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Preface

Sexual and reproductive health is at the core of people's lives and well-being. The ability to develop in a supportive environment and grow into a sexually responsive and responsible adult, the ability to enjoy one's sexuality without harming or infecting oneself or one's partner, and the ability to have children by choice and not by chance are among the unique attributes that define us as human. A strong focus on sexual and reproductive health is justified not only on the grounds of human rights, equity, and social justice. There are strong public health arguments, too, since reproductive ill-health contributes in such large measure to the global burden of disease and since we have at our disposal cost-effective ways of preventing, or at least managing, much of this ill-health.

Thirty years ago, when our programme was established, the global international health and development agenda was dominated by unwanted fertility and the impact of rapid population growth on development. Today, the nature of the discourse has changed. Today, the focus is on poverty, demographic and epidemiological transitions, and the impact of HIV/AIDS on development. Clearly, this evolution reflects changing realities. But it also reflects the fact that our common efforts have been remarkably successful in providing people with the information and services they need to manage their fertility. Over the last three decades, contraceptive prevalence has risen dramatically (more than sixfold in developing countries) and fertility has fallen in almost every corner of the world. I believe few people question the key role our programme has played in this achievement. Obviously, there remain unanswered questions and there remain areas of the world untouched by this achievement. We are committed to completing the job.

HIV/AIDS in particular is an area where our programme can justifiably claim a comparative advantage, since many of the interventions needed to prevent the spread of this epidemic can only be delivered through sexual and reproductive health services, including family planning.

While in fertility regulation much of the basics are in place, in other aspects of sexual and reproductive health our knowledge base remains inadequate. This is true of maternal health and of adolescent sexual and reproductive health, and even more so of HIV/AIDS. I strongly believe that our programme is, among international research organizations, one of the best placed to extend the boundaries of knowledge in these areas. It is

eminently equipped to apply the knowledge and experience that we have accumulated in our work on fertility to these other still relatively uncharted areas of sexual and reproductive health. HIV/AIDS in particular is an area where our programme can justifiably claim a comparative advantage, since many of the interventions needed to prevent the spread of this epidemic can only be delivered through sexual and reproductive health services, including family planning.

Much of our programme's comparative advantage springs from the global research network that it has built up over the 30 years of its existence. Today, that network harnesses the resources of more than 120 research institutions in nearly a third of the world's countries and more than half of its developing countries. Thanks to this network, we can provide data on human reproduction that are pertinent to people living in the most diverse circumstances and cultures.

This report contains numerous examples of studies completed during the 2000–2001 biennium that could not have been carried out and may not have had such an impact had they not involved such a vast network.

An interesting finding of the analysis was that well over half the married couples in the study abandoned the use of condoms within a year of adopting the method.

Our programme's social science studies offer perhaps the most direct example of the need for a multicultural approach in seeking answers to questions concerning reproductive health and sexuality. Increasingly, our epidemiological and clinical work is conducted in parallel with investigations of the behavioural and social underpinnings of sexual and reproductive behaviour and reproductive ill-health. One example is an analysis of Demographic and Health Survey data on contraceptive use among 20 000 women in 16 developing countries, described on page 10: an interesting finding of the analysis was that well over half the married couples in the study abandoned the use of condoms within a year of adopting the method. Our programme is also investing heavily in a large number of social science studies probing the "mysteries" of adolescent sexual and reproductive behaviour in a wide variety of cultural contexts (pages 43–46).

Since its inception, our programme has been heavily committed to strengthening the evidence-base for reproductive health practices, a commitment aimed at dispelling or confirming doubts about the safety or claims about the efficacy of family planning methods and other reproductive technologies. Studies, for exam-

ple, completed during the biennium on the safety of implantable contraceptives, and involving more than 15 000 women in eight developing countries, have confirmed that the levonorgestrel-releasing implantable contraceptive, Norplant, is highly effective and safe (pages 11–12). Other studies (pages 14–15), on the safety of IUDs, show the copper-bearing device TCu-380A to be just as safe, but almost twice as effective, as more expensive "rival" devices.

Studies completed during the biennium have confirmed that the levonorgestrel-releasing implantable contraceptive, Norplant, is highly effective and safe.

Emergency contraception is another area where our programme has played a pioneering, catalytic role over the past two decades. Research we have funded, again spanning vast areas of the globe, has been instrumental in confirming the effectiveness of levonorgestrel and in making it easier and safer to use—today, women in more than 80 countries (page 19) are using it as a "second chance" contraceptive option following unprotected intercourse.

Practical results have also emerged during the biennium from research on ways of making pregnancy safer. In the so-called Magpie trial—probably the largest clinical study of its kind, involving 10 000 women attending 175 hospitals in 33 countries—a natural, inexpensive chemical, magnesium sulfate, was found to halve the risk of convulsions in women with pre-eclampsia (page 27).

Part of our programme's efforts to make pregnancy safer is its work on distilling and disseminating the best available evidence on the best health care practices in pregnancy and childbirth. An example is our virtual WHO Reproductive Health Library, described on page 29, which is increasingly appreciated as one of the most useful sources of information for practitioners of public health care.

In the so-called Magpie trial, a natural, inexpensive chemical, magnesium sulfate, was found to halve the risk of convulsions in women with pre-eclampsia.

Not all the results presented in this report are reassuring. The findings, for example, of a study conducted, with some support from our programme, by the International Agency for Research on Cancer, suggest that long-term use of oral contraceptives may well double or even triple the risk of cervical cancer in women with human papillomavirus infection. The data were reviewed at a March 2002 meeting of experts, who concluded that, from a risk–benefit perspective, the findings do not warrant changes in oral contraceptive use at the present time (page 34).

"Investments in reproductive health, including family planning and access to contraceptives, are crucial accompaniments to investments in disease control."

Our programme has also been engaged in wide-ranging, long-term efforts to find the least expensive, most convenient, but highly effective drug regimen for non-surgical abortion. Eight studies are still under way in more than 6000 women in 20 countries, but already a low-dose regimen of mifepristone plus a prostaglandin appears to be just as effective as the higher doses originally proposed for medically induced abortion (page 39).

All in all, the biennium has produced a wealth of usable results that are having an impact on policy and practice. The work reported here clearly vindicates, I believe, our confidence in carefully planned, well-designed collaborative research as a means of expanding and refining the knowledge needed for the best reproductive health care. It also strengthens our conviction that we can have a positive impact on areas of reproductive health where new knowledge is needed—and needed urgently.

It should therefore come as no surprise to readers that the Commission on Macroeconomics and Health specifically mentioned our programme as one of the groups that should benefit from the US$ 1.5 billion annual increase in research and development funding. "Investments in reproductive health, including family planning and access to contraceptives," the Commission reasoned, "are crucial accompaniments to investments in disease control" in the global fight against poverty.

Paul F.A. Van Look, MD, PhD, FRCOG
Director

Chapter 1
Family planning—expanding the choices

Today, more than half of the world's one billion couples of reproductive age use some form of contraception and so are able to choose how many children they will have and when. In developing countries, about 55% of couples use contraceptives, compared to only 9% nearly fifty years ago. Much of the increase reflects a greater availability of reliable contraceptive methods. It also reflects continuing efforts by the international reproductive health community to promote the use of those methods. Since its inception in 1972, the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a member of that community, has stimulated and funded research aimed at expanding the choice of contraceptive methods available to couples. By generating, collating and disseminating the evidence produced by this research, HRP has built up a knowledge base such that this choice need no longer be based on intuition, hearsay, faith or dogma, but rather on scientifically sound information.

Yet, there are still many unanswered questions. For one thing, no method is perfect, either in itself or in the way it is used. Indeed, worldwide, somewhere between 6 million and 27 million unintended pregnancies occur annually among people practising contraception. For another, many couples—an estimated 120–150 million, mainly in developing countries—do not use contraceptives despite an apparent need for some form of family planning and an apparent lack of obstacles to acquiring it.

Certainly, most existing methods have or are perceived to have shortcomings that limit their acceptability and constrain couples' choices. Surveys indicate that some 300 million couples are dissatisfied with the methods they use. Moreover, although sexual intercourse, pregnancy and birth are central to human life everywhere, the sociocultural settings in which these events are played out are so diverse that family planning methods and products cannot be equally acceptable everywhere.

Clearly, there is a need to expand the array of products from which couples can make their choices and to do so through a greater understanding of how people, in a wide range of settings, make those choices. There is also a need to dispel, or confirm, fears and doubts about the safety and effectiveness of existing methods.

In short, there is a need for continuing research to devise products and methods that are even safer, more effective, and more widely acceptable than those currently available. This chapter describes research activities, backed by HRP, that address these needs and that have been conducted, reported or planned during the 2000–2001 biennium.

As the end-users see it

Tailoring reproductive health services and products to people's needs and expectations calls for information about how people perceive and use these services and products, including the reasons why people favour

one family planning method over another, or stop using one method and switch to another. HRP has devoted considerable resources to social science projects that seek answers to these questions in developing countries, where more than 80% of the world's couples of reproductive age live.

Contraceptive methods—selecting, staying, stopping, switching

One such project is a study conducted in 2000, in which HRP collaborated with the London School of Hygiene and Tropical Medicine to investigate contraceptive use among over 20 000 women in 16 developing countries—Bangladesh, Bolivia, Brazil, Colombia, Dominican Republic, Egypt, Guatemala, Kenya, Indonesia, Morocco, Nicaragua, Paraguay, Peru, Philippines, Turkey, and Zimbabwe. The women had been interviewed in the 1990s in the course of a Demographic and Health Survey (DHS). The 16 countries have a total population of 853 million and about 80 million contraceptive users. The study found that over a third of users had abandoned whatever method they had been using within 12 months of starting it.

Topping the list of discontinued methods in the 16 countries were diaphragms, foams, and jellies (abandoned by 67% of users in the first year of use), condoms (58%), the withdrawal method (46%), and periodic abstinence (42%). Also relatively high on the list were the pill (39%) and injectable contraceptives (32%). Among methods least likely to have been dropped during the first year of use were Norplant (discontinued by only 3.3% of users) and intrauterine devices (IUDs) (13%) (Figure 1.1).

Couples who abandoned their chosen method did so for a variety of reasons, the study found—the desire to have a child, inconvenience of use, the husband's objections, expense, difficulty in obtaining the contraceptive, and, particularly in the case of condoms, failure of the method.

The DHS data also served to compare how married couples use condoms with how they use the pill. Although condoms are more popular in developed than in developing countries, in some countries with high HIV prevalence rates condoms are being increasingly promoted as part of an effort to stem HIV transmission, even among couples in a stable relationship. The study showed that married couples using condoms were more likely to abandon the method during the first year of use than those using the pill (58% of condom-using couples did so vs 46% of pill users). They were also more likely than pill users to do so because of dissatisfaction with the method (46% vs 35%) and to experience higher failure rates than pill users (9% vs 6%). Moreover, when the chosen method failed, condom users were more likely than users of the pill to resort to abortion (21% of condom users did so vs 14% of pill users) or to switch to another method (76% vs 58%), and less likely to have an unwanted or mistimed pregnancy (10% vs 17%).

The relative infrequency of condom use, particularly among married couples, and the fact that condoms were abandoned within a year by well over half of the married couples in the study, argue in favour of a dual contraceptive approach, such as a condom plus the pill or an injectable contraceptive, but there is little evidence that such a strategy would be feasible or acceptable in developing countries even where HIV infection is prevalent.

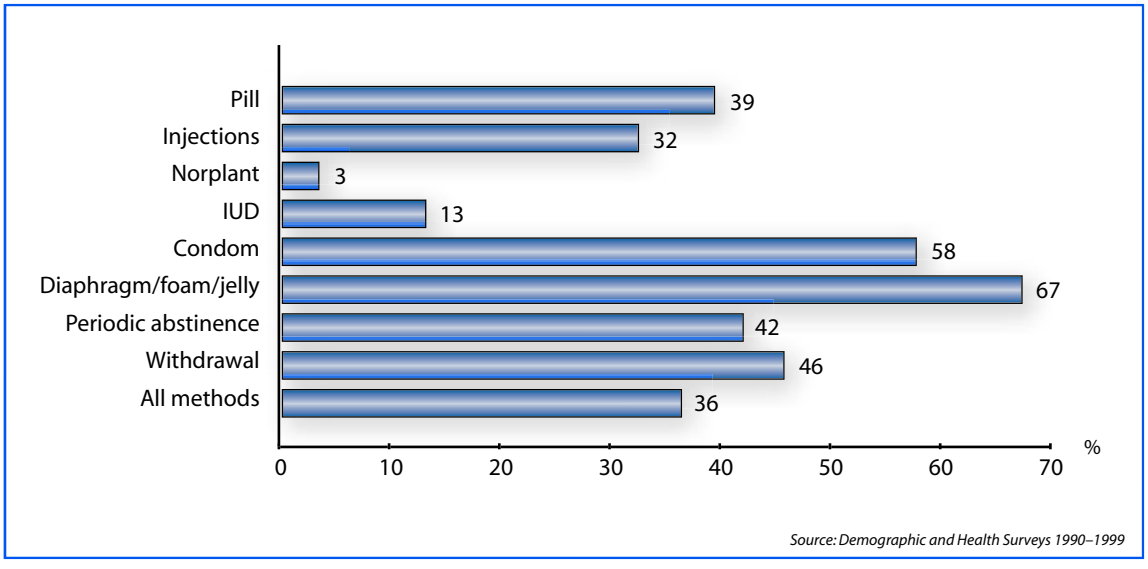


Figure 1.1. Percentages of women discontinuing use of contraceptive methods within one year of starting

Married couples—over 7500 "just married" couples, in fact—were also the subject of a prospective study carried out in Shanghai, China. Results published in 2000 showed that despite a high rate of contraceptive use (about 80% of married couples), nearly half of the couples with one child had experienced one or more unintended pregnancies following the birth of their first child. In a third of these couples, miscalculating the safe period was to blame; in nearly a fifth, incorrect use of the condom; in another fifth, failure of an IUD still in place; and in 13%, expulsion of an IUD (primarily the Chinese stainless steel ring).

Safety of existing family planning methods

Family planning methods, like vaccines, are used by large numbers of mostly healthy people. To prevent an unwanted pregnancy, nearly 600 million healthy people use some form of family planning method today. Not surprisingly, the discovery of damage to health from any of these methods may assume dramatic proportions.

An important part of HRP's role is, therefore, to monitor the safety and effectiveness of all family planning methods available today, so that couples choosing a method or health officials wondering which methods to incorporate into their national family planning programmes can base their decisions on accurate information about the extent to which a given method is safe and fulfils its intended purpose.

The following section describes studies supported by HRP on the safety and efficacy of several widely used methods—implants, oral and injectable contraceptives, IUDs, vasectomy, and condoms.

The safety of implants

In the 14th century, European women seeking contraception are believed to have consumed drinks containing natural substances reputedly endowed with contraceptive properties—oils, fruits, grains, and even urine, mercury, arsenic, strychnine. But it wasn't until the mid-20th century that the first synthetic oral contraceptive, "The Pill", appeared on the scene.

The pill, which contains a combination of two synthetic hormones—a progestin, which acts like the natural hormone progesterone, and an estrogen—is used today by nearly 80 million women in the world, making it the third most popular method of contraception for women after female sterilization (187 million users) and IUDs (130 million). The main drawback of these combined oral contraceptives is that they must be taken daily, a drawback that over the past half-century has fuelled a sustained quest by researchers to find alternatives that could be taken less frequently. That quest came up with products that could be taken monthly or every two or three months.

Meanwhile, in the late 1960s, researchers at the New York-based Population Council took another tack that has proved fruitful: they "packaged" a progestin into tiny silicone rubber rods that could be implanted under a woman's skin, usually on the inside surface of the upper arm, and that would continuously release the hormone over several years.

In 1983, Norplant, which releases the progestin levonorgestrel through six capsules over at least five years, became the first of these implantable contraceptives to receive the regulatory green light for human use. Today, some six-to-seven million women in about 60 countries are Norplant users. Second-generation implants with fewer capsules or rods have appeared in the past five years, bringing to about 10–11 million the total number of women using an implantable contraceptive.

Clinical trials of Norplant have documented its contraceptive efficacy: over five years of use, fewer than two in a thousand users are likely to have an unwanted pregnancy. The trials also showed the method to be safe, with severe adverse events extremely rare and an overall safety profile much the same as for other hormonal contraceptives. One major shortcoming of implantable contraceptives, however, is their tendency, common to all progestin-only contraceptives, to disrupt the normal vaginal bleeding pattern, a problem that occurs in a third to a half of users.

Clinical trials, however large, are conducted under well-controlled conditions. They may therefore not detect problems that arise under less well-controlled circumstances, particularly in developing countries. For this reason, in the mid-1980s HRP teamed up with the nongovernmental organization Family Health International and the Population Council to design a five-year post-marketing surveillance study aimed at determining the long-term contraceptive effectiveness and safety of Norplant in developing countries compared with IUDs and sterilization.

The study, which began in 1987, recruited over 16 000 women attending 32 family planning clinics in eight developing countries—Bangladesh, Chile, China, Colombia, Egypt, Indonesia, Sri Lanka, and Thailand. By the end of the five-year follow-up period, the study had accumulated 78 323 woman-years of observation.

The full results of the study, published in 2001,

confirmed the contraceptive effectiveness of Norplant (a 1.5% pregnancy rate over the five-year follow-up, vs 4.2% for copper IUDs and 13% for non-copper IUDs). The findings were also reassuring as regards safety: users of Norplant had about the same number of health problems as study participants who had chosen IUDs or sterilization. More specifically, Norplant users showed no increased risk of cancer or cardiovascular disease, including stroke. The study also confirmed the already well-documented link between Norplant use and enlarged ovarian cysts. Not unexpectedly, bleeding problems were relatively common with Norplant, consisting mainly of excessive menstrual bleeding and amenorrhoea. These problems prompted 13.7% of users to abandon the method over the five years, vs 6.4% of users of copper IUDs and 4.7% of users of non-copper IUDs.

