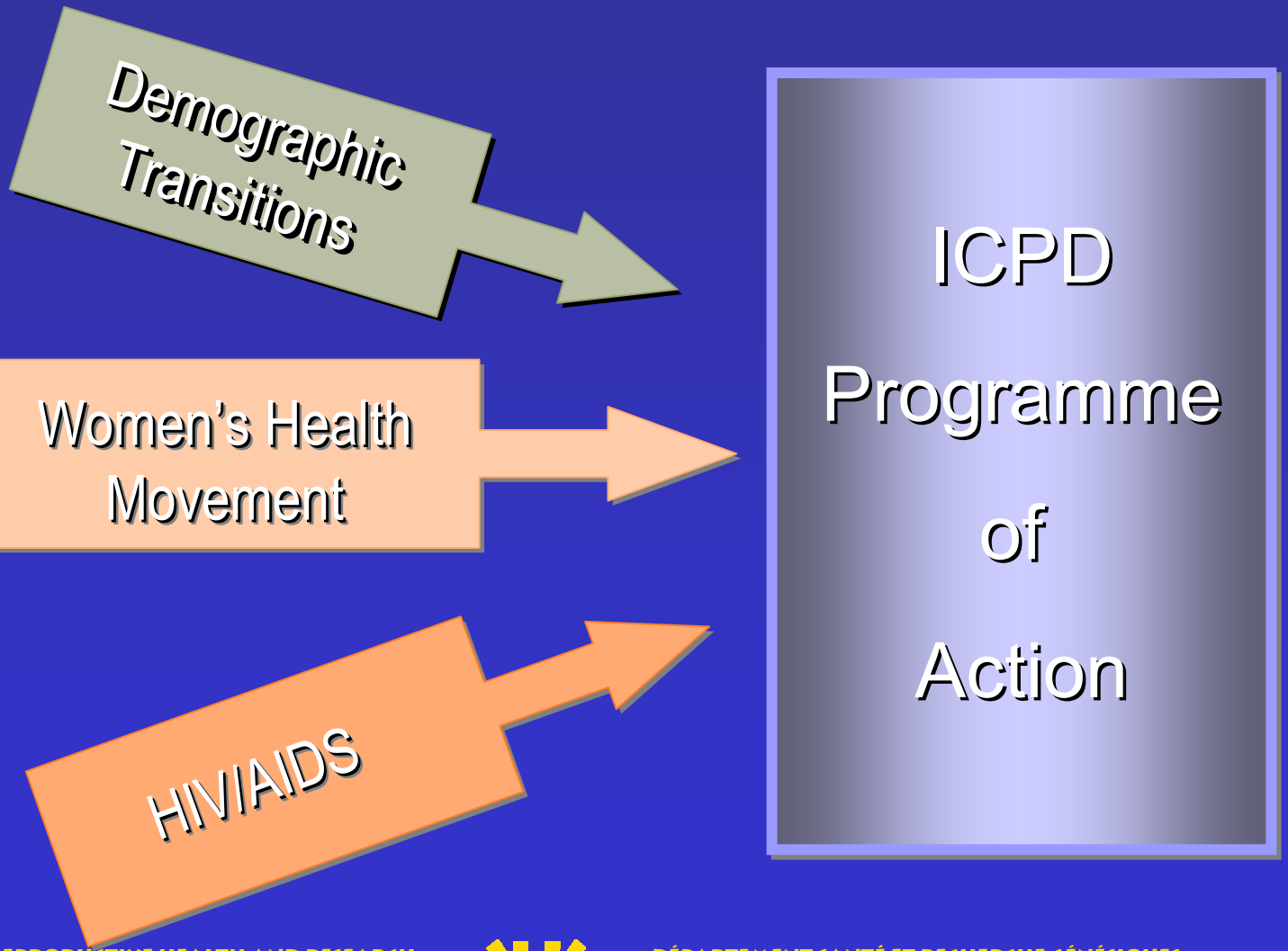
Research capability strengthening

Countries collaborating with the Department in the year 2001 (n = 99 countries)



AFRO AMRO EMRO EURO SEARO WPRO

The ICPD paradigm shift



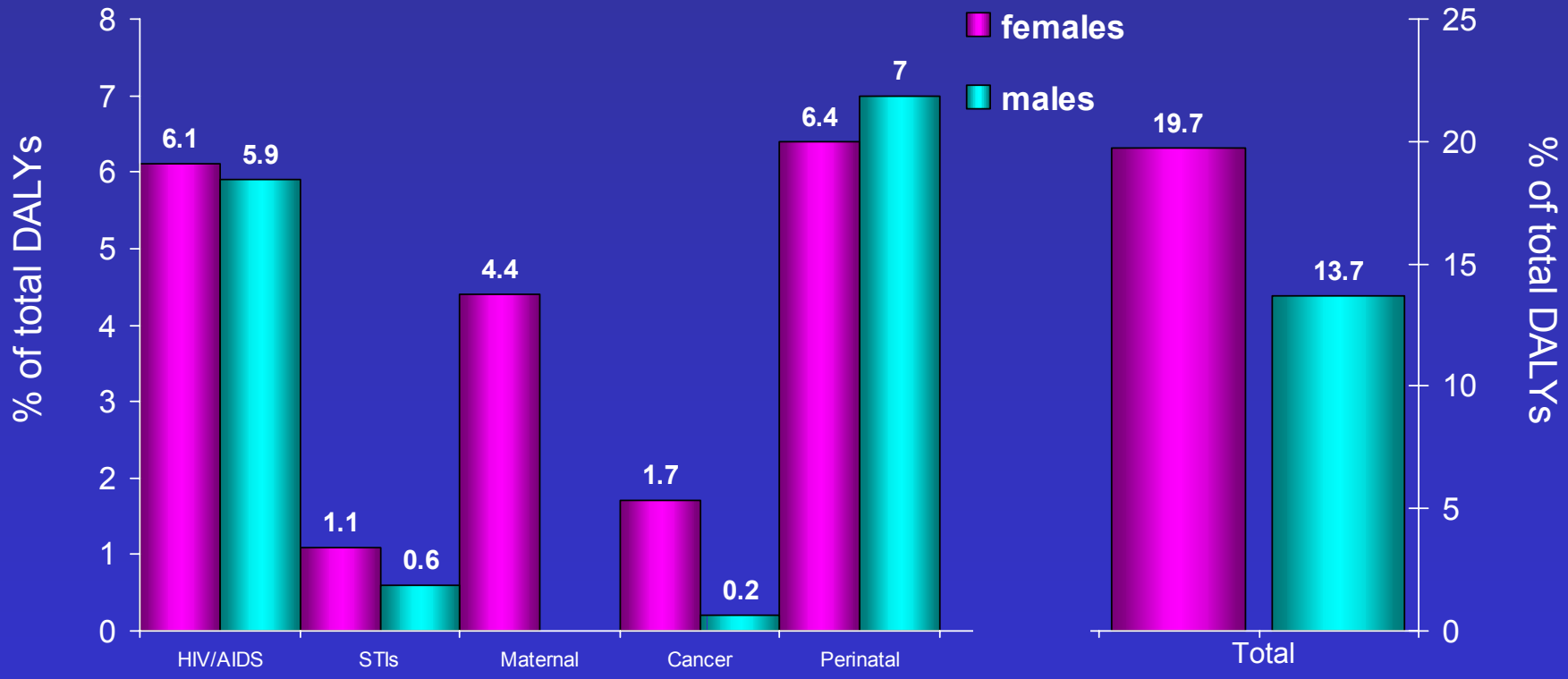
The ICPD Programme of Action - A radical departure

- a new language
- a broader agenda to be addressed in a holistic, comprehensive,"horizontal", integrated way
- a new way of working: client-centred, rights-based, gender-sensitive
- a place for neglected groups: young people, men, refugees
- a concern for neglected issues: violence against women, female genital mutilation

"All countries should strive to make accessible through the primary health-care systems, reproductive health to all individuals of appropriate ages as soon as possible and no later than the year 2015."

(ICPD Programme of Action, para. 7.6)

Reproductive ill-health accounts for substantial portions of global burden of disease



(Source: World Health Report 2002)

Risks to sexual and reproductive health

Risk factor	Rank	Attributable deaths (% of total)	Attributable DALYs	Measured adverse outcomes of exposure
Unsafe sex	2	2.9 million (5.2%)	91.9 million (6.3%)	HIV/AIDS, STIs, cervical cancer
Lack of contraception	19	149,000 (0.3%)	8.8 million (0.6%)	maternal mortality and morbidity

(Source:WHO,World Health Report 2002)

"***Investments in reproductive health***, including family planning and access to contraceptives, ***are crucial accompaniments of investments in disease control***. The combination of disease control and reproductive health is likely to translate into reduced fertility, greater investments in the health and education of each child, and reduced population growth."