Minor health problems, such as headache or migraine, weight gain, mood disturbances, itching, eczema, and acne, were also marginally, but significantly, higher among Norplant users compared to the other study participants not using a hormonal method of contraception. The study also revealed a weak but statistically significant association between use of Norplant and three relatively serious conditions—gallbladder disease, high blood pressure, and respiratory disorders. However, a similar association for gallbladder disease has been reported for users of combined oral contraceptives, and the study researchers believe that the weak link with high blood pressure and respiratory disease could be partly due to bias in the reporting of these problems. Norplant users experienced no increased risk of depression or connective tissue disease, including systemic lupus erythematosus (that had been postulated as a theoretical risk). Again, unsurprisingly, pelvic inflammatory disease was less common with Norplant than with IUDs and ectopic pregnancies were half as frequent. An unexpected positive finding of the study was a lower frequency of lower genital tract disorders, such as cervicitis, leukorrhoea and vaginitis, in Norplant users than in the other study participants.

Two new progestin implant devices have recently appeared. One is Jadelle, which was also developed by Population Council researchers and is identical to Norplant except for having two rods instead of six capsules releasing levonorgestrel. Jadelle has been registered in the USA and some European countries (for up to five years' use), and in Thailand and Indonesia (for up to three years' use) and is currently awaiting the outcome of registration applications in a further 30 countries or so. The second implant is Implanon, a single-rod system delivering the progestin etonorgestrel: made by the Dutch manufacturer Organon, it was first registered in Indonesia in 1998, and has since been registered in a further 12 countries.

In the summer of 2001, HRP brought to Geneva, Switzerland, a group of experts to review current evidence on implantable contraceptives for women. The 13 background papers prepared for this meeting were published in the January 2002 issue of the international journal *Contraception*. At this writing, the final report of the meeting is awaiting acceptance for publication in another journal. The gist of the report is that the implantable contraceptives Norplant, Jadelle, and Implanon are "safe and highly efficacious".

HRP has designed a trial due to begin in 2002 to compare Jadelle and Implanon for safety, efficacy, and acceptability. The trial will recruit 1000 women in 10–12 centres in each of WHO's six regions, and should end in 2005. It will take a close look at the frequency of bleeding problems and possible difficulties in inserting or removing the implants.

The safety of progestin-only contraceptives

Over 20 million women in the world today are believed to be using systemic contraceptives containing only progestins. These progestin-only products owe their popularity to their high degree of contraceptive efficacy (a 0.3–1% failure rate over 12 months of use) combined with a long duration of action that allows for relatively infrequent doses. They are delivered in the form of subdermal implants, such as Norplant (duration of action up to five years, see above), injectable products (up to three months), IUDs (see below), and vaginal rings. The main drawbacks of these progestin-only products is their tendency to cause highly irregular endometrial bleeding or even amenorrhoea (see Box 1.1).

Estrogen, in addition to its effects on the reproductive system, is known to enhance the uptake of calcium by bone tissue and in this way to ensure maintenance of normal bone density. Low estrogen levels, as in amenorrhoea and following the menopause, are associated with a decline in bone density and mass, and an increased risk of osteoporosis. To some extent, all hormonal contraceptives suppress the production of estrogen by the ovaries. Theoretically, though, this effect would be expected to be greater with contraceptives containing only progestin than with the combined progestin-estrogen products. In 1991, New Zealand researchers reported that in a group of women using depot-medroxyprogesterone acetate (DMPA)—the most popular progestin-only contraceptive, with 13 million users—bone density was 7% lower than in

Box 1.1. Endometrial bleeding—back to basics

Over 20 million women use contraceptives containing, not two hormones, as in the pill, but just one, a progestin, or progesterone-like synthetic hormone. The most widely used progestin-only contraceptive, with about 13 million users, is depot-medroxyprogesterone acetate (DMPA), an injectable product. Next in popularity, with some six-to-seven million users, is Norplant, the levonorgestrel-releasing implant (see text). Both Norplant and DMPA are effective and convenient because of their long duration of action.

Progestin-only contraceptives, however, have a troublesome downside: many users (50–90%, depending on the particular product) experience disruption of their normal menstrual bleeding pattern. Bleeding may be irregular, frequent, prolonged, or altogether absent (amenorrhoea). Although in the vast majority of cases this does not have any ill-effects on health, it can pose problems for women in their daily lives, particularly in societies that bar or restrict women from certain social and religious activities during menses. About 10–30% of women abandon their progestin-only contraceptive because of this problem.

No satisfactory treatment is available. Estrogens, such as those in the pill, can shorten episodes of menstrual bleeding and could theoretically in the long term reduce the efficacy of progestin-only products. But the major drawback of estrogens is that they have to be taken frequently, which cancels out the main virtue of the progestin-only products, namely, their ability to free users over a relatively long period of time from having to do anything about contraception.

HRP has backed several clinical studies on potential treatments of irregular bleeding.

One study, conducted in Chile, China, Dominican Republic, Indonesia, and Tunisia found little or no beneficial impact on bleeding problems from vitamin E and/or low-dose aspirin given to 480 Norplant users.

A second study, in Chile, found that the antiprogestin mifepristone significantly reduced the duration of bleeding episodes in 120 women using Norplant. The number of subjects, however, was too small to warrant any definitive conclusions. There are also concerns that an antiprogestin could reduce the contraceptive efficacy of the progestin (and one of the women using Norplant in this study did become pregnant after receiving mifepristone). And, finally, mifepristone is relatively expensive.

HRP has therefore shelved plans for further clinical trials on potential remedies for abnormal endometrial bleeding in users of progestin-only contraceptives. It is, however, continuing to support a series of basic research studies on the biological mechanisms underlying the problem.

Studies carried out in Australia and Indonesia have examined endometrial tissue biopsies from women using Norplant and have identified several basic mechanisms involving estrogen and progesterone receptors, vessel growth, and the stability of the endometrial tissue surrounding vessels. Follow-up studies are in progress to explore to what extent these findings could point to potential treatment targets.

a group of non-DMPA users. Subsequent studies have confirmed this bone demineralizing effect, which is more pronounced in long-term users, although apparently reversible on discontinuing the contraceptive.

Since little was known about whether other progestin-only contraceptives might have an effect on bone mineral density, in 1994 HRP launched a three-year study in Bangladesh, Brazil, China, Egypt, Mexico, Thailand, and Zimbabwe involving more than 2500 women, 30–34 years of age, who had recently begun to use either Norplant, DMPA, or combined oral contraceptives. The results of this study were published in 2000. They showed a significant but relatively minor loss of bone density in users of Norplant and DMPA, but the change appeared to be reversible after the method was discontinued.

In 1997, a second HRP-backed study began in Durban, South Africa, to explore whether and to what extent progestin-only contraceptives might affect bone mass among adolescent girls who had not attained their peak bone mass, as well as among older premenopausal women facing a natural decline in bone mass. The study, which involves over 400 women using either DMPA or another progestin-only injectable contraceptive, norethisterone enanthate, or combined oral contraceptives, will run to 2004.

The safety of intrauterine devices (IUDs)

With 130 million users, or 13% of the world's women of reproductive age, the IUD is the second most popular contraceptive method worldwide, after sterilization (187 million, or 19%). Much of the popularity of IUDs stems from their effectiveness—a 0.6–3.0% failure rate—combined with their long duration of action—from five to at least ten years for several IUDs currently on the market. Because of their long lifespans, IUDs require fewer visits to health providers, which means less expenditure of money, time, and effort—an asset much appreciated in developing countries.

One drawback of IUDs is their tendency to cause heavy, sometimes painful, menstrual bleeding. Other problems, although relatively infrequent, are expulsion of the device and ectopic pregnancy. A more serious problem is the almost twofold risk of pelvic inflammatory disease, which sometimes results in infertility. This risk is particularly high in women with a sexually transmitted disease. It is also greatest in the first few weeks after insertion of the IUD. In fact, the fewer insertions a woman undergoes, the lower her risk over her lifetime. The newer copper-bearing IUDs, for example, can remain safely in place for ten years, and possibly longer, and therefore carry a lower risk of pelvic inflammatory disease than the earlier copper-bearing or even the more recent hormone-releasing IUDs, that require replacement within a few years.

IUD technology has certainly come a long way since the first plastic IUDs (the Lippes Loop, Margulies Spiral, Saf-T-Coil, and others) appeared on the scene in the 1960s. Towards the end of that decade, researchers discovered that adding copper to the plastic produced an IUD that was more effective in preventing pregnancy and caused less frequent bleeding problems. The first copper-bearing IUDs—Copper-7, TCu-200, and Nova T—appeared in the early 1970s, but required replacement every two or three years. Further research at the end of the 1970s produced a second-generation copper IUD, carrying greater amounts of copper. Among the better known are TCu-380A, TCu-220C, and Multiload-375. These devices not only reduced the incidence of side-effects compared with previous IUDs but also had significantly lower failure rates.

Meanwhile, in the mid-1970s, HRP had entered the scene in response to the need for independent well-designed studies that would enable the scientific and public health communities to judge the relative merits of the plethora of devices available at the time and would help governments and nongovernmental organizations to make informed choices about which device to include in their family planning programmes.

In 1975–1976, HRP launched a study involving nearly 3000 women in nine countries, comparing three of the most popular IUDs at the time: the Lippes Loop, TCu-220C, and Copper-7. By 1979, the TCu-220C had broken from the pack, with lower failure rates and lower expulsion rates than the other two devices.

In the mid-1980s, however, the popularity of IUDs plummeted when researchers linked one IUD, the Dalkon Shield, to relatively frequent septic abortions (i.e. abortions or threatened abortions associated with pelvic infection) in the second trimester of pregnancy. This IUD, which was launched in 1971 in the USA, was withdrawn in 1974 in the face of litigation and adverse press coverage. The whole IUD market, however, became tarnished with the Dalkon brush. Asked to pronounce on the issue, in 1986 WHO convened a scientific group of experts, who concluded that "the use of IUDs in both developed and developing countries should continue to be supported as a reliable and safe method of reversible fertility regulation". The group also observed that the newer copper devices, notably Multiload-375 and TCu-380A, were, after two years' use, significantly better at preventing pregnancy than their predecessors. They also judged that the results that had become available from long-term HRP studies justified an extension of the lifespan of these copper IUDs from two to at least five years.

By this time, starting in 1979, HRP had launched five international multicentre studies on several IUDs, including Multiload-250 (predecessor to Multiload-375), Nova T, and a new type of hormone-releasing device, Progestasert, a progesterone-releasing IUD introduced in 1976. At the time of the 1986 WHO expert group meeting, the large multicentre cohort studies on TCu-220C (begun in 1974) and on TCu-380A (begun in 1979) were still running. After the meeting, HRP launched studies on Multiload-375 (introduced in 1985) and Flexigard, a frameless IUD consisting of six copper sleeves on a surgical nylon thread, introduced in the mid-1990s, and in 1989–1990 began a trial comparing Multiload-375 and TCu-380A.

By the end of 2001, three IUDs had emerged from the fray—TCu-380A, Multiload-375, and Mirena (or LevoNova), a levonorgestrel-releasing device intro-

duced in 1984—and HRP was still fielding three long-term international multicentre trials involving large cohorts of women.

One of these trials, on the TCu-380A, will continue up to 2004, by which time the evidence may warrant extending the device's lifespan beyond the currently approved ten years.

The second trial, that began in 1989–1990 to compare TCu-380A and Multiload-375, has been extended and now involves about 4000 women attending 19 centres in eight countries: after ten years, the results show TCu-380A to be just as safe as Multiload-375, but nearly twice as effective (Table 1.1) and far less expensive (up to an eighth of the price of Multiload-375). What's more, TCu-380A has an approved lifespan of ten years, vs only two years for Multiload-375.

A third HRP study, begun in 1993 to compare TCu-380A with the Mirena levonorgestrel-releasing IUD, is still continuing, with nearly 4000 women in 20 centres and ten countries. Interim results after six years' use, as of the end of 2001, show lower pregnancy rates for Mirena than for TCu-380A (0.6% vs 2.0%) but far more cases of menstrual problems (36% vs 11%) (Table 1.2).

In contraceptive efficacy, the operation is in the same class (less than 1% failure rate) as Norplant, combined (estrogen-progestin) injectable contraceptives, progestin-only contraceptives in the form of implants or injectable products, copper-bearing IUDs, and female sterilization. It is much simpler and safer, however, than female sterilization.

The main advantage of vasectomy—its permanence (reversal is only rarely successful)—is also its main drawback. Otherwise, the procedure, which has been used to control fertility for about the last 100 years, has no major untoward effects.

In the late 1970s, however, experimental results from a US study of ten vasectomized monkeys, stirred concerns about a possible excess risk of heart disease in vasectomized men. A study conducted in more than 10 000 men in the late 1980s and backed by the US National Institute for Child Health and Human Development laid these fears to rest. But new fears, this time of a link with prostate cancer, arose from three US hospital-based studies reported in 1990.

Results released during the past biennium from three HRP-backed studies are reassuring.

Table 1.1. The cumulative ten-year probability (as of June 2001), expressed as a percentage, of a woman discontinuing the TCu-380A and Multiload-375 intrauterine devices, by reason for discontinuing*

	TCu-380A %	Multiload-375 %	Significant (at 5%)
Total pregnancy	3.4	5.4	yes
Ectopic pregnancy	0.8	0.1	yes
Intrauterine pregnancy	2.7	5.3	yes
Expulsions	11.6	14.9	yes
Removed for medical reasons	29.9	30.3	no
For pelvic inflammatory disease	0.4	0.5	no
Lost to follow-up	11.3	10.6	no
Continuation rate	39.7	36.7	no

** covering a total of 9923 woman–years for the TCu-380A and 9794 woman–years for the Multiload-375*

The safety of vasectomy

About 40–50 million men living today—representing about 5% of couples of reproductive age—have undergone a vasectomy, or male sterilization procedure, putting this operation fourth in the world contraceptive popularity roster, after female sterilization (19%), IUDs (13%), and the pill (8%), and just ahead of the male condom (4%).

One study, funded jointly by HRP and Family Health International in China, the Republic of Korea, and Nepal—three countries where vasectomy is popular—found no significant excess risk of prostate cancer from vasectomy. The study involved 353 men hospitalized for prostate cancer and 879 control subjects hospitalized for reasons not related to cancer.

Table 1.2. The cumulative six-year probability (as of December 2001), expressed as a percentage, of a woman discontinuing the TCu-380A intrauterine device and the Mirena levonorgestrel-releasing device*

	TCu-380A	Levonorgestrel IUD	Significant (at 5%)
	%	%	
Total pregnancy	2.0	0.6	yes
Intrauterine pregnancy	1.8	0.6	yes
Ectopic pregnancy	0.1	0.0	no
Total expulsion	8.2	7.8	no
Complete expulsion	1.7	3.0	yes
Partial expulsion	6.6	4.9	no
Perforation	0.0	0.1	no
Pelvic inflammatory disease	0.0	0.3	yes
Menstrual reasons	10.7	36.2	yes
Amenorrhoea	0.6	23.8	yes
Reduced bleeding	3.0	11.2	yes
Increased bleeding	7.0	5.6	no
Pain	5.9	5.2	no
Hormone-related	0.1	4.9	yes
Other device-related	0.6	0.9	no
Total device-related removals	24.9	47.9	yes
Non-device-related removals	11.3	15.9	yes
Method continuation rate	66.6	43.8	yes

** covering a total of 7200 woman–years for the TCu-380A and 6139 woman–years for the Mirena*

Also reassuring were the findings of a study launched, again by HRP and Family Health International, in 1997 in New Zealand, a country with one of the world's highest vasectomy rates (Figure 1.2). This study, involving nearly 1000 men with prostate cancer and a similar number of age-matched control subjects, also found no increased risk from vasectomy.

The third study found 46 cases of prostate cancer in a cohort of nearly 60 000 vasectomized Danish men followed up since the early 1990s. Since 47 cases would have been expected from national incidence rates for Denmark, no excess risk could be linked to vasectomy, whatever the length of time since the vasectomy was performed and whatever the man's age at which the operation was performed.

Taken together, these three studies confirm the absence of any demonstrable link between vasectomy and prostate cancer.

Efficacy of existing family planning methods

In its final premarketing research and development stages, a new family planning method will run the standard gauntlet of clinical trials to determine its safety and efficacy. After regulatory approval, a system of postmarketing surveillance will enable health care providers to report on any flaws in safety that occur in everyday use of the method or product. Finding out how well a method actually performs in a vast, heterogeneous public in developing as well as developed countries, may require much more specific research covering a wide range of geographical and social contexts. The studies HRP is planning on the female condom illustrate this need.

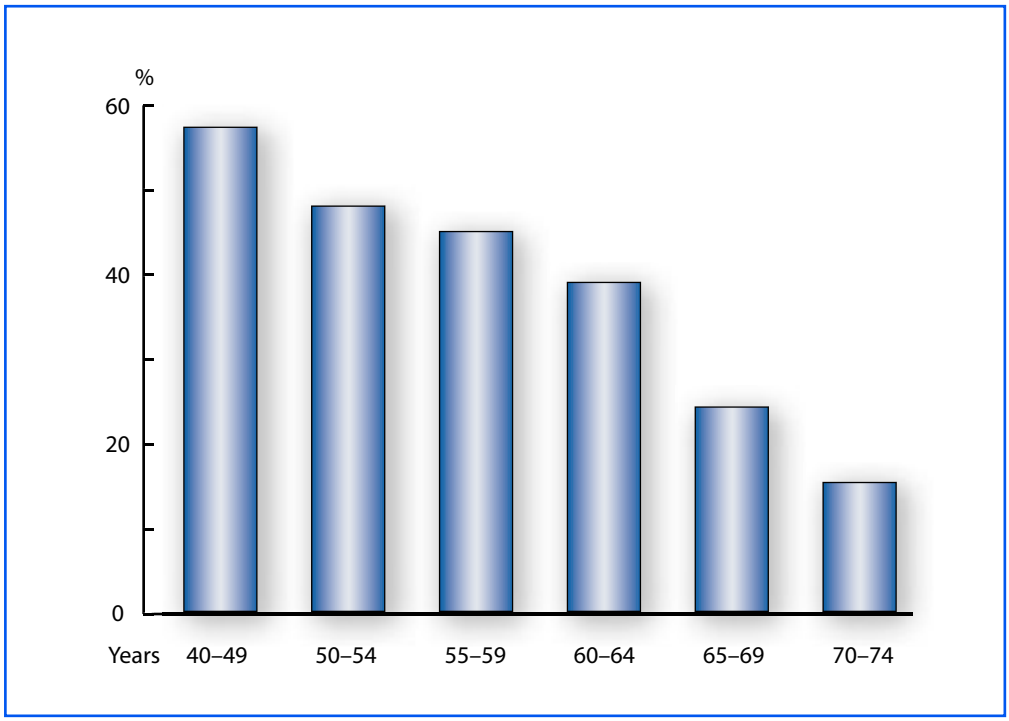


Figure 1.2. Percentage of men who have undergone vasectomy in New Zealand, by age-group

The effectiveness of the female condom

The female (or vaginal) condom is a strong, loose-fitting polyurethane sheath about 17 cm long with two flexible rings at either end: one ring lies within the condom in the vagina; the other remains outside the vagina and covers the vulva.

Since its introduction in Europe in 1992 and in the USA the following year, the female condom has become increasingly popular. The Female Health Company, in London, United Kingdom, manufacturer of Reality, the only female condom on the market, has sold about 30 million of its female condoms in over 45 countries and is currently selling well over four million a year, compared with just over one million four years ago.

Unlike its male counterpart, the female condom can be inserted and worn several hours before intercourse. However, the female condom is much larger than the male condom and some women complain that it is unattractive, difficult to insert, or noisy and hard to keep in place during intercourse. It certainly costs much more—62 US cents for bulk purchases vs 3 US cents for the male condom.

The efficacy of the female condom in preventing pregnancy has been documented in three studies conducted in developed countries: it is roughly as effective as the male condom (failure rate over 12 months 5–21%, depending on how carefully it is used, vs 3–14% for the male condom). Considerable hope is being pinned on the female condom for its promise in preventing transmission of sexually transmitted infections, particularly HIV: laboratory research has shown the female condom to be impermeable to bacteria and also to HIV.

Altogether, though, solid clinical evidence, particularly from field studies in developing country settings, is still lacking regarding the effectiveness of the female condom in preventing pregnancy and sexually transmitted infections. HRP, therefore, is planning two studies to provide the needed evidence.

- One study will compare the contraceptive effectiveness of the female condom with the male condom in women attending family planning clinics in China, Nigeria, Panama, and South Africa.

- The second study will compare the two condoms for efficacy in preventing sexually transmitted infections, notably gonorrhoea, chlamydial infection, and trichomonas vaginitis. These infections, in addition to being troublesome in their own right, are known to favour infection by HIV. This study, for which suitable sites are still being sought, will involve female sex workers, who are at high risk for these infections.

Expanding choice through new or better methods

Today, couples seeking a family planning method can choose from six broad categories of products or techniques: steroid hormones (in the form of oral pills, injectable preparations, or implants); IUDs; barrier devices (condoms, caps, or diaphragms); chemical products (spermicidal foams, tablets, or gels); surgery (ligation or partial or total removal of the fallopian tubes, for women; vasectomy for men); so-called traditional methods (such as withdrawal or periodic abstinence)—and various combinations of these approaches. Within each category, there may be several options.

Yet, overall, the choice is limited. These methods have indeed found wide acceptance in many parts of the world and their use has had a major impact on family planning around the world. Yet, all have drawbacks that, taken together, still limit the range of options available to couples. These drawbacks, which include concerns about safety of long-term use, convenience of use, reliability, and duration of effect, limit the acceptance and availability of the different products in the widely differing social, cultural, religious, and personal settings of users in many countries, particularly in the developing world.

At the same time, faith in the power of science and technology is fuelling an insistent call—among users, reproductive health care providers, and the reproductive health community at large—for better methods with fewer shortcomings and for an ever-wider range of family planning options.

As a scientific programme, HRP must respond to this call. This section describes how it has done so through its attempts, over the biennium, to improve existing methods and bring new methods to fruition.

Emergency contraception

Also called "postcoital" or "second-chance" contraception, emergency contraception has been available for more than a quarter of a century. Its use could prevent millions of unintended pregnancies and many induced abortions every year.

There are several reasons why women seek emergency contraception to prevent an unwanted pregnancy. The commonest (in 45–67% of cases, according to recent research) is because the couple did not use a contraceptive during intercourse. Next comes failure of a barrier method (in 25–48% of cases). At the end of list (in 7–14% of cases) comes a mixed bag of reasons, including failed coitus interruptus, vomiting of contraceptive pills, and rape.

Rape victims, in fact, were the first beneficiaries of modern emergency contraception, which began in the 1960s with the administration of high doses of estrogen. Side-effects, notably nausea and vomiting, were very common.

In the 1970s, the Canadian physician Albert Yuzpe introduced a method involving the administration of combined pills containing an estrogen (ethinyl estradiol) and a progestin (levonorgestrel) taken in two doses, the first within 72 hours of unprotected intercourse, followed by a second 12 hours later. This "Yuzpe regimen" has been the standard emergency contraceptive method for the past 30 years. Its efficacy, however, is limited (it prevents about 75% of pregnancies that would otherwise have occurred). And side-effects, including nausea and vomiting, breast tenderness, irregular bleeding, fluid retention, and dizziness, are relatively frequent. Over the past decade, therefore, HRP has explored other, potentially more effective and more trouble-free, approaches. One is levonorgestrel alone. Another is mifepristone, the antiprogestin originally developed in the 1980s for termination of pregnancy (see Chapter 4, pages 38–39).

In the late 1980s, HRP began a research effort aimed first of all at developing these compounds as emergency contraceptives and in recent years at refining them and making their use safer, more acceptable, and less expensive. The effort began with a study on the emergency use of levonorgestrel alone, taken in two 0.75 mg doses, the first within 48 hours of intercourse and the second, 12 hours later. The study showed significantly fewer side-effects, notably nausea and vomiting, with levonorgestrel than with the Yuzpe regimen.

Subsequent work over the past decade has confirmed the safety and efficacy of the levonorgestrel-only method. In a landmark multicentre, multinational study by HRP and reported in 1998, levonorgestrel alone, taken within 72 hours of intercourse, clearly proved its superiority over the standard Yuzpe regimen in both efficacy (preventing 86% of pregnancies that would have otherwise occurred) and tolerability.

To date over 80 countries have approved levonorgestrel alone for emergency contraception and the method is progressively replacing the Yuzpe regimen (Figure 1.3).

There is, of course, room for further improvement. Women would find levonorgestrel more convenient to use if they could take the second dose 24 hours after the first dose instead of 12 hours (which can sometimes mean taking the second dose in the middle of the night). It would be even more convenient if they could take a single 1.5 mg dose of levonorgestrel rather than two 0.75 mg doses.

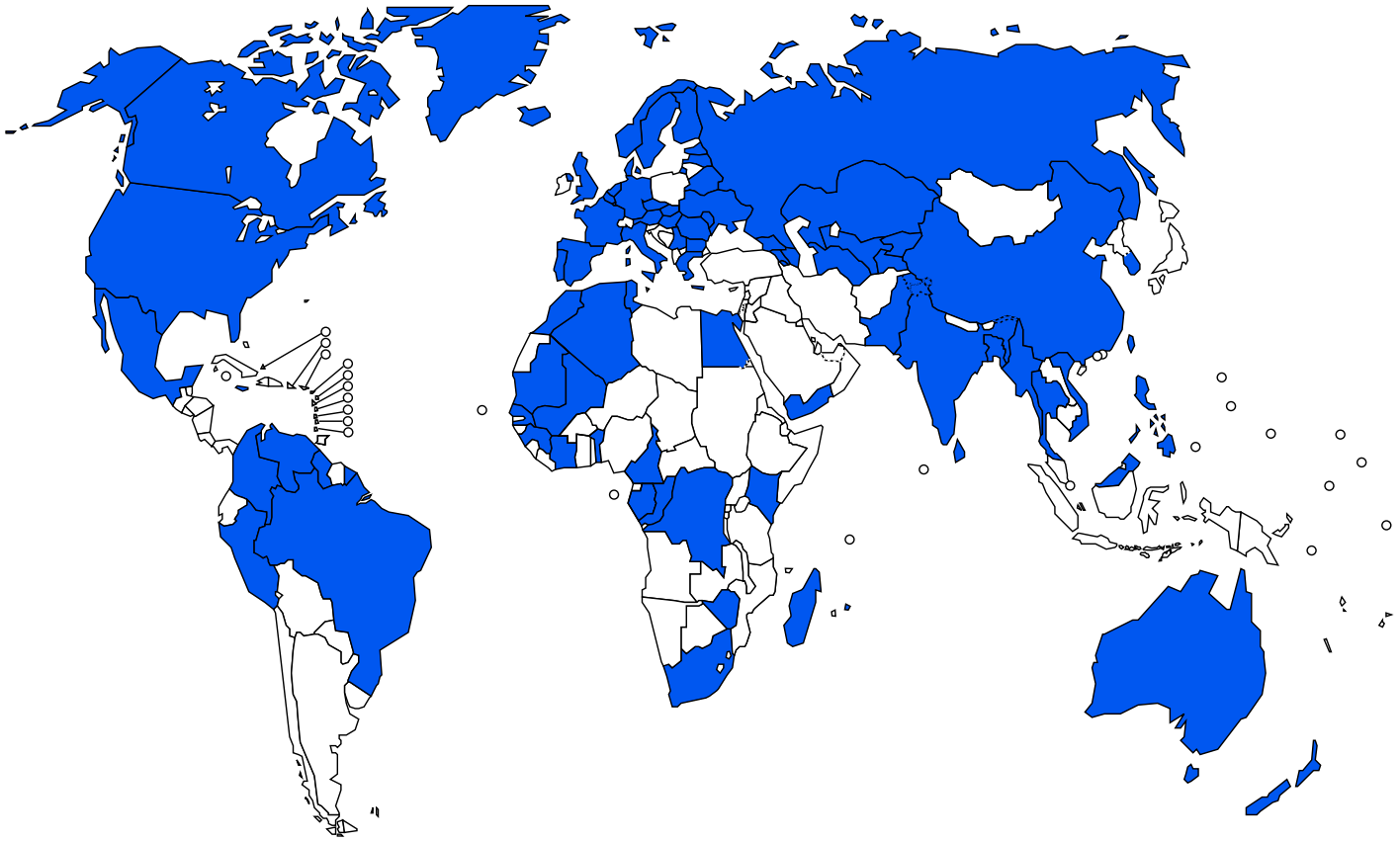


Figure 1.3. Countries using levonorgestrel alone for emergency contraception

HRP has therefore launched a trial in China to explore whether a levonorgestrel schedule with the second dose taken 24 hours, not 12 hours, after the first, would be just as effective. The trial will recruit about 2000 women attending five centres.

A second study has started in 2002 in Nigeria involving over 3000 women in seven centres to compare the 24-hour two-dose regimen with a single 1.5 mg dose of levonorgestrel taken within 72 hours of intercourse.

Mifepristone, too, has been the subject of several HRP-supported studies over the past decade. A study in 1999, for example, involving about 1700 women in six countries spanning four continents, found that a dose as low as 10 mg of mifepristone taken within 120 hours after unprotected coitus is as effective in preventing pregnancy as 600 mg (the dose used in two initial pilot studies) or 50 mg. Moreover, with the 10 mg dose, there was less disturbance of the menstrual cycle than with the higher doses and also a shorter delay before resumption of menstruation (i.e. before a user can be sure that the procedure has worked).

The efficacy of low-dose mifepristone was confirmed in another study begun in 1999 and involving more than 3000 women attending ten family planning centres in China. The study found 25 mg and 10 mg of mifepristone equally effective, with failure to avoid pregnancy occurring in only 1.1% of cases. The risk of pregnancy, the study showed, was 2.3 times higher in women treated more than 48 hours after intercourse than in those treated within 48 hours (Figure 1.4). In the light of these findings, Chinese regulatory authorities have approved the 10 mg dose for emergency contraception.

Taken together, the above studies on levonorgestrel and mifepristone confirm the superiority of either product over the Yuzpe regimen. Two questions remained: Is levonorgestrel as effective in one 1.5 mg dose as in two 0.75 mg doses, the second taken 12 hours after the first? How does levonorgestrel, in either dose, compare with mifepristone?

Both questions have now received answers, thanks to a major HRP study begun in 1998 and due to be published in 2002. The study,

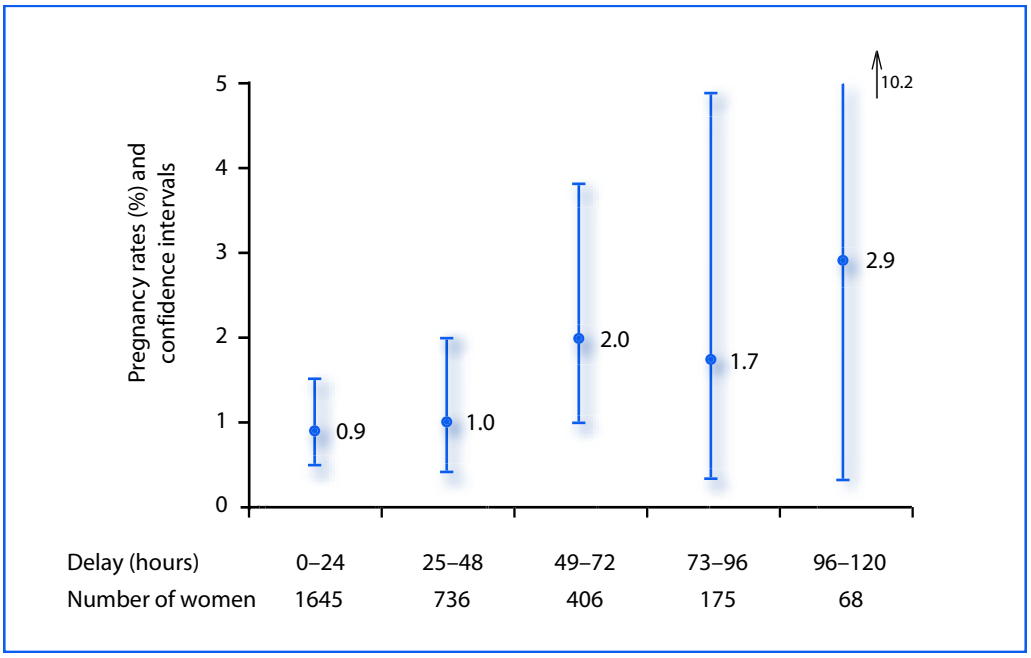


Figure 1.4. Effect on pregnancy rates of delay in taking 10 mg or 25 mg of mifepristone after unprotected sexual intercourse (data from a multicentre study in China)

which recruited more than 4000 women attending 15 family planning centres in ten countries—China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the United Kingdom—compared a single 1.5 mg dose of levonorgestrel with the 12-hour two-dose (totalling 1.5 mg) schedule and with a single 10 mg dose of mifepristone. The three regimens, given within 120 hours of intercourse, proved equally safe and equally effective in preventing pregnancy.

The findings of this study, which HRP scientists believe are likely to change the future practice of emergency contraception, imply that women need no longer take levonorgestrel in two doses: a single dose is enough. They also show that levonorgestrel and low-dose mifepristone are equally safe and effective. And thirdly, they suggest that either product can be taken up to 120 hours, or five days, after intercourse, rather than within 72 hours, as previously recommended (although failure rates tend to be higher among women taking levonorgestrel more than 72 hours after intercourse).

Since, as this study shows, there is little to choose from between levonorgestrel and mifepristone in safety, efficacy, and convenience of use, why would women prefer one over the other?

One reason why they might opt for levonorgestrel is

Box 1.2. Team work for implantation research

A basic research project initiated at the end of 1997 by the Rockefeller Foundation and HRP, and due to end in 2003, is exploring novel ways of preventing implantation of the early embryo in the endometrium and thereby allowing normal menstruation to occur. The aim is to develop a method, to be added to the current arsenal of contraceptive methods, that a woman could use once per menstrual cycle only, on an as-needed basis or as a back-up in case of failure of another method.

The six centres working on this project—in Australia, China, Germany, India, the United Kingdom, and the USA—are looking for molecules in the reproductive system, particularly the endometrium, that are specific to implantation and have potential as targets for substances capable of blocking them. A number of promising leads have been identified, although at this writing the research is still in an exploratory stage.

Box 1.3. Intrauterine devices—any time

For long-term use, IUDs are usually best inserted during a woman's menstrual period, when the cervix is more dilated than at any other time in the monthly cycle. In 1976 came the first report of an IUD being used postcoitally to prevent an unintended pregnancy. Since then, insertion of an IUD within five days of intercourse has been shown to be safe and 98–99% effective when used for emergency contraception. Clearly, for use as an emergency procedure, waiting for the "right" moment, i.e. the woman's period, is not an option. Would an IUD, however, not inserted during menstruation, be more liable to be expelled than if it were inserted during menstruation?

Findings released in 2000 of a multicentre study launched by HRP in China in 1998 and involving nearly 2000 women showed that the TCu-380A copper-bearing IUD inserted within five days of intercourse but outside a woman's menstrual bleeding period is just as effective—100% effective for all menstrual cycles in which it was used for emergency contraception in this study—just as safe and just as reliably lodged in the uterus as it is when inserted during a woman's period.

the fact, demonstrated in this study, that mifepristone delays ovulation more often than levonorgestrel, and in doing so, lengthens the menstrual cycle, delays resumption of menstruation, and increases the risk of a pregnancy after treatment if unprotected intercourse occurs within this lengthened cycle. (In the above study, delayed resumption of menstruation affected nearly twice the proportion of women taking mifepristone compared with those taking levonorgestrel.)

A second reason might be that mifepristone, unlike levonorgestrel, has acquired a reputation as an abortifacient (whereas in the low doses used for emergency contraception it simply prevents pregnancy): this reputation could limit its acceptability in countries where abortion is legally restricted.

Male hormonal contraceptives

Attempts to provide men with a reversible hormonal method of contraception as safe, as convenient, and as effective as the hormonal options available to women have not yet produced a marketable product, despite more than three decades of research. Fuelling that research has been the need to expand the options available to men beyond the three current options: condoms, withdrawal, and vasectomy.