(Commission on Macroeconomics and Health, 2001)

Maternal health intervention research during 1995 -2002 with leading/active participation of the Programme

	Countries	Women	Status
Antenatal care	4	24 678	Published (2001)
Postpartum haemorrhage	9	18 530	Published (2001)
Caesarean section	5	149 276	Publications submitted (2002)
Treatment of pre-eclampsia (MAGPIE trial)	31	10 141	Published (2002)
The WHO Reproductive Health Library	2	76 053	Ongoing (evaluation phase)
Primary prevention of pre-eclampsia (calcium supplementation)	6	8 500	Ongoing (6500 recruited)
Screening and treatment of urinary tract infection	4	18 000	Recruitment start 2003
Treatment of postpartum haemorrhage	4	1 000	Recruitment start 2003
Total	**25***	**306 178**	

* Some countries have been involved in more than one study

WHO Antenatal Care Trial

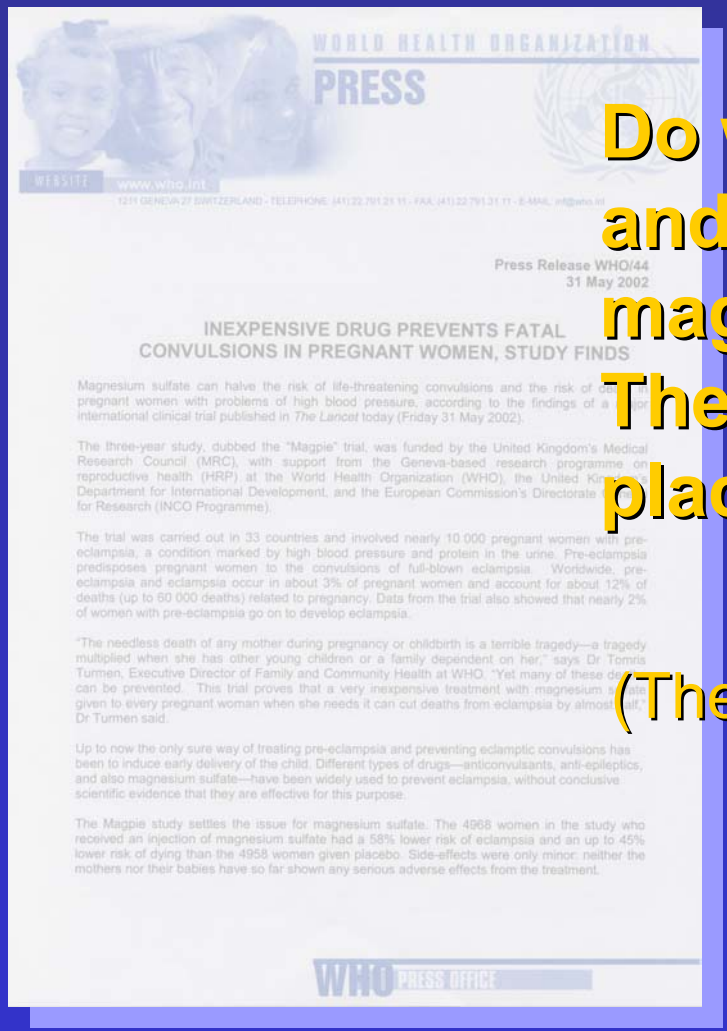
Primary outcome	New model	Standard model	Adjusted odds ratio (95% CI)
Low birthweight (<2500g)	7.68 %	7.14 %	1.06 (0.97-1.15)
Pre-eclampsia/ eclampsia	1.69 %	1.38 %	1.26 (1.02-1.56)
Postpartum anaemia	7.59 %	8.67 %	1.01[a]
Treated urinary tract infection	5.95 %	7.41 %	0.93 (0.79-1.10)

[a] Confidence interval not computed because of heterogeneity between sites and strata

WHO Misoprostol Trial
Primary outcomes

Outcome	Misoprostol	Oxytocin	RR (95% CI)
Blood loss ≥ 1000 ml	4.0 %	2.9 %	1.39 (1.19-1.63)
Use of additional uterotonics	15.2 %	10.9 %	1.40 (1.29-1.51)

(Gülmezoglu et al.,The Lancet, 2001)



WORLD HEALTH ORGANIZATION

PRESS

WEBSITE www.who.int

Press Release WHO/44
31 May 2002

INEXPENSIVE DRUG PREVENTS FATAL CONVULSIONS IN PREGNANT WOMEN, STUDY FINDS

Magnesium sulfate can halve the risk of life-threatening convulsions and the risk of ... pregnant women with problems of high blood pressure, according to the findings of a ... international clinical trial published in *The Lancet* today (Friday 31 May 2002).

The three-year study, dubbed the "Magpie" trial, was funded by the United Kingdom's Medical Research Council (MRC), with support from the Geneva-based research programme on reproductive health (HRP) at the World Health Organization (WHO), the United Kingdom Department for International Development, and the European Commission's Directorate ... for Research (INCO Programme).

The trial was carried out in 33 countries and involved nearly 10 000 pregnant women with pre-eclampsia, a condition marked by high blood pressure and protein in the urine. Pre-eclampsia predisposes pregnant women to the convulsions of full-blown eclampsia. Worldwide, pre-eclampsia and eclampsia occur in about 3% of pregnant women and account for about 12% of deaths (up to 60 000 deaths) related to pregnancy. Data from the trial also showed that nearly 2% of women with pre-eclampsia go on to develop eclampsia.

"The needless death of any mother during pregnancy or childbirth is a terrible tragedy—a tragedy multiplied when she has other young children or a family dependent on her," says Dr Tomris Turmen, Executive Director of Family and Community Health at WHO. "Yet many of these ... can be prevented. This trial proves that a very inexpensive treatment with magnesium ... given to every pregnant woman when she needs it can cut deaths from eclampsia by almost ... Dr Turmen said.

Up to now the only sure way of treating pre-eclampsia and preventing eclamptic convulsions has been to induce early delivery of the child. Different types of drugs—anticonvulsants, anti-epileptics, and also magnesium sulfate—have been widely used to prevent eclampsia, without conclusive scientific evidence that they are effective for this purpose.

The Magpie study settles the issue for magnesium sulfate. The 4968 women in the study who received an injection of magnesium sulfate had a 58% lower risk of eclampsia and an up to 45% lower risk of dying than the 4958 women given placebo. Side-effects were only minor: neither the mothers nor their babies have so far shown any serious adverse effects from the treatment.

WHO PRESS OFFICE

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate?
The Magpie Trial: a randomized placebo-controlled trial.

(The Magpie Trial Collaboration Group. Lancet 2002; 359: 1877-90)

The Magpie Trial

	Magnesium sulphate (n=5055)	Placebo (n=5055)	Relative risk (95% CI)
Eclampsia	40 (0.8%)	96 (1.9%)	0.42 (0.29 to 0.60)
Maternal death	11 (0.2%)	20 (0.4%)	0.55 (0.26 to 1.14)
Baby death (total)	576 (12.7%)*	558 (12.4%)†	1.02 (0.92 to 1.14)

* n=4538; † n=4486

(Lancet 2002; 359: 1877-90)

Activities in STI and HIV during 2001-2002

- Cellulose sulphate as microbicide
- Male and female condoms (pregnancy and STI prevention)
- HAART during breastfeeding
- Infant feeding and MTCT of HIV
- COL-1492 (nonoxynol-9)

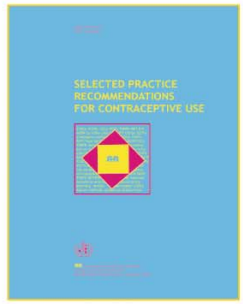
Getting research into practice

Evidence-based technical and policy guidance

- family planning (global consensus guidelines)

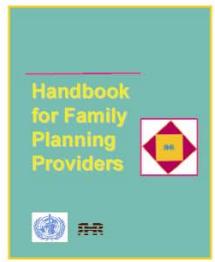
Medical Eligibility Criteria for Contraceptive Use