HRP has been a major catalyst in the pursuit of a male contraceptive. Early work explored the use of an androgen, like testosterone, to suppress sperm production. Several testosterone derivatives, including testosterone enanthate, testosterone buciclate, and testosterone undecanoate, have been explored for their potential as male contraceptives.

In a large nine-country, 15-centre HRP study reported in 1996, testosterone enanthate showed a high degree of efficacy (1.4% one-year failure rate), but the variability of results between various ethnic groups and the need for weekly injections spurred a search for better approaches.

In 2000, an early (Phase II) trial of testosterone undecanoate in six centres in China gave very promising results (Figure 1.5). After one year, no pregnancies had occurred among the 290 couples meeting the long-term study criteria. The dosage regimen consisted of a 1000 mg injection followed by 500 mg every four weeks. Only minor side-effects occurred, consisting of weight gain, acne, and discomfort at the injection site.

HRP is supporting a large (Phase III) follow-up trial using the same dosage regimen but involving 1000 couples attending ten Chinese family planning clinics. If this study, which began in 2001, confirms the earlier results, Chinese authorities could approve the use of this hormone as a male contraceptive, making it the first male hormonal contraceptive to be introduced into routine use.

Even more encouraging results come from a Phase II trial in Indonesia of an androgen-progestin combination, consisting of testosterone undecanoate and DMPA, given to a total of 20 men from two centres. In this trial, the combination regimen produced a more complete and much more rapid loss of sperm production than the androgen alone (Figure 1.6). Most of the men participating in the trial complained of transient pain at the injection site. Not altogether unexpectedly, many participants also reported increased energy and sexual activity. Generally, the men found the dosage regimen acceptable, although it would probably be

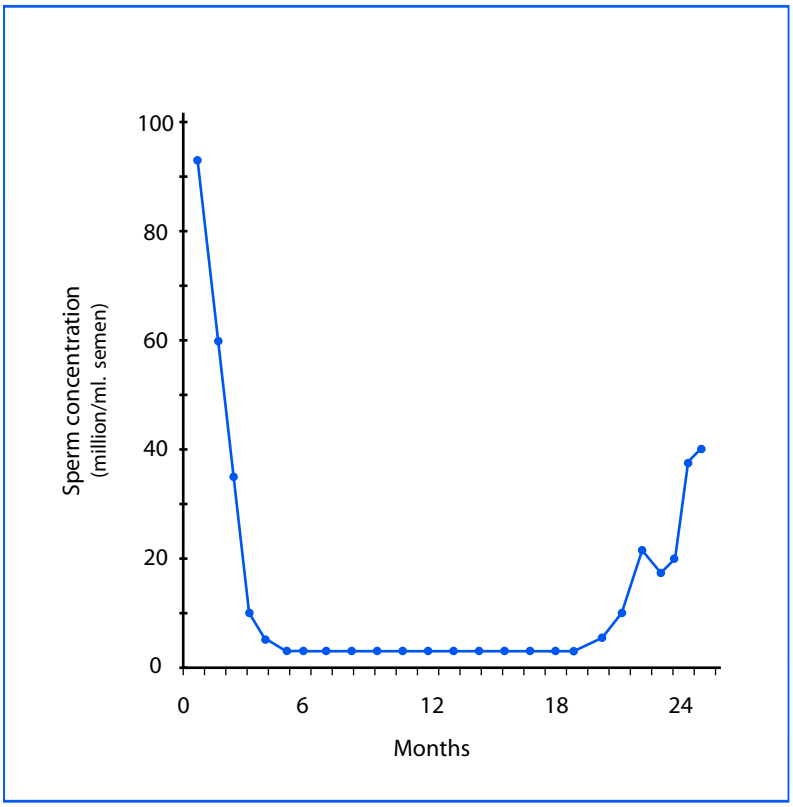


Figure 1.5. Sperm concentrations in men receiving testosterone undecanoate during a multicentre trial in China

complicated for health care providers, since an injection every six weeks of testosterone undecanoate would have to be juggled with an injection every 12 weeks of DMPA.

HRP plans to test a more easily administered regimen (500 mg testosterone undecanoate plus 250 mg or 150 mg DMPA given at eight-week intervals) in a larger trial that will recruit up to 64 men at various sites in Asia and that is due to start in 2002.

Immunocontraception for women

Within a few years of its creation in 1972, HRP began exploring the feasibility of developing an "anti-fertility vaccine" (or "immunocontraceptive", a term subsequently introduced to avoid confusion with vaccines protective against infection or disease).

Such a contraceptive could theoretically avoid many of the side-effects—nausea, irregular bleeding, and other menstrual problems, for example—associated with hormonal contraceptives. Moreover, unlike hormonal contraceptives, which are generally not recommended for women over 35 who smoke because of a greater risk of cardiovascular or metabolic diseases compared with younger women, an immunocontraceptive could theoretically be taken by all women at any time during their reproductive years.

In addition, the duration of contraceptive action of such an immunocontraceptive is expected to be at least six months and possibly a year—long enough to offer an advantage over the majority of hormonal contraceptives, which require a daily pill or injections at monthly or three-monthly intervals. Compared with IUDs, an immunocontraceptive would not carry a risk of expulsion, menstrual disturbances, or pelvic infection.

Several stages in the reproductive process in women involve molecules that could be used as a basis for immunocontraception. Two in particular—the sperm-ovum interaction and implantation of the fertilized ovum—offer molecular targets likely to elicit immune responses specific enough to avoid interference (through cross-reaction) with other biological processes or systems. One research pathway focuses on the jelly-like coat, or zona pellucida, around the ovum. Others are investigating proteins present on or in the precursor cells of the placental tissue. But the bulk of the research effort, including that supported by HRP, has focused on human chorionic gonadotrophin (hCG), the hormonal protein that the early embryo produces

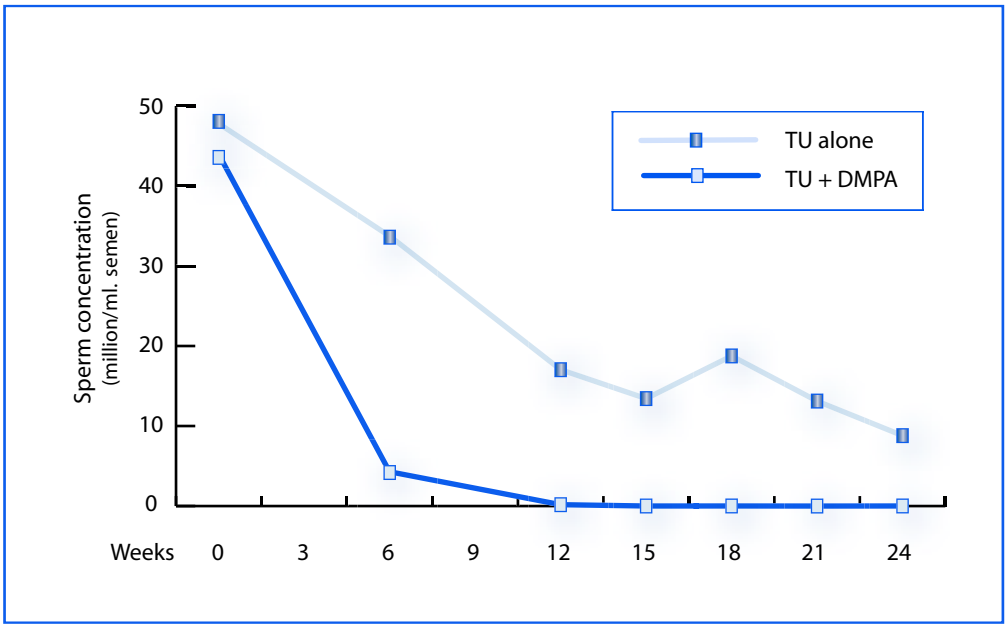


Figure 1.6. Sperm concentrations in men receiving testosterone undecanoate (TU), either alone or with depot-medroxyprogesterone acetate (DMPA), during a trial in Indonesia

in order to ensure its successful implantation in the endometrium.

Three anti-hCG vaccines have reached clinical testing. Two, both based on a relatively large fragment of the hCG protein, were developed 10–15 years ago: one, made by the Population Council, did not progress past the Phase I stage and the second, developed by India's National Institute of Immunology, reached Phase II. But both have since been put on hold. The third vaccine, based on a small fragment of the hCG molecule, is the focus of HRP research.

Between the mid-1970s and mid-1990s, after producing several prototype vaccines, this research finally put a candidate hCG vaccine into early clinical trials, only to come up against a roadblock in 1994 when participants in a Phase II clinical trial developed painful reactions at the injection site. A second candidate hCG immunocontraceptive, formulated quite differently, has shown promise in animal studies conducted during the biennium, and is currently awaiting regulatory approval by the Swedish national control authorities for clinical testing.

Chapter 2
Making pregnancy safer

Every year, about 210 million women become pregnant. An estimated 30 million, or about 15%, of these women develop complications, which are fatal in 515 000, or 1.7%, of cases. Of all health statistics, those for maternal mortality represent the greatest disparity between developing and developed countries: more than 99% of maternal deaths occur in developing countries, where a woman runs an average risk of dying from a pregnancy-related disorder about 250-fold greater than a woman in most developed countries.

More than 70% of maternal deaths are caused by just five conditions: bleeding after delivery (25% of deaths), infection after delivery (15%), unsafe abortion (13%), hypertensive disorders (12%), and obstructed labour (8%). In addition, about 20% of maternal deaths are due to diseases that are aggravated by pregnancy, such as malaria and cardiovascular diseases, not to mention HIV infection, which adds to the risk of maternal death. Severe conditions, such as chronic anaemia, fistulas, gynaecological infection, pyelonephritis, chronic renal disease, chronic pelvic pain, uterine prolapse, and depression, also affect large numbers of women (Table 2.1).

Many of the causes of maternal deaths and disabilities also jeopardize the survival and health of newborn infants. Every year, on average, nearly four million newborn babies die and millions more are disabled because of inadequately managed pregnancies and deliveries, and because of women's poor health and poor nutritional status. Neonatal infections account for 33% of deaths in newborn babies; asphyxia and trauma at birth, 28%; premature delivery and low birth weight, 24%; and congenital anomalies, 10%.

Tragically, most maternal and neonatal deaths and diseases are preventable. Yet, despite repeated calls for action over the past decade by target-setting international conferences and by international and nongovernmental agencies, there have been few signs of progress in turning around these distressing statistics.

Against this backdrop, in September 2000, WHO launched a *Making Pregnancy Safer* initiative, for which HRP is handling all research-related activities. The following paragraphs outline progress made in two areas covered by these activities: identifying effective practices that could improve maternal and neonatal health, and documenting the extent and major determinants of maternal mortality and morbidity.

Table 2.1. Causes of maternal and neonatal deaths, and principal interventions required

Causes of maternal deaths	%	Proven interventions
Bleeding after delivery *(postpartum haemorrhage)*	25	Treat anaemia in pregnancy. Skilled attendant at birth: prevent/treat bleeding with correct drugs, replace fluid loss by intravenous drip/transfusion if severe.
Infection after delivery	15	Skilled attendant at birth: clean practices. Antibiotics if infection arises.
Unsafe abortion	13	Skilled attendant: give antibiotics, empty uterus, replace fluids if needed, counsel, and provide family planning. Access to safe abortion where not against the law.
High blood pressure *(hypertension)* during pregnancy: most dangerous when severe *(eclampsia)*	12	Detect in pregnancy; refer to doctor or hospital. Treat eclampsia with appropriate anticonvulsive (magnesium sulfate). Refer unconscious woman for expert urgent assistance.
Obstructed labour	8	Detection in time and referral for operative delivery.
Other direct obstetric causes	8	Refer ectopic pregnancy for operation.
Indirect causes	19	Disease-specific interventions (malaria, HIV, etc.).

Causes of neonatal deaths	%	Proven interventions
Infections *(septic meningitis, pneumonia, neonatal tetanus, congenital syphilis)*	33	Maternal tetanus toxoid immunization, syphilis screening and treatment, clean delivery, warmth, support for early and exclusive breastfeeding, early recognition and management of infections.
Birth asphyxia and trauma	28	Skilled attendant at birth: effective management of maternal obstetric complications.
Preterm birth and/or low birth weight	24	Anti-malarials for women at risk during pregnancy. Attention to warmth, breastfeeding counselling and support, infection control and early detection and management of complications. Sexually transmitted disease treatment. Smoking cessation.

Improving maternal health

Preventing eclampsia

Pre-eclampsia is a disorder of pregnancy affecting several body systems, including the brain, liver, and kidneys. Its hallmark symptom is high blood pressure, its hallmark sign, an excessive amount of protein in the urine. Other symptoms include gastric distress, limb swelling (oedema), headache, and visual disturbances. About one in 200 patients with pre-eclampsia develops eclampsia, which is marked by convulsions and can be fatal without treatment. Together, pre-eclampsia and eclampsia affect about 10% of all pregnancies and account for about 12% of all maternal deaths. However, in the least developed countries, they can complicate up to an estimated 50 000 deliveries a year. In industrialized countries about 15% of preterm deliveries are induced because of pre-eclampsia/eclampsia.

Children, too, are at risk: a recent large study showed that up to 12% of babies born to mothers with pre-eclampsia/eclampsia die within the first month of life. Those who survive have an excess risk of impaired mental development, diabetes, and cardiovascular disease later in life.

To date, there is no sure way, other than by inducing early delivery, of treating pre-eclampsia and so preventing the convulsions of eclampsia. Traditionally, tranquillisers and anticonvulsant, anti-hypertensive, and anti-epileptic drugs have been used for this purpose, but there is little or no evidence of their efficacy in preventing eclampsia. Not without reason, the pre-eclampsia/eclampsia syndrome has been dubbed "the disease of theories", since so many hypotheses have flourished in the absence of convincing scientific data on its causes, diagnosis, and proper management.

Sixteen years ago, strong evidence emerged that magnesium sulfate can prevent recurrent convulsions in women with eclampsia. Since then, this inexpensive natural chemical has been used by obstetricians in certain countries, notably the USA, to treat women with pre-eclampsia. However, despite its relatively widespread use, conclusive evidence of its efficacy in preventing progression of pre-eclampsia to eclampsia has been lacking.

In 1998, HRP joined an international effort to conduct the largest clinical study yet of any drug with potential to treat pre-eclampsia . The study, known as the "Magpie trial"—from MAGnesium sulfate in Pre(I)Eclampsia—recruited 10 000 women with pre-eclampsia attending 175 hospitals in 33 countries: half the women received magnesium sulfate, half, placebo. The results, which will be published in 2002, show that magnesium sulfate nearly halved the risk of eclampsia and, at the doses used in the study, caused no harmful effects in the mothers or their newborn babies.

The Magpie trial confirms the efficacy of magnesium sulfate in treating pre-eclampsia and therefore in preventing the convulsions of eclampsia. An obvious follow-up question is how to prevent pre-eclampsia. A systematic review of the evidence has found that daily calcium supplements given to pregnant women could achieve this goal.

In 2001, in an attempt to clinch the issue, HRP launched a new trial on calcium supplementation in the prevention of pre-eclampsia that will involve 8500 women from seven countries.

A third development during the reporting biennium, emblematic of growing concern over pre-eclampsia/eclampsia, was the launch of a *Global Programme to Conquer Pre-Eclampsia/Eclampsia*. The programme will involve teams from the University of Pittsburgh, Pennsylvania, in the USA, the University of Oxford and the Cochrane Centre in the United Kingdom, the Mexico office of the Population Council, and the University of Natal in Durban, South Africa—all working under the overall coordination of HRP. For starters, the programme aims to implement in high-risk populations in developing countries those interventions known to be effective in managing severe pre-eclampsia/eclampsia. It will also conduct systematic reviews of current knowledge about the disorder and, on the strength of these reviews, will take advantage of HRP's worldwide research network to launch large-scale collaborative studies of promising leads for preventing and treating the disorder.

Identifying the most effective antenatal care strategy

In many developing countries, the number of visits and the different procedures that pregnant women undergo as part of a nationally recommended antenatal care programme generally follow the traditional pattern used in most industrialized countries. As a rule, this pattern requires women to submit to an impressively large battery of clinical examinations and laboratory tests crammed into about a dozen antenatal care visits. The trouble is, firstly, that not all the tests and procedures have been shown through rigorous study to be necessary to ensure a successful outcome to a healthy pregnancy. And secondly, this western model is clearly not the most cost-effective for developing countries.

To find out if a leaner, more rational antenatal care approach could do the job just as well and as safely, an HRP team decided to test clinically a model that provides only components scientifically validated for their efficacy in minimizing the risks of ill-health to mother and baby.

The team compared the proposed model with the traditional model in a study that recruited about 25 000 women attending 53 antenatal care units in Argentina, Cuba, Saudi Arabia, and Thailand. The women were randomly allocated to the traditional or the new model. The study found no demonstrable difference in babies' birth weight, severe postpartum anaemia, or urinary tract infection, between the two models. (The new model *was* associated with a marginally significant increased risk, amounting at most to 0.67%, of pre-eclampsia.) However, by cutting down the number of antenatal tests and procedures, the proposed new model was able to fit them into as few as four visits for women whose pregnancies were free of complications. (Women with specific needs and risks underwent additional tests and other procedures.)

Social scientists in the study team questioned a sample group of 1600 women plus all the antenatal care providers participating in the trial to find out how they perceived the new model. Responses

were positive, on the whole, although some women were concerned about the long intervals between visits. The main study also included a cost-effectiveness analysis, which found that the new antenatal care model generally did not increase, and in some sites actually reduced, the costs of antenatal care.

Based on the findings of this study, HRP has prepared a manual to help health providers, policy-makers, managers of reproductive health programmes, and interested agencies and organizations, to implement the new antenatal care model. The four countries that participated in the study have begun to introduce the model on a large scale, with other countries likely to follow.

Reducing postpartum haemorrhage

Despite the presence of a skilled attendant and proper management, about 3–4% of women will still experience postpartum blood loss of more than 1000 ml during the third stage of labour. Overall, every year, on average, 130 000 women bleed to death while giving birth. In about 90% of cases the cause is uterine atony, or failure of the uterus to contract properly after childbirth.