Selected Practice Recommendations for Contraceptive Use



Guidance for guides

Guidance for providers and clients



Process for keeping the guidance up-to-date

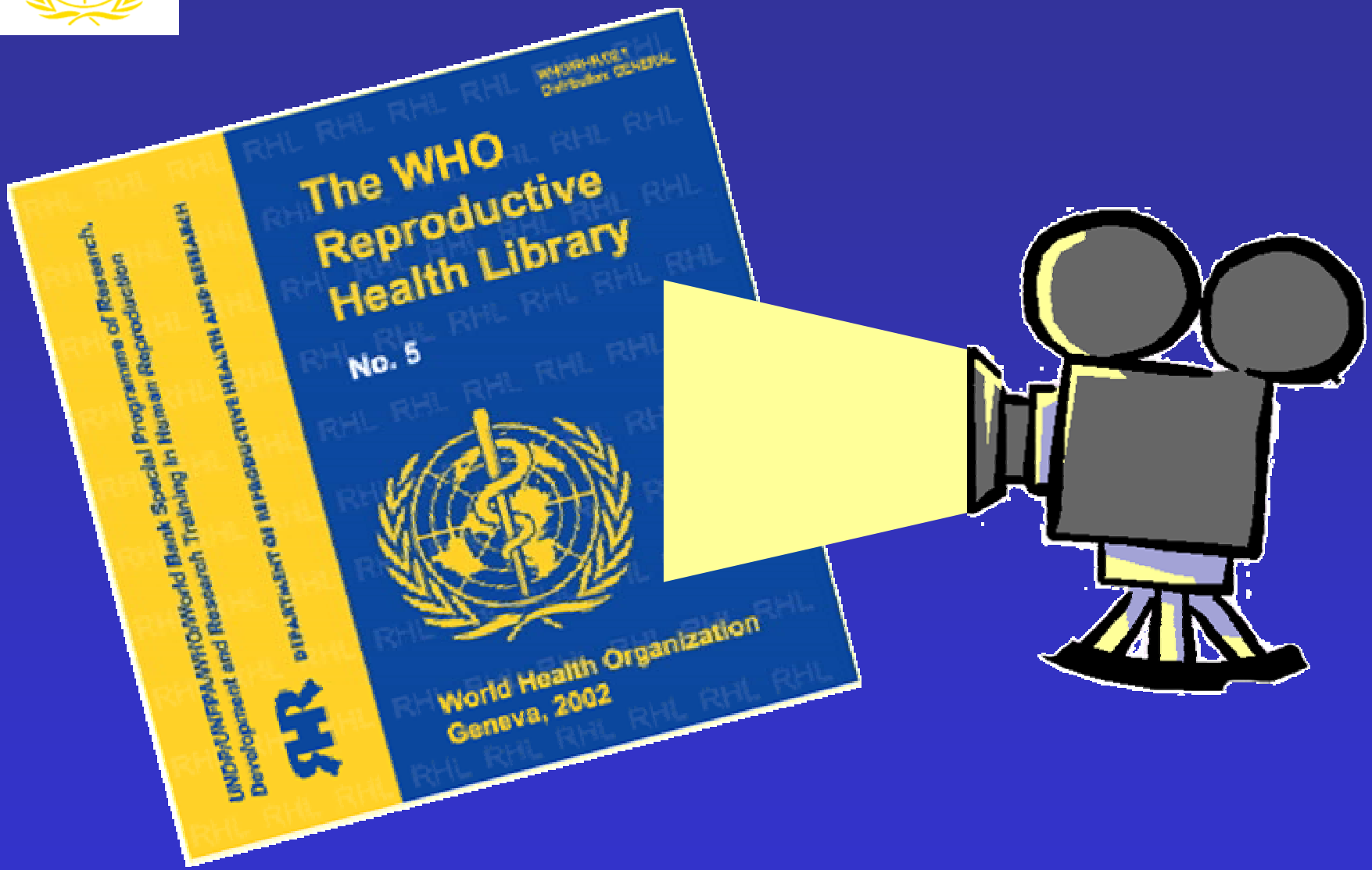
Decision-Making Tool for Family Planning Clients and Providers

Handbook for Family Planning Providers

Getting research into practice

Evidence-based technical and policy guidance

- family planning (global consensus guidelines)
- *WHO Reproductive Health Library Issue No.5*


The WHO Reproductive Health Library
No. 5
World Health Organization
Geneva, 2002
RHR
DEPARTMENT OF REPRODUCTIVE HEALTH AND RESEARCH
UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction

Broadening choice and improving quality of care of reproductive health services

Main areas of ongoing/planned research

- Family planning
  - male hormonal contraception
  - emergency contraception
  - long-term safety (IUDs; bone mineral density)
- Making pregnancy safer
  - prevention of pre-eclampsia
  - asymptomatic urinary tract infections

Main areas of ongoing/planned research

- Controlling RTIs/STIs
  - dual protection methods (microbicides, female condom)
  - contraceptives and HIV
  - HAART for breastfeeding women
- Preventing unsafe abortion
  - non-surgical termination of pregnancy
  - provision of abortion by mid-level providers
  - post-abortion care

Main areas of ongoing/planned research

- Technical cooperation with countries
  - enhancing operations research capability
  - improved utilization of research findings
  - strengthening of regional research networks
  - widening scope and use of the Strategic Approach
  - health sector reform and reproductive health

"Eradicating polio, curbing the tobacco epidemic, stimulating research in the developing world — this is our corporate strategy in practice."

Dr Gro Harlem Brundtland, Statement to the Executive Board at its 105th session, 29 January 2000