The hormone oxytocin, which increases uterine tone, is frequently used to prevent or reduce postpartum bleeding. However, because it can be administered only by injection, alternatives are being considered. One, the prostaglandin misoprostol, is inexpensive and easily administered.

An HRP study—the most comprehensive to date on this topic—launched in nine countries and involving nearly 19 000 women was completed in 2001. All the women were receiving "active management" procedures, such as traction of the umbilical cord, massaging of the uterus, and so on. The study found that in such women oxytocin was more effective than misoprostol in reducing postpartum blood loss.

Reducing unnecessary caesarean sections

Caesarean section is a surgical procedure to be used only in specific situations, such as when the life of mother or baby is in danger. In the past three decades, caesarean section rates have spiralled in many places, accounting, for example, for 21% of deliveries in Australia, 22% in the United Kingdom (vs 4% 30 years ago), 24% in the USA (4% 20 years ago), 40% in Chile and in Brazil, and 22–48% in Thailand (depending on type of hospital).

One proposed strategy for reducing these rates, at least in Latin America, is to require a mandatory second opinion for all intended caesarean sections. This strategy should, it was thought, reduce caesarean section rates by at least 25% without endangering the fetus, newborn baby or mother.

A joint HRP–European Union study, however, that started in mid-1999, with the participation of more than 130 000 women attending 34 hospitals in five Latin American countries, found that in most cases the second opinion simply endorsed the first opinion, so that, overall, the strategy failed to produce a substantial reduction in caesarean section rates.

The rising popularity of caesarean section is clearly a complex social and medical phenomenon, requiring a detailed comprehensive research effort. HRP is launching such an effort, which, among other things, should set an internationally agreed upper safety limit for caesarean section rates.

Measuring maternal mortality and its causes

How many women in the world die every year from causes related to pregnancy and childbirth? What are the most frequent causes of these deaths and what proportion of deaths does each cause account for? Where are most of these deaths occurring? How is the epidemiological pattern of maternal mortality and of its causes changing globally, regionally, and nationally? How does ill-health arising from pregnancy affect men and children?

Considerable work, in WHO and elsewhere, has gone into finding answers to these questions. But the data available are often only best estimates, based on partial information obtained from a wide range of different sources—hospital data, population surveys, national registries of births, deaths, and marriages, and so on—using a variety of methods and definitions.

In a systematic attempt to put the collection of statistical information about maternal morbidity and mortality on a much firmer footing, HRP has begun what is believed to be the first systematic review of epidemiological data on maternal mortality and morbidity in developing countries. The review, which will cover the period 1996–2001, will clearly indicate the sources for all data selected and will make it possible to identify gaps in information where sound sources are lacking.

Box 2.1. The best evidence at a click

What is probably the best, the most up-to-date, and the most useful information for practitioners of reproductive health care is available from HRP's virtual *WHO Reproductive Health Library*. From a single CD-ROM, users can access reviews of the latest research on a large range of reproductive health topics and find practical guidance on common problems they encounter in their daily work. The reviews, which are prepared by the Cochrane Collaboration, an international organization specializing in systematic reviews of health-related issues, come with commentaries and practical tips by experts.

Launched in 1997, the library, which is the result of a collaboration involving nine reproductive health organizations in eight countries, is updated annually. It is available in English and Spanish, and a Chinese version is in preparation. Subscribers in developing countries receive it free of charge; those in other countries pay a small fee.

During the 2000–2001 biennium, the third and fourth versions of the library appeared and were sent to about 7000 and 9000 subscribers, respectively. The fifth and latest version became available in May 2002 and will be distributed to at least 10 000 subscribers. About 80% of subscribers are physicians, health workers, and medical libraries in developing countries. The library is also a recommended component of the medical curriculum in at least four universities in three countries and has become a rich resource for postgraduate training courses in a growing number of countries.

Issue No.5 of the library contains 70 Cochrane reviews accompanied by 63 commentaries, 63 practical recommendations, and a wealth of useful information (web links to funding agencies, for example). Topics in the issue include the use of antiretroviral drugs to reduce mother-to-child transmission of HIV, population-based interventions against sexually transmitted infections, drug therapy for mild-to-moderate hypertension in pregnancy, prostaglandins for preventing postpartum haemorrhage, the optimal duration of breastfeeding, and so on. There are also two videos on *external cephalic version of breech presentation* and *companionship during labour.*

The *WHO Reproductive Health Library* is a key tool in HRP's efforts to ensure that reproductive health care in developing countries is based on the latest, soundest scientific evidence. HRP is testing a proposed method of exploiting the library's potential to fulfil this intended role. In this method, practitioners are asked to attend three workshops where they receive instruction about the use of evidence-based medicine generally and the library in particular. The method is being tested in a randomized controlled trial that began in 2001 and involves the staff and 40 000 women patients in 40 hospitals in Mexico and Thailand.

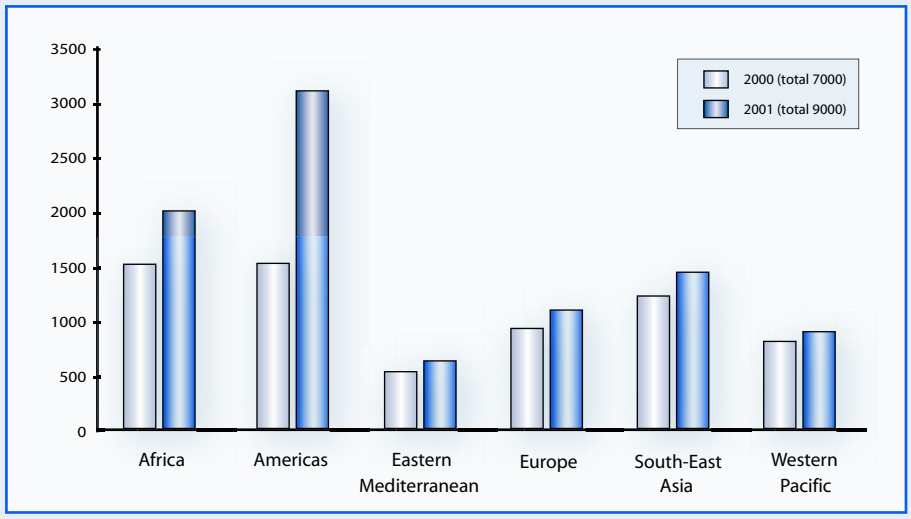


Figure 2.1. Number of subscriptions, by WHO region, to the WHO Reproductive Health Library *during the reporting biennium*

The entire process will involve four steps, of which the first two have been completed: step 1—the development of a protocol, including a universally applicable data collection form for gathering the basic information and collating it according to agreed criteria (age, country, type of study, quality assessment method used, and so on); step 2—the collection of data available from WHO and similar institutions and derived from large, well-designed, and well-run "gold-standard" population studies; step 3—achieving consensus among experts on how best to assess, collate, and analyse this heterogeneous information so that it is of greatest practical use and can be most easily updated; step 4—extension of the database to cover all sources of potentially pertinent information not yet covered by step 2.

A major outcome of this project will be a series of universally accepted, readily updated indicators of incidence, prevalence, case-fatality rate, relative risk, and consequences of ill-health related to pregnancy in developing country populations.

Chapter 3
Preventing reproductive tract infections

Reproductive tract infections, which include sexually transmitted infections (STIs), threaten health both directly and, in predisposing to HIV infection, also indirectly. Complications from reproductive tract infections can be serious. Pelvic inflammatory disease, for example, can cause infertility, ectopic pregnancy, and chronic pain. A mother with syphilis exposes her children to a risk of pneumonia, prematurity and low birth weight, and blindness. And human papillomavirus (HPV) infection is strongly linked to a risk of cervical cancer.

Some 340 million cases of curable STIs, caused mainly by bacteria, are estimated to occur worldwide every year, the majority in developing countries. In addition, every year several million *incurable* STIs occur, caused mainly by viruses—one of these viruses, HIV, is responsible for an estimated five million of these infections. In many countries, STIs are among the top five conditions for which men and women seek care and thus constitute a considerable drain on resource-strapped health services. (Tables 3.1 and 3.2)

Among the STIs, HIV is a primary public health concern. In many developing countries, the HIV epidemic is raging unchecked, particularly in sub-Saharan Africa, where in the past 15 years it has cut average life expectancy by nearly two years, to the current 47.5 years. In some areas of South Africa, HIV infects up to 50% of pregnant women.

Moreover, an estimated 600 000 children contract HIV infection every year, most of them from their mothers during pregnancy or at delivery or while breastfeeding. In the absence of any intervention, the rate of transmission of HIV infection from mothers to children can be as high as 35% in developing countries vs 15%–25% in developed countries. Antiretroviral therapy, caesarean section, and the avoidance of breastfeeding can cut the rate to less than 1%.

Over the 2000–2001 biennium, HRP has focused on obtaining data on the prevalence of reproductive tract infections and on identifying the social and behavioural determinants of these infections, as well as their impact on the lives of a wide range of populations and population groups in developing countries. The ultimate goal of HRP's work in this area is to develop affordable ways of preventing these infections.

Table 3.1. Estimated annual incidence of curable sexually transmitted infections worldwide for 1999 (the latest year for which reliable estimates are available)

Disease	New cases
Gonorrhoea	62 million
Chlamydial infection	92 million
Syphilis	12 million
Trichomoniasis	174 million
Total	**340 million**

Table 3.2. Estimated annual incidence and incidence rate of curable sexually transmitted infections in the 15–49-year age-group by region and worldwide for 1999 (the latest year for which reliable estimates are available)

Region	Total new cases/year (x 1000)	Incidence/1000 15–49-year-olds
North America	14 000	90
Latin America and the Caribbean	38 000	146
Western Europe	17 000	84
Eastern Europe and central Asia	22 000	107
East Asia and the Pacific	18 000	22
South and south-east Asia	151 000	158
Australasia	1 000	91
North Africa and the Middle East	10 000	61
Sub-Saharan Africa	69 000	257
Total	**340 000**	**112**

Source: Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections—Overview and Estimates. WHO, 2001.

Mapping the prevalence of reproductive tract infections

Most information about the prevalence of reproductive tract infections relates to developed countries, and then often to very specific population groups. Few epidemiological studies have measured the prevalence of these infections in developing countries. Those that have, have been concerned principally with infections due to *Chlamydia trachomatis, Neisseria gonorrhoeae*, and HPV. The other main causative organisms of reproductive tract infections have not received the attention they deserve. And some countries, notably China, have been almost completely left out of the epidemiology research agenda in this area.

To redress the balance, over the reporting biennium, HRP launched three prevalence studies in China. One is looking at chlamydial and gonococcal lower genital tract infections among married women in Sichuan; another, at trichomoniasis and gonorrhoea in women attending family planning clinics and in sex workers and their clients in Hefei and Shanghai; and the third, in Nanjing, is screening over 800 construction workers for trichomoniasis, chlamydial and gonococcal infections, and syphilis. A fourth study in China is under way to determine not only the incidence but also the causes of, and risk factors for, postabortion infections among 2000 women in Beijing.

HRP has also five studies under way in other countries of the Asia-Pacific region, where STIs are believed to be on the increase. One is looking at the prevalence of lower genital tract infection among 600 women in Yangon, Myanmar. A second, in Mongolia, is testing vaginal swabs from 400 girls for infectious organisms, notably *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis*, and *Candida*. A third is measuring the prevalence of syphilis, gonorrhoea, chlamydia, and bacterial vaginosis in 500 antenatal patients in Vientiane, capital of the Lao People's Democratic Republic. A fourth is determining the prevalence of occult chlamydial urethritis in 500 male and female adolescents in Surabaya, Indonesia. And the fifth is measuring the prevalence of reproductive tract infections in Ho Chi Minh City, Viet Nam.

Preventing reproductive tract infections

The means available today for preventing sexually transmitted infections are essentially condoms, both for men and for women. Dual-purpose contraceptive—microbicidal gels or creams applied vaginally would be an attractive alternative and are therefore the subject of intense research by several groups.

Condoms for men

Condoms protect not only against unintended pregnancy but also against the most common STIs, including HIV. The effectiveness of condoms, however, whether for single- or dual-purpose protection, depends very much, of course, on how assiduously people, particularly men, accept and use them. And that depends on how highly they rate the importance and convenience of condoms both as contraceptives and as barriers to infection, and in relation to other single-purpose contraceptive methods.

To find answers to both questions, HRP has launched a wide-ranging series of social science studies in countries where HIV is highly prevalent or threatens to become so in the near future.

A project involving six sub-Saharan African countries—Kenya, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe—has been probing the reasons why more people do not use condoms more often for dual protection. The project involves a total of 4000 men and women, and uses focus group discussions, in-depth interviews, and a survey questionnaire to explore their views. During the biennium, results became available from Kenya and South Africa. In both countries a major obstacle to greater use of condoms seems to be the fear among potential users that they will be perceived as having multiple partners and as being unfaithful to a regular partner. Other obstacles include opposition on religious grounds, male dominance in decision-making, and women's difficulty in convincing their partners to use condoms. Not unexpectedly, women, who do appear to appreciate the gravity of HIV infection and who say they do not have enough information about condoms, turn increasingly to methods of protection against pregnancy, such as oral or injectable contraceptives, that do not involve confrontation with their partners but nor do they protect against infection.

Men were the focus of three other in-depth, qualitative HRP social science studies, whose findings were reported during the 2000–2001 biennium.

In a study in Samsun Province, Turkey, the prevailing view among 123 married men was that condoms should be used for pre- or extramarital relations but not within a stable marriage. Attitudes to the withdrawal method of contraception were surprisingly negative, given the widespread use of this method in Turkey.

In a São Paulo, Brazil, study, involving 40 men spanning two generations, condoms were chosen mainly when other methods proved unsatisfactory.

Findings from a Shanghai, China, study in 203 men attending STI clinics suggest that improving STI services could increase the use of condoms among men.

Condoms for women

Public health authorities are pinning considerable hope on the female condom as a means of preventing STIs, particularly HIV infection (see also Chapter 1, page 17). A major advantage of the female condom is that a woman can use it without the cooperation of her partner. One drawback is its cost. In some countries, cost considerations prompt women to reuse the condom several times. The polyurethane material used to make the female condom is very resistant, but reuse without proper washing and disinfecting could increase the risk of infection.

Experts convened by HRP and UNAIDS to a June 2000 meeting stressed the lack of sufficient sound data to justify the conclusion that washing and disinfecting do not jeopardize impermeability of the condom to infectious organisms.

In response, HRP organized experiments at the National Reference Centre for Sexually Transmitted Diseases in Johannesburg, South

Africa, which were able to define the amount of soap and bleach needed to wash and disinfect a female condom without damaging it. WHO is preparing guidelines for reuse of the female condom based on these findings.

Microbicides and spermicides

Dual-purpose microbicidal–spermicidal products are also on HRP's research agenda. One in particular, a cellulose sulfate gel, has shown promising spermicidal and viricidal activity in *in vitro* experiments.

An early (Phase I) clinical trial found the gel to be slightly less, but certainly no more, irritating to the vaginal mucosa than other vaginal preparations. HRP is preparing an expanded Phase I trial on this product in three centres, two in Africa and one in India.

Human papillomavirus and cervical cancer

About 500 000 new cases of cervical cancer are diagnosed annually and some 230 000 women, particularly poor, multiparous women in developing countries, die each year from this disease. In fact, cervical cancer has become the commonest cause of cancer deaths among women in developing countries. Moreover, it has been clearly shown to be linked to persistent long-term infection with HPV.

In 1990, a comprehensive review undertaken by HRP of steroid hormone contraception and cancer concluded that taking oral contraceptives for more than five years is associated with a modest (1.3- to 1.8-fold) increase in risk of cervical cancer. The review noted that it was still unclear whether the increased risk reflects a biological link or is due to other factors, such as lifestyle or STIs, particularly HPV infection. Since 1990, several studies have shown an increased risk of cervical cancer in long-term users of oral contraceptives, but only in women with persistent HPV infection.

In 2000, findings were released of a case-control study begun 15 years ago in eight countries—Brazil, Colombia, Morocco, Paraguay, Peru, Philippines, Spain, and Thailand—and involving nearly 5000 women. The study, which was conducted by the International Agency for Research on Cancer, based in Lyon, France, with some support from HRP, confirmed the strong link between cervical cancer and HPV: 91% of the 2288 women in the study with a histologically confirmed diagnosis of cervical cancer had evidence of HPV infection, vs only 14% of the 2513 control subjects.

The study then looked at hormonal contraceptive use among the HPV-positive women. Those who had used hormonal contraception at any time in their lives had a 1.4-fold higher risk of cervical cancer compared with those who had never used hormonal contraception. (Although the study did not identify the types of hormonal contraception taken by the women participants, recruitment into the study had begun in 1985, when the combined low-dose pill was in wide use and was therefore likely to be the commonest type of contraceptive used by the women in this study.) The HPV-positive women with cervical cancer who had used the pill for two-to-four years showed no increased risk. However, those with a five-to-nine-year history of oral contraceptive use had a 2.8-fold higher risk and those who had been taking the pill for more than ten years had a four-fold higher risk.

These findings raised concerns about the long-term safety of combined oral contraceptives in women living in areas of the world where HPV is prevalent and where facilities for early detection and treatment of cervical cancer are meagre or non-existent.

In March 2002, HRP convened a meeting of experts, who recommended no change in prescribing practices for oral contraceptives. They gave several reasons for this recommendation:

- First, in countries where cervical cancer is most common, use of oral contraceptives is uncommon.
- Second, among women who use oral contraceptives, the number of cervical cancers linked to this use is likely to be very small.
- Third, for young, healthy, non-smoking women, the health benefits of oral contraceptive use (including a reduced risk of endometrial and ovarian cancer) far exceed the risk to health.
- Fourth, because parity appears to be a risk factor for cervical cancer, oral contraceptives, in preventing pregnancy, may actually reduce the risk of cervical cancer attributable to parity.
- Fifth, in places where adequate cancer screening services are not available, rates of disease and death associated with pregnancy are also usually high, and combined oral contraceptives are one of the few contraceptive methods widely available: the risk, therefore, of maternal mortality from failure to use contraception would be likely to far exceed any additional risk of cervical cancer.

Box 3.1. Preventing mother-to-child transmission of HIV—an expert view

A four-day technical consultation convened in October 2000 to lay the foundations for HRP's research activities on mother-to-child transmission of HIV came to these conclusions:

On antiretroviral drugs

- Short courses of antiretroviral drugs given to women at or just before childbirth can slash mother-to-child transmission of HIV by more than two-thirds: the benefits of these short-course regimens greatly outweigh concerns about exposure of children to any potential adverse effects from these drugs or about the development of resistance to them.
- Antiretroviral regimens used for prophylaxis and shown to be effective in well-designed clinical trials (such as Zidovudine alone or with Lamivudine, or Nevirapine alone) can be adopted for general use and should not be restricted to pilot projects or research.
- Preventing mother-to-child transmission of HIV should be part of the minimum standard package of care for women who are known to be HIV-infected.
- Research is needed on the prophylactic use of antiretrovirals and the potential for drug resistance, on their possible impact on the subsequent course and treatment of HIV disease, and on the subsequent risk of sexual HIV transmission.

On breastfeeding and HIV

- HIV-infected mothers should avoid breastfeeding when replacement feeding is acceptable, feasible, affordable, sustainable, and safe. Otherwise, they should breastfeed exclusively over the first few months after birth.
- Mothers should be encouraged to discontinue breastfeeding as soon as possible, taking into account local circumstances, the individual mother's situation, and any risks attached to replacement feeding (including risk of exposure to infections other than HIV and risk of malnutrition).
- Research is needed on the impact of different feeding patterns on mother-to-child transmission of HIV, overall infant morbidity and mortality, and birth spacing, and on the efficacy of antiretrovirals in preventing transmission of HIV through breastfeeding.

Preventing HIV infection

In addition to its work on the prevention of HIV infection through research on male and female condoms, and on microbicides, in the past three years HRP has begun a research programme on the prevention of mother-to-child transmission of HIV. Most HIV-infected children under ten have contracted the infection from their mothers. Mother-to-child transmission of HIV can occur during pregnancy (in 5–10% of cases), labour (10–20%), and breastfeeding (up to 20%) (Table 3.3).

In October 2000, HRP brought about 40 experts together to review scientific data on mother-to-child transmission and discuss ways of reducing it. A major goal of the meeting was also to lay the foundations for HRP's new research agenda on the topic. (see Box 3.1)

One research topic recommended by the experts was the possible influence of breastfeeding on mortality in HIV-infected mothers. This recommendation stemmed from the finding of a study conducted in the mid-1990s in Nairobi, Kenya, which revealed a three-fold higher mortality rate within two years of delivery among breastfeeding HIV-positive mothers compared with HIV-positive mothers giving replacement feeding to their babies. The reasons for this increased mortality are not clear.

Table 3.3. Rate (%) of mother-to-child transmission of HIV in relation to breastfeeding

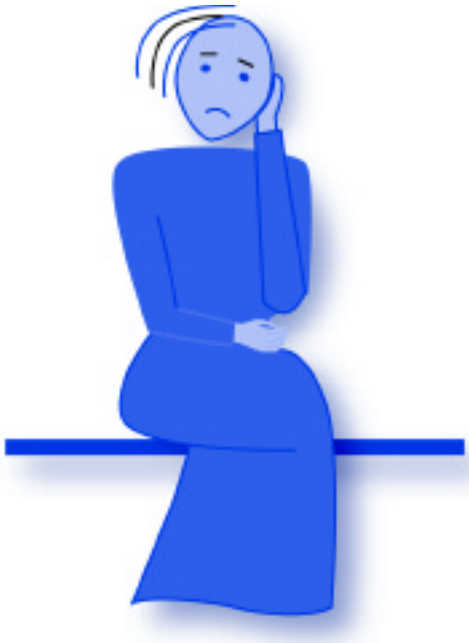
Timing	No breastfeeding	Breastfeeding for 6 months	Breastfeeding for 18-to-24 months
During pregnancy	5–10	5–10	5–10
During labour	10–20	10–20	10–20
During breastfeeding			
Early (first 2 months)		5–10	5–10
Late (after 2 months)		1–5	5–10
Overall	15–30	25–35	30–45

Source: De Cock et al., JAMA, March 1, 2000.

In an effort to clarify this finding and to assess the risk of maternal mortality in relation to different infant feeding patterns, HRP has been working over the biennium in close collaboration with a team from the US National Institute of Child Health and Human Development and the University of Bordeaux, France, on a meta-analysis of completed studies of mother-to-child transmission of HIV. The results of this work should become available in 2002.

The risk of an HIV-positive mother transmitting the virus to her child while breastfeeding depends on a number of factors, such as duration of breastfeeding, the mother's state of health, and breast condition. Evidence is emerging that an important factor could be the way the child is fed—by breastfeeding alone? breastfeeding plus other foods? and in what quantities? Studies seeking to identify which specific infant feeding pattern might be linked to the lowest risk of HIV transmission are beginning to proliferate. The problem is that different studies tend to use different sets of variables, with different definitions and terms for each variable.

In an attempt to impose some order on this growing heterogeneity and facilitate comparison of the findings of the different studies, HRP, in collaboration with other agencies and research groups, has devised a tool that allows all studies to collect the same essential "core" data, use the same methods to analyse the data, and report their findings using standard definitions. The tool proposes definitions of the different infant feeding patterns and a questionnaire with a minimum number of questions designed to elicit the core information that all studies on the topic should obtain from study subjects. The ultimate aim is to provide public health authorities with guidelines on infant feeding patterns that are least likely to favour HIV transmission. A paper describing the tool in detail was published in 2001 (*Statistics in Medicine, 2001;* ***20****:3525–3537*).



Chapter 4
Preventing unsafe abortion

Every year, on average, about 210 million women throughout the world become pregnant. About 40–50 million of these women resort to abortion, 30 million of them in developing countries. Of the 40–50 million abortions performed annually in the world, 20 million are thought to be unsafe, i.e. carried out by people lacking the necessary skills or in a setting lacking the minimum medical standards, or both. About 90% of unsafe abortions are performed in developing countries. Altogether, in an average year, unsafe abortion is believed to result in the death of about 80 000 women and in disability in a further five million women.

An unintended pregnancy is the reason why most women resort to abortion. The commonest causes of an unintended pregnancy are lack of access to, or failure to use, a contraceptive method and failure of the method itself. Forced sexual intercourse and male dominance in matters of sexuality and reproduction may be indirectly involved in many cases.

Since its inception in the 1970s, HRP has been generating and synthesizing scientific data on the determinants and consequences of abortion, especially unsafe abortion. To this end, it promotes biomedical research aimed at devising better methods of abortion and epidemiological research aimed at assessing the obstetric sequelae of non-surgical abortion and the link between induced abortion and the outcome of subsequent pregnancies.

During the 2000–2001 biennium, results became available from a series of large-scale clinical trials designed to identify the best drug regimens, including the lowest possible doses and the best routes of administration, needed to achieve safe yet effective non-surgical abortion.

The biennium also saw the release of findings from social science studies on the frequency of abortion, on the reasons why couples choose abortion rather than

contraception, and on how health care providers view the decriminalization of abortion in countries where abortion is legally restricted.

Safe abortion everywhere—without surgery

About 25–30 million of the annual abortions performed worldwide every year are done so in relatively safe conditions. But even safely performed surgical abortion carries some risks, albeit minor: injury to the cervix or uterus, haemorrhage, incomplete evacuation, and pelvic infection are possible complications. Medical, or drug-induced, abortion appears to offer a generally safer alternative to surgical abortion for first- and second-trimester pregnancies.

In the 1970s, HRP began a programme of research on the development of a medical method of terminating pregnancy. The programme began by testing the use of prostaglandins alone for terminating early pregnancy, but the prostaglandin compounds available at the time—sulprostone, gemeprost, and meteneprost—were effective only at such high doses that they produced unacceptable side-effects. When the antiprogestin mifepristone became available in the early 1980s, HRP researchers found it was not effective enough to be given alone. Used, however, in conjunction with sulprostone, gemeprost or misoprostol (a prostaglandin that appeared in the late 1980s), mifepristone showed great promise as an alternative to surgical abortion. What has become the standard sequential regimen consists of an oral dose of 200 mg or 600 mg of mifepristone (or six 25 mg doses, in China), taken up to the seventh week of pregnancy, followed 36–48 hours later by two 0.2 mg tablets of misoprostol or a 1 mg vaginal dose of gemeprost. This regimen is now used routinely in China, Israel, Tunisia, the USA, and most European countries (in Sweden and the United Kingdom, it is used in women up to nine weeks pregnant).

Since the early 1980s, HRP has been engaged in a sustained research effort, ultimately involving more than 25 centres spanning the five continents, to find the best regimens, including the lowest possible—and thus the least expensive—effective doses to be used for the two compounds, mifepristone and a prostaglandin, of the sequential regimen. An initial study, conducted in the early 1990s as part of this effort, showed that a 200 mg dose of mifepristone was just as effective as 600 mg.

During the 2000–2001 biennium, a further eight multicentre, multinational studies on different drug regimens for medical abortion were completed, are still under way, or were begun (see Box 4.1).

The dynamics and determinants of abortion

Family planning and preference for male babies

Since the mid-1970s, Bangladesh has witnessed a steep rise in the proportion of couples using contraception—from less than 10% to about 50% today. Despite increasing contraceptive use, however, over the past six-to-seven years the total fertility rate in the country has remained relatively unchanged, at about 3.3 births per woman (over her lifetime).

An HRP-backed study in the district of Matlab (population about 500 000), in south-eastern Bangladesh, examined the extent to which couples' preference for male babies could be preventing a further decline in fertility through an impact on contraceptive use and on recourse to abortion—two of the most critical factors that determine fertility rates.

The study chose the Matlab district for two reasons: Studies conducted in the district over the past two decades have produced what is today arguably the largest and most comprehensive population dataset in the developing world. It is also the site of a project that since 1977 has integrated family planning activities within the district's maternal and child health care programme, so that detailed information is available about reproductive status and contraceptive use among couples in the district. Interestingly, in the project area, which covers about half of the district, contraceptive rates over the past two decades have risen to 67% of the population, compared with only 45% in the non-project half of the district. However, over the same period, abortion rates have also risen in the project area, by about 50%.

Preference for sons among Matlab couples, the study showed, did not curb contraceptive use. However, it could partly explain the rise in recourse to abortion. As the fertility rate fell, the study showed, there was an almost linear rise in preference for male children. One reason for this could be that with falling fertility rates, couples had to achieve the desired number of male children—usually two—within a smaller overall number of children. For reasons not entirely clear, they prevented further births by resorting to abortion rather than contraception.

To reduce couples' preference for sons and their recourse to abortion, health policy-makers should, according to the study investigators, make every effort to improve the status of women—and thus of female children. At the same time, family planning services should encourage couples to place less reliance on abortion and more on family planning.

Box 4.1. Smaller is better for medical abortion

The highly effective sequential mifepristone–prostaglandin regimen used in an increasing number of countries for non-surgical abortion consists of a 200 mg or 600 mg oral dose of mifepristone followed two or three days later by an oral or vaginal dose of a prostaglandin. In its quest to identify the lowest effective dose—and thus the most readily tolerated and least expensive—for this regimen, HRP has over the past decade launched a series of large-scale clinical trials, outlined below, involving nearly 6000 women in over 20 countries.

A trial in 1224 women less than 57 days pregnant attending 13 centres in 12 countries compared 50 mg vs 200 mg of mifepristone followed by 0.5 mg vs 1.0 mg of gemeprost. The lowest dose, i.e. 50 mg of mifepristone followed by 0.5 mg or 1.0 mg of gemeprost, was inadequate for medical abortion.

A trial involving 896 women 57–63 days pregnant from ten centres in eight countries compared 200 mg vs 600 mg of mifepristone followed by 1 mg of gemeprost and confirmed that the smaller dose was just as effective as the higher dose.

A trial involving 1589 women in 17 centres in 13 countries compared 200 mg vs 600 mg of mifepristone followed by 0.4 mg of misoprostol taken orally. This study further confirmed the equal efficacy of the two mifepristone doses but showed that for women more than seven weeks pregnant a regimen using the oral, rather than the vaginal, route for administration of misoprostol is not effective enough for medical abortion.

A trial involving 2219 women attending 15 centres in 11 countries compared three different misoprostol regimens to be taken 48 hours after a 200 mg dose of mifepristone: 0.8 mg orally, followed a day later by 0.4 mg orally twice a day for seven days; 0.8 mg vaginally followed a day later by 0.4 mg orally twice a day for seven days; a single vaginal 0.8 mg dose. The trial showed that for women less than eight weeks pregnant all three regimens were equally effective. For women more than eight weeks pregnant the *exclusively oral* misoprostol regimen was less effective than the regimens using the prostaglandin vaginally.

A trial still under way in 2100 women up to nine weeks pregnant attending 14 centres in ten countries is exploring whether misoprostol can be taken 24 hours, instead of 48 hours, after a 100 mg vs a 200 mg dose of mifepristone.

A trial has also started in 2100 women up to nine weeks pregnant attending 11 centres in six countries to verify whether misoprostol used alone can safely and effectively terminate a first-trimester pregnancy. The study will examine four different misoprostol regimens, each using three 0.8 mg doses either sublingually or vaginally at either 3- or 12-hour intervals.

A study in Hong Kong compared a 0.2 mg vaginal to a 0.4 mg oral misoprostol dose following a 200 mg dose of mifepristone for second-trimester medical abortion in 142 women 14–20 weeks pregnant. The study found no significant difference in efficacy, but 82% of the women preferred the oral route of administration.

Currently under way is a trial in 680 women 14–20 weeks pregnant on the use of misoprostol alone (0.4 mg vaginally or sublingually every three hours for up to five doses) for second-trimester medical abortion. This trial involves 12 centres in eight countries.

Medicine vs surgery

"Experience is the best teacher", as the saying goes. This was the principle behind an HRP study conducted in Tianjin, China, to find out which type of abortion, medical or surgical, women prefer and why. The study investigators interviewed 400 women, all of whom had had experience of both methods over the previous five years.

The women gave surgical abortion higher marks (Table 4.1) for five items: efficacy, rapidity, frequency of gastrointestinal symptoms, familiarity of doctors with the procedure, and short duration of bleeding. Medical abortion fared better on only two items, it caused less fear and it avoided anaesthesia. Nevertheless, 58% of the women said they would prefer the medical procedure for any subsequent pregnancy they might want to terminate and the same proportion of women said they would recommend it to others over the surgical method.

The investigators concluded from these findings that efforts should be made to enhance doctors' knowledge and skills about medical abortion and that research should focus on improving the efficacy of medical abortion and shortening the duration of bleeding associated with it.

Emergency contraception vs abortion

The increasing frequency of induced abortion over the past two decades among both married and unmarried women in Shanghai, China, is a cause for concern among the city's public health authorities. Yet, emergency contraception has been available, if not widely, over the past decade.

During the biennium, findings became available from an HRP study launched in 1997 to find out why more Shanghai women are not using emergency contraception. Investigators interviewed over 600 women attending a health care centre for the purpose of terminating their pregnancies. They found that 98% of the pregnancies in these women were unintended and of these, about two-thirds would have been suitable for emergency contraception. Altogether, nearly half (47%) of the induced abortions performed could have been avoided if emergency contraception had been more widely available.

One explanation for these figures is that only 29% of the women were aware of emergency contraception and among these women, less than 15% knew that an emergency contraceptive pill should be taken within 72 hours of intercourse. Most (86%) of the women said they would be willing to use emergency contraception to prevent future unwanted pregnancies. Women likely to use emergency contraception to avoid future pregnancies are, the study found, more likely to be under 25, unmarried, seeking abortion for the first time, and to have relied on condom use to prevent pregnancy. The typical woman less likely to use emergency contraception is more likely to be an IUD user, over 30, and to have a history of at least one abortion.

Table 4.1. Preferences between medical and surgical abortion among 400 women with experience of both methods, interviewed in Tianjin, China

	Medical abortion	Surgical abortion
Complete abortion achieved	95% of women	99% of women
Time taken to achieve abortion	more than 2 days	about 12 minutes
Abdominal pain, nausea, vomiting, diarrhoea	56% of women	39% of women
Tension, fear, stress	40% of women	58% of women
Women likely to recommend	58% of women	42% of women
Women likely to adopt for future pregnancies	58% of women	42% of women
Duration of bleeding	long	short
Practitioner familiarity with procedure	poor	good

Legal constraints

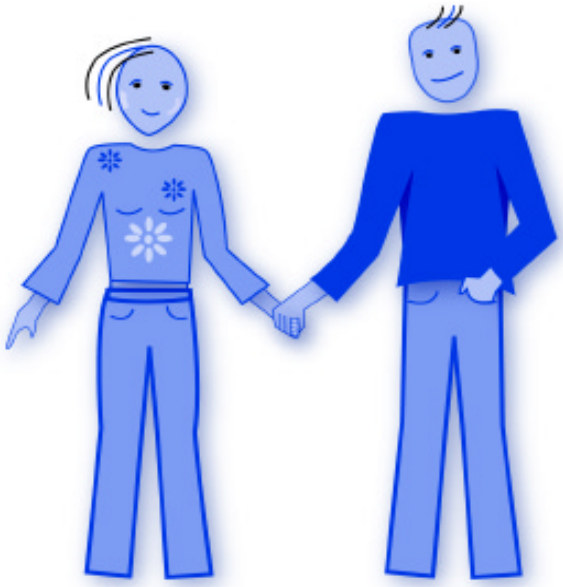
Obtaining reliable information about the frequency of abortion is understandably difficult in countries where the law is very restrictive about the procedure. As a recent HRP study in Colombo, Sri Lanka, showed, information obtained from health professionals can give a fairly accurate estimate about the proportion of women resorting to abortion.

Investigators interviewed 67 health professionals likely to have come across cases of abortion. From the information obtained in these interviews, they calculated an incidence of 40 abortions per 1000 women of reproductive age in the city. This estimate is consistent with that calculated for WHO's entire South-East Asia region and therefore validates to a certain extent the use of professionals as a source of information about abortion.

Health professionals were also participants in another HRP study, conducted in Argentina, where the law is restrictive about abortion. Responses from 450 Buenos Aires obstetricians and gynaecologists to a questionnaire showed that most of them (79%) believed that decriminalizing abortion would reduce the number of maternal deaths caused by unsafe abortion practices.

Physicians vs non-physicians

HRP is planning a study that will determine how safely and effectively non-physicians can perform vacuum-aspiration abortions in early first-trimester pregnancies compared with physicians. The study will look at abortions performed in Marie Stopes International clinics in South Africa and Viet Nam, where physicians and non-physicians legally perform these procedures, and will use the magnitude or frequency of complications as a measure of safety and efficacy.



Chapter 5
Exploring adolescent reproductive health

Adolescence is a time of transition, during which young people are no longer children but have not yet assumed the roles and responsibilities of adulthood. Today, social, economic, and political forces are rapidly changing the ways in which young people experience their adolescence. Adolescents are spending more time in school than they did in the past, experiencing puberty at a younger age, and marrying and having children later.

Clearly, the way adolescents experience this transitional period varies widely in relation to many factors, including the socio-economic and cultural context. As a group, however, adolescents have needs in regard to sexual and reproductive health that differ significantly from those of adults—needs that are poorly understood or poorly served in much of the world. Neglect of these needs has major implications for the future, since sexual behaviour during adolescence has far-reaching consequences for later life.

HRP's work in this area addresses this neglect. Its main focus is on promoting research on the sexual health of adolescents and related health service needs. During the 2000–2001 biennium, more than 30 research projects were under way or completed in more than 25 countries spanning a wide variety of social and cultural settings around the globe. Highlighted below are findings from studies that fall roughly into two areas: on the one hand, risky and unwanted sexual behaviour and its adverse consequences; on the other, health-seeking behaviour and obstacles to appropriate and timely care.

Risky sexual behaviour

Many young people engage in sexual activity before marriage, and do so at an early age, often with multiple, casual partners and often without any protection against pregnacy or STIs. Studies supported by HRP's initiative on adolescent sexual and reproductive health are exploring the factors underlying risky and safe behaviours among different groups of adolescents in various settings.

To date, few studies on sexual and reproductive health in adolescents have been conducted in the Eastern Mediterranean region.

A study recently launched in Syria is exploring awareness of, and attitudes to, reproductive health issues among male and female adolescents attending secondary school.

A study in Iran is looking at awareness of sexual health issues, sexual experience, and risky sexual behaviour in adolescent boys.

Plans are under way for a study in Goa, India, that will follow up adolescents aged 12–16 years over 18 months in order to explore their high-risk behaviours and the factors, including those relating to family life, that contribute to risky and to safe behaviour over time.

Adolescents in vulnerable settings

Several HRP studies have focused on vulnerable groups of adolescents in different settings.

In China, for example, there are 70–80 million migrant workers. Women account for 30–50% of this so-called floating population. About half of these women are under 25. To find out what they know about reproductive health, how they view premarital sex, contraceptives, and reproductive health services, and what experience they have of unwanted pregnancy and abortion, HRP conducted a study involving about 200 of these women, about a third of them married, living in five Chinese cities.

From focus group discussions and in-depth interviews the investigators learned that most of the young women considered premarital sex acceptable but were concerned about the social consequences of an unwanted pregnancy. Few of them reported having engaged in premarital sex. Most of the unmarried women had never used contraceptives and most of them did not know where to acquire them. Many of the women named fear of disclosure as an obstacle to seeking professional advice about contraceptives.

Overall, the investigators concluded that migrant women run a particularly high risk of unwanted pregnancy and unsafe abortion because of misconceptions about contraception, poor quality of professional care, and dominance of male partners in decisions about sexuality and contraception. The risk is compounded by the fact that, being migrants, these women are excluded from local health services, which are available only to residents.

Other studies are under way on young migrants and refugees in vulnerable settings in Cape Verde, China, Colombia, the Lao People's Democratic Republic, Myanmar, South Africa, Thailand, and Viet Nam. All of these studies are exploring the ways in which a vulnerable situation affects adolescents' high-risk behaviour and their ability to exercise choice. The findings should provide useful information for programmes aiming to protect these vulnerable adolescents from the adverse effects of their environments.

Unwanted or non-consensual sexual activity

For significant proportions of young females, and even males, sexual activity can be forced or coerced.

A study of sexual coercion in about 1000 adolescent students and apprentices in Ibadan, Nigeria, shows how they define and perceive sexually coercive behaviours. The young participants in this study identified 13 types of behaviour they viewed as coercive, including rape, unwanted touching, verbal abuse, forced viewing of pornography, and incest. Many had experienced one or more coercive incidents: *female apprentices* clearly fared worst, with over 45% experiencing unwanted touching and 19%, coerced sex; *female students* were only slightly better off, with over 40% experiencing unwanted touching and 19%, coerced sex. Interestingly, 9% and 7% of *male students and male apprentices*, respectively, reported forced sex experiences (Figure 5.1). Perpetrators of sexual coercion reported by females included a male friend or a known (or at least identifiable) adult male residing in the community; adolescent males also reported coercion by adult males in the community and some reported unwanted touching by a female friend or peer.

In a qualitative study among out-of-school adolescents in two rural wards of Magu district, in north-western Tanzania, both females and males acknowledged the practice of providing gifts and money to partners in return for sexual favours. In ten narrative workshops attended by 87 female and male adolescents, and in in-depth interviews with 81 adolescents, young males reported that they were only able to persuade partners to engage in sex by promising money or gifts. They perceived money and not romance to be the main reasons why out-of-school girls would consent to sex. Although several females in the study also acknowledged that recent sexual encounters had been accompanied by material gain, none admitted that this had motivated consent to sex. Rather, in group discussions and in-depth interviews, female participants noted that exchange of gifts was a symbol of a partner's love and commitment.

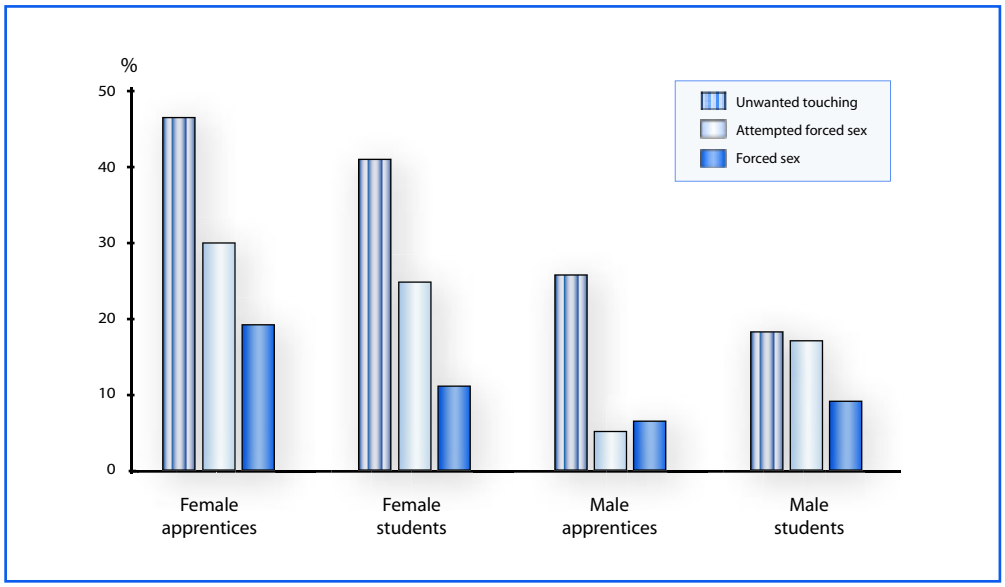


Figure 5.1. Percentages of adolescents reporting sexual coercion in a study in Nigeria

Consequences of risky sexual behaviour

A prospective study in Fortaleza, Brazil, explored the consequences of pregnancy in adolescence. It compared a group of 367 adolescents attending a health facility for antenatal care with a second group, of 125 adolescents, seeking post-abortion care. The adolescents were followed up at one and five years following the pregnancy. The study found that the adolescents who continued the pregnancy were more likely than those who opted for abortion to have dropped out of school as a result of the pregnancy. Yet, those who underwent induced abortion reported significantly lower levels of self-esteem, a difference attributed in part to the circumstances surrounding the unwanted pregnancy and in part to the difficulty of seeking an abortion in a setting in which the practice is legally restricted.

Obstacles to seeking care

A number of HRP studies have explored the obstacles young people face in obtaining appropriate and timely service relating to contraceptives and other sexual health matters. Some obstacles stem from within the community, particularly those affecting females, and include a fear that information about their sexual activity would be disclosed to parents and other members of the community. Other obstacles are linked to health facilities and include threatening attitudes on the part of health care providers, and fear of violation of confidentiality and privacy.

In a study in Guinea, West Africa, adolescents complained of long waiting times (reported by 42% of participants), lack of privacy and fear of being identified as sexually active by their elders (39%), poor rapport with a clinic counsellor (24%), dissatisfaction with quality of service (16%), and high fees (15%).

Adolescents' fears of disclosure were echoed by parents in a study involving eight centres in China. Focus group discussions with mothers and fathers indicated parental ambivalence: On the one hand, parents recognized that premarital sexual activity was common, feared its adverse consequences, and were in support of sex education for young people. On the other, they felt uncomfortable about discussing sexual matters with their adolescent children and were not in favour of providing young people with free access to contraceptive and abortion services.

Other studies showed that perceptions of youth concerning unfriendly providers are reinforced by the providers themselves.

Four studies in Asia detected a number of hurdles that providers encounter in attempting to cater for the sexual health needs of unmarried adolescents. In all four settings, providers

recognized that sexual mores are changing and that there is a growing need to provide information, counselling, and contraceptive and other services to unmarried youth. However, the attitudes and perceptions of the providers were ambivalent about serving unmarried youth.

A study in eight sites in China involving nearly 2000 providers found that up to 84% appreciated the need to provide information and services to unmarried university students but 45% were not willing to provide contraceptive services to these students and 74% said they would not provide contraceptive services to high (or secondary) school pupils.

In two sites in the Lao People's Democratic Republic, over one third of the 250 providers participating in a study reported difficulty in discussing contraception with unmarried youth, and attributed this to their own shyness and embarrassment but also to a lack of co-operation on the part of the adolescents.

In a study in northern Thailand, many of the 44 providers interviewed said they felt uncomfortable about discussing sexual issues with unmarried clients and were unwilling to take the time to gain their clients' confidence. They argued that young clients were "confused" about their problems and tended to "lie", and that these were obstacles to their receiving proper care.

In a study of about 400 providers in Myanmar, in-depth interviews showed that they recognized the need to provide services to unmarried youth but not the need to refrain from informing parents of their clients' visits.

Chapter 6
Cooperating with countries

Most developing countries aspire to self-sufficiency in meeting the health needs of their populations. Reproductive health needs, however, pose a special challenge because of the wide disparity between and within countries in people's needs for reproductive health services and also because of the diversity of cultural, religious, and economic factors that affect sexual behaviour and sexual relationships.

Countries are also diverse in their capacity to translate scientific information into health policies, to plan and implement health programmes, and to carry out the necessary research to fill gaps in knowledge and thereby improve the practice of reproductive health. In many countries, this research capacity has to be built; in others, it has to be enhanced.

Since it began operating in 1972, HRP has worked with countries to strengthen their capacity to undertake reproductive health research that is pertinent to their own needs and those of their regions, but also to the global research effort relating to reproductive health. This work has resulted in the creation of a network of more than 120 institutions, that have the capacity to conduct research and training in research, in nearly 60 developing countries (Figure 6.1). HRP sustains this network through a variety of grants (see Box 6.1) and through its regional advisory panels, which are made up of experts from each region, and which foster and monitor research and programme development within their respective regions.

Working with regions

HRP activities are under way in all six WHO regions, which HRP breaks down into four groupings: Africa and the Eastern Mediterranean, the Americas, Asia and the Pacific, and Eastern and Central Europe.

During the 2000–2001 biennium, 123 research centres in 59 countries participated in HRP activities (Figure 6.1). These 123 centres, of which 51 are officially designated WHO collaborating centres, together make up HRP's global research network. The biennium saw the launch or continuation of nearly 400 research projects begun or being conducted by centres participating in this network.

Figure 6.1. During the 2000–2001 biennium, 123 research centres in 59 countries (shaded in this map) participated in HRP activities and/or received some form of support from HRP. Together they make up HRP's global research network

Box 6.1. Grants for building research capacity

HRP has developed a system of grants, described below, that it uses to build and strengthen the capacity of developing countries to conduct research on reproductive health and to apply the findings of that research to policy and practice.

- *Long-term institutional development grant (LID)*—Renewable annually for up to five years, subject to satisfactory progress, this grant is HRP's main instrument for strengthening the research capacity of institutions. It offers a technical support package that provides training, expert advice, equipment, and other resources to support a research programme that meets a country's needs. The grant may be extended for a further five years if approved by an external panel of experts and the regional advisory panel for the region concerned.

- *Resource maintenance and capital grant (RMC)*—This grant aims to help maintain the capacity of an institution to respond to specific national research needs or to contribute to a global research activity.

- *Small grant (SSG)*—This is a relatively small grant awarded to an institution to enable it to overcome foreign exchange difficulties that could hinder its access to research resources (such as subscriptions to scientific journals or the purchase of laboratory supplies).

- *Research training grant (RTG)*—HRP's main mechanism for strengthening human resources, this grant enables scientists from a developing country to undertake training in institutions other than their own. Where such training leads to a higher degree, HRP encourages trainees to split their training period between their home country, a field site, and the host institution.

- *Re-entry grant (REG)*—When research trainees have completed their training under a research training grant, they are encouraged to apply for a re-entry grant, which enables them to apply their newly acquired skills to the design and implementation of a research project.

- *Grant for courses, workshops and seminars (CWS)*—Part of HRP's effort to build research capacity in developing countries is to provide institutions with financial support to hold courses, workshops, and seminars on topics related to research on reproductive health. This type of grant is usually given on a one-time-only basis, but can be renewed, depending on the nature of the activity and satisfactory performance by the recipient institution.

- *Competitive intraregional research (CIR) grant*—These grants are awarded to institutions to facilitate collaborative multicentre research on a topic of regional or national priority.

Altogether, during the biennium, HRP awarded research capability strengthening grants to 48 institutions (Table 6.1) and training grants to 24 individual researchers (Table 6.2).

Africa and the Eastern Mediterranean

A major focus of HRP's activities in the region is the strengthening of the capacity of institutions to conduct research relevant to the needs of the region and its individual countries. During the 2000–2001 biennium, HRP collaborated with 35 institutions or research groups in 23 countries in the region.

Among its research training activities during the biennium, HRP organized several workshops and short training courses, and awarded six grants to enable researchers to study abroad. HRP support also went into an M.Sc. course in biostatistics held in Nigeria and into several training courses for professional and technical staff from national institutions, and for service providers. The workshops and courses were on a variety of topics—designing research protocols and implementing research (in Tunisia and Guinea), semenology (South Africa), development of a regional reproductive health directory (Burkina Faso and Egypt), ethics and reproductive health (Egypt and Zimbabwe), and scientific writing (Tunisia and Uganda).

Table 6.1. Numbers of HRP grants awarded to institutions during the 2000–2001 biennium, by region and type of grant

Type of grant	Africa and Eastern Mediterranean	Americas	Asia/Pacific	Eastern and Central Europe	TOTAL
Long-term institutional development grant	5	2	7	-	14
Resource maintenance and capital grant	7	7	4	-	18
Small grant	16	0	0	-	16
TOTAL	**28**	**9**	**11**	**0**	**48**

Table 6.2. Numbers of researchers who received individual HRP research training grants during the 2000–2001 biennium, by sex, research area, and region

Area of training	Africa and Eastern Mediterranean		Americas		Asia/Pacific		Eastern and Central Europe		TOTAL
	F	M	F	M	F	M	F	M	
Epidemiology	-	2	2	-	1	3	-	-	8
Lab-based microbiology and molecular biology	-	-	-	-	3	1	-	-	4
Clinical	-	1	-	1	1	2	-	-	5
Social sciences	-	-	-	-	1	1	-	-	2
Biostatistics	1	1	-	-	-	1	-	-	3
Research methodology/management	-	1	-	-	-	1	-	-	2
Subtotal female/male	1	5	2	1	6	9	0	0	
TOTAL	**6**		**3**		**15**		**0**		**24**

Furthermore, HRP teamed up with several organizations and institutions to provide financial and/or technical support for courses on epidemiology and applied statistics (in Senegal), gender and reproductive health (Kenya and South Africa), cervical cancer (Nigeria), and reproductive health in the context of health sector reform (Senegal).

Some highlights of activities undertaken in the region during the biennium:

HRP is managing an operations research project aimed at improving reproductive health services for adolescents in five French-speaking countries of West Africa—Benin, Cameroon, Côte d'Ivoire, Guinea, and Senegal. A unique feature of this project is the inclusion of representatives of youth organizations in the multidisciplinary research teams working in the participating countries. In 2000, HRP and its partners in this project held a workshop for health service providers on adolescent reproductive health.

The project consists of a baseline survey on adolescent users of health services and the quality of the services offered. The survey is followed by an

Box 6.2. Workshops debate ethics

HRP requires that all proposals for research projects involving human subjects be approved in the first instance by a local or national ethical review body. To strengthen this process, HRP organizes regional workshops on ethical issues in research on reproductive health. The first workshop was held in Thailand in 1997 and the second in Chile in 1998.

During the reporting biennium, HRP held the third workshop in Kadoma, Zimbabwe, in November 2000, with 47 participants from ten English-speaking countries in sub-Saharan Africa. The fourth workshop, held in Cairo, Egypt, in November 2001, attracted 37 participants from ten countries in WHO's Eastern Mediterranean region.

Although both workshops used the same programme, format and background information, participants raised issues reflecting the different perspectives and priorities of people in the two regions. In Kadoma, for example, the discussion centred on the importance of involving men in attempts to improve the reproductive health of the community. In Cairo, it centred on the fact that decision-making, in reproductive health and fertility, is seen as a joint, rather than individual, responsibility.

In both workshops, HRP encouraged participants to organize national workshops within their own countries and several participants have indicated that they have already done so or are planning to do so. Moreover, many participants requested assistance from WHO in developing a curriculum in medical ethics, particularly bioethics in medical research, for inclusion in the teaching programmes of medical schools in their respective regions.

intervention based on the findings of the survey and geared to the needs expressed by adolescents for information and services, and to the training needs of providers. A final survey will evaluate the usefulness of the intervention. One of the five countries, Senegal, is already at the stage of implementing the intervention; two countries, Côte d'Ivoire and Guinea, have developed a strategy for the intervention but are not yet implementing it; the remaining two countries, Benin and Cameroon, are in the process of conducting the baseline survey.

A similar initiative is under way in WHO's Eastern Mediterranean region, notably in Iran, Oman, and the Syrian Arab Republic, where research projects on adolescents' needs and perspectives relating to reproductive health have begun. Following a workshop on the topic in Beirut, Lebanon, in December 1999, HRP ran a training course in Damascus, Syrian Arab Republic, in September 2000.

HRP and WHO's Africa regional office have developed a core protocol for a large-scale study on community involvement in maternal health, particularly on how pregnant women, community members, and health personnel perceive, and react to, the complications of pregnancy. The study will involve several countries, including Ethiopia, Nigeria, South Africa, and Uganda. Its ultimate aim is to develop strategies to prepare women and their families for childbirth in the hope that they will react properly to danger signs, and to ensure that deliveries are attended by skilled personnel.

The Americas

One goal of HRP activities in the region is to strengthen the capacity of institutions and groups to conduct research on reproductive health through participation in well-designed research projects pertinent to the needs of the region and its individual countries. A second goal is to ensure the widest possible dissemination and utilization of research findings.

Three HRP-backed research networks are operating in the Americas, relating, respectively, to basic reproductive biology, clinical–epidemiological research, and social sciences. Since some participating centres have less experience and expertise than others, the multicentre studies launched by the network serve to strengthen the overall research capacity of the region.

During the biennium, four centres in Argentina, Chile, and Mexico, that are part of the basic sciences network, conducted research on the mechanisms of action of hormonal emergency contraception. The researchers published a comprehensive review of the literature on the subject

Box 6.3. Female genital mutilation

A key HRP project in Africa focuses on female genital mutilation. This practice, which involves partial or total removal of the external female genitalia, is particularly common in Africa, although it also occurs in other regions and increasingly in parts of Europe, Australia, India, and North America among immigrants from Africa and the Middle East. Between 100 million and 140 million women are believed to have undergone the procedure and a further two million are estimated to be at risk of being submitted to it in any one year (Figure 6.2).

Information about female genital mutilation, particularly its consequences, is fragmentary. It is evident, however, that complications from the practice are many and varied, ranging from severe pain to fatal shock. Pelvic infection, recurrent urinary tract infection, infertility, menstrual disorders, painful intercourse, and difficult childbirth are reportedly linked to the practice.

With financial support from the United Nations Foundation Inc., HRP has launched a prospective study involving about 20 000 women in nearly 30 maternity hospitals located in six countries—Burkina Faso, Ghana, Kenya, Nigeria, Senegal, and Sudan. The study, which should be completed before the end of 2003, will explore the harmful effects of female genital mutilation on health, in particular the incidence of obstetric complications associated with the different types of mutilation commonly practised. The investigators also hope to obtain leads to possible ways of preventing and treating these complications, within the overall aim of eradicating the practice globally.

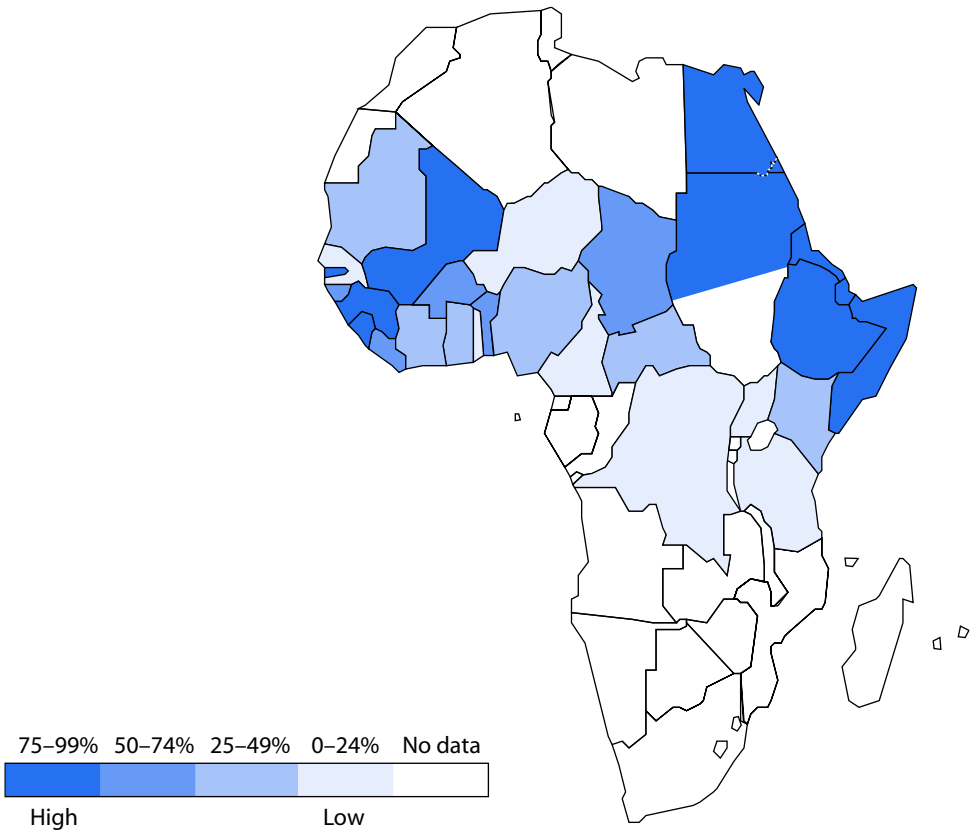


Figure 6.2. Estimated prevalence rates of female genital mutilation in Africa

and are conducting two studies on the mechanism of action of levonorgestrel used for emergency contraception (see Box 6.4).

The clinical–epidemiology network completed a multicentre study that involved hospitals in Argentina, Brazil, Cuba, Guatemala, and Mexico, and that assessed a strategy for reducing the frequency of caesarean sections in the region (see Chapter 2, page 28). In addition, four of the network's centres—in Argentina, Colombia, Cuba, and Venezuela—completed work on the multicentre "Magpie" trial on magnesium sulfate for the treatment of women with pre-eclampsia (see Chapter 2, page 27). Of the approximately 10 000 women participating in this trial, which involved 175 hospitals in 33 countries, these four Latin American centres contributed about 1500 participants.

The social sciences network, which is coordinated by the Centre for Population Studies in Buenos Aires, Argentina, has completed a project on the topic: *Reality and beliefs in the sexual and reproductive decision-making process: men's perceptions and behaviour.* The project involved social science groups in Argentina, Bolivia, Cuba, and Peru and recruited more than 3000 young men from the four countries. A unique feature of the project was the submission of the final reports from the four countries to external reviewers. By accelerating the peer-review process in this way—without pre-empting it, as all the reports will be submitted to a peer-review journal—the investigators hope to disseminate the findings of the project with as little delay as possible.

During the biennium, HRP awarded two long-term institutional development grants (see Box 6.1) to enable the respective institutions to carry out specific research projects.

One long-term institutional development grant went to the Instituto de Medicina y Biologia Experimental in Buenos Aires, Argentina, for a study on the identification of proteins in the male reproductive system (notably, the epididymal duct used for the storage, transit, and maturation of spermatozoa) that might have potential as targets for a male contraceptive.

A second long-term institutional development grant was awarded to the Guatemalan Research Centre on Epidemiological Research to study possible interventions that could improve the quality of family planning services and of maternal and neonatal care services, as well as expand access of the population to these services.

Asia and the Pacific

This region is the largest of HRP's four regional groupings. It comprises WHO's South-East Asia and Western Pacific regions, which, with a total of 46 countries, account for about 60% of the world's population. Not surprisingly, the sheer size of the population, added to its social, cultural, and geographical heterogeneity, poses a daunting obstacle to the achievement of HRP's goals in the region. One of these goals is to raise public awareness about reproductive ill-health and to enlist political and community commitment to improving it. A second goal is to increase integration of reproductive health services within public health care systems and expand access of these systems to hitherto underserved population groups. A third goal is to strengthen the capacity of research institutions to monitor and evaluate reproductive health programmes. And a fourth goal is to foster a culture of reproductive health research backed by supportive national reproductive health research systems.

During the biennium, the region witnessed the launch of two large-scale joint research projects, one on caesarean section, the other on reproductive health in adolescent migrants in the Greater Mekong region.

The study on caesarean section has enlisted the participation of ten countries—Bangladesh, China, Indonesia, Mongolia, Myanmar, Nepal, Philippines, Sri Lanka, Thailand, and Viet Nam. It will compare three procedures—vaginal delivery, elective caesarean section, and emergency caesarean section—for frequency of complications and other variables, including costs to patients.

Five countries are participating in the adolescent migrant study—China, Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam. Researchers will interview selected groups of adolescent migrants to determine why they are migrants, what they know of and how they view reproductive health issues, and the extent to which they use reproductive health services.

Eastern and Central Europe

The region comprises Eastern and Central Europe, the Newly Independent States (of the ex-Soviet Union), the Central Asian Republics, and Kazakhstan.

HRP's concerns in the region are set against a background of steeply declining fertility, underuse of effective contraceptive methods, overuse of abortion, escalating incidence rates of sexually transmitted infections, and a dearth of information about, and services for, reproductive health. One HRP objective for the region is to strengthen its capacity for research, largely

Box 6.4. A patient path from research to public policy

Chilean investigators collaborating with Brazilian and Mexican colleagues in an HRP study on the acceptability of emergency contraception have had a busy time during the biennium dealing with spin-offs from the study—

- First, a gratifying spin-off: Proponents of a bill on reproductive rights to be submitted to the Chilean parliament decided to use a background paper prepared for the study—a "situation analysis of sexual and reproductive health and rights in Chile"—as a basis for part of the text of the bill.
- Then, a success story: The study investigators, working with nongovernmental organizations, developed and successfully implemented a strategy for introducing emergency contraception in Chile. Capping this success, the Chilean health ministry gave its approval to emergency contraception.
- Third, a conflictual spin-off: When a manufacturer of levonorgestrel tried to have its product approved for emergency contraception, the Chilean Supreme Court vetoed the idea, provoking a flurry of interviews in the electronic and written media: the Chilean study investigators were invited to comment and duly championed the cause of emergency contraception.
- And a happy ending: Towards the end of 2001, the Chilean regulatory authorities approved a different brand of levonorgestrel for emergency contraception, without encountering Supreme Court opposition.

through training. A second is to work with WHO's European regional office in providing countries with the technical support they need to implement their reproductive health programmes.

A highlight during the biennium was the decision to create a regional advisory panel for the region. Such panels exist for each of the other three HRP regions. The decision was taken by a joint meeting in Barcelona, Spain, in May 2000 of HRP's scientific working group on reproductive health research and the scientific advisory group on training in reproductive health for Central and Eastern Europe and the Newly Independent States of WHO's European regional office. The HRP's new Eastern and Central Europe regional advisory panel held its first meeting in Copenhagen, Denmark, in September 2001.

Other highlights:

HRP is participating in a UNFPA-funded study, one of the largest of its kind, on the possible impact on reproductive health of radiation exposure in the area of the nuclear test site in Semipalatinsk, Kazakhstan. The study will examine the fertility of, and babies born to, women possibly exposed to radiation before and during their reproductive years. It will also determine fertility and mortality due to congenital malformations, cancer and other causes, in people exposed to radiation before birth and also in people born after 1957 whose mothers might have been exposed before conception.

A course on operations research was held in Targu Mures, Romania, in October 2001, with 17 participants from eight countries in the region. Proposed research projects that emerged from the course covered such topics as reducing caesarean section rates, adolescent sexual education, educating primary health care physicians about breastfeeding, and many others.

WHO's European regional office, with support from HRP, began preparing a reproductive health strategy for the region. Work on the strategy continued at three meetings, one in Denmark, two in Latvia.

Working with countries

Increasingly, countries are seeking guidance in planning and implementing their reproductive health programmes and in ensuring that these programmes provide the best quality of care to their end-users. Flexible approaches that seek input from a wide range

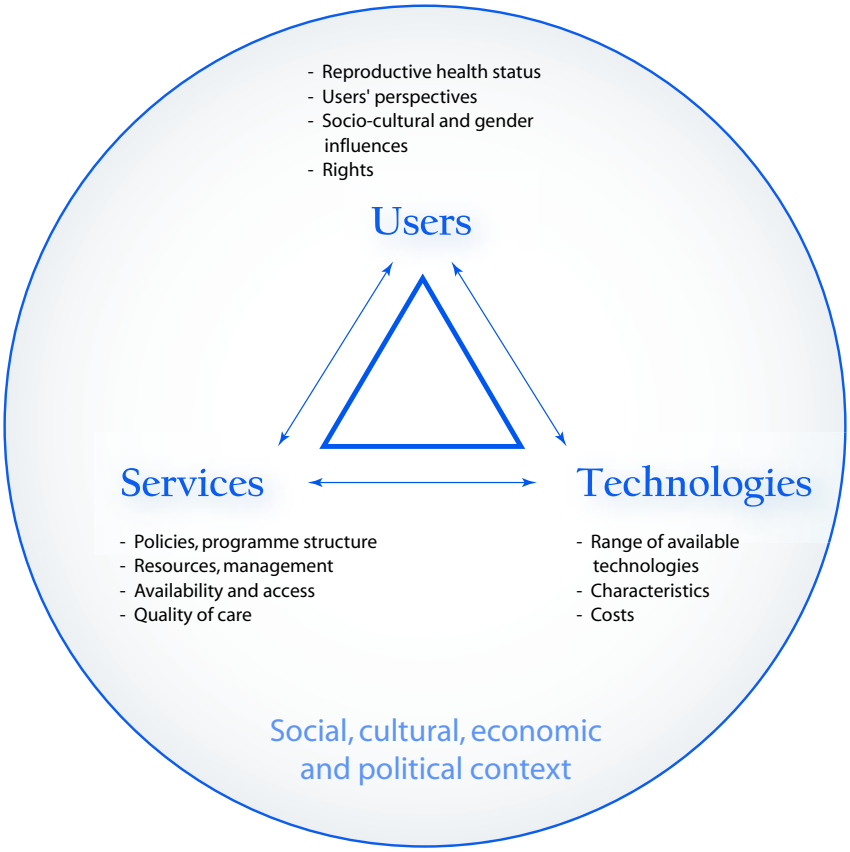


Figure 6.3. A "systems framework", that HRP has borrowed from business management to develop its "strategic approach" to countries wishing to improve the quality of reproductive health care they provide to their populations

of concerned individuals can best assist countries in making better use of their existing services and technologies and, if need be, in introducing new delivery strategies and technologies that would improve quality of care.

One such flexible approach that was developed by HRP and its partners over the past half-decade and is proving its worth in a dozen countries around the globe is a strategic approach for improving the quality of care provided by reproductive health services. Originally devised and used to expand and improve family planning options and services, this approach has broadened its scope to include other areas of reproductive health, including reproductive tract infections, unsafe abortion, maternal health, and adolescent reproductive health.

This so-called *strategic approach* is based on a "systems framework" borrowed from modern management principles (Figure 6.3). It does not simply focus on introducing new methods or technologies into a country's reproductive health care system. Rather it explores *all* pertinent aspects of that system in order to determine what could be done, given the country's resources and circumstances, to make its system more responsive to the needs of its end-users. That might mean removing a method or technology that is not effective or safe or relevant enough to the users' needs. Or making better use of existing methods and technologies. Or trying to convince people to use existing services and methods more often or more effectively. And so on.

Application of the strategic approach involves three stages: a strategic assessment (Stage I), action research (Stage II), and scaling-up (Stage III). In Stage I, a team representing a wide range of concerned parties makes an assessment of existing resources and what is needed to achieve a better reproductive health care system. In Stage II, small- or pilot-scale research determines whether the recommendations of the Stage I assessment can and should be implemented and, if so, how best they might be implemented. In Stage III, decisions are made about how and when to move from small- or pilot-scale projects to implementation over large areas of a country or even on a national scale.

By the end of the 2000–2001 biennium, activities involving the strategic approach were under way or being planned in 11 countries—three at Stage I, six at Stage II, and two at Stage III (See Box 6.5).

Box 6.5. Countries using the HRP strategic approach

A growing number of developing countries are working with HRP and its partners in applying a novel strategic approach (see text) to improve the quality of their reproductive health care services. The following list shows the stages reached by these countries during the 2000–2001 biennium in applying the approach and the main reasons for their interest in doing so.

Stage I: Strategic assessment

China
Introducing contraceptives, especially intra-uterine devices

Guatemala
Improving access to, and the quality of, family planning and maternal health services, especially emergency obstetric care

Romania
Reducing recourse to abortion and improving the quality of family planning and abortion services

Stage II: Action research

Bolivia
Strengthening family planning and related reproductive health services during introduction of depot-medroxyprogesterone acetate (DMPA) and the combined monthly injectable Cyclofem

Ethiopia
Expanding access of young people to contraceptive methods linked to coitus (e.g. condoms, foams, emergency contraception, etc.) and promoting the principles and practice of dual protection (against pregnancy and infection)

Lao People's Democratic Republic
Expanding the availability and utilization of essential obstetric care in districts and communities

Myanmar
Improving the quality of district family planning services and other reproductive health services

South Africa
Introducing emergency contraception and the female condom, and improving the quality of family planning services

Zambia
Expanding contraceptive choice and improving the quality of care, through, among other things, the introduction of DMPA and emergency contraception, and the training of providers in providing all available contraceptive methods and in managing sexually transmitted infections

Stage III: Scaling-up

Brazil
Expanding contraceptive choice and other reproductive health services

Viet Nam
Wider introduction of DMPA and improvement of the quality of care in providing contraceptive methods

Box 6.6. Women's and men's rights in reproductive health

After a five-year gestation nurtured by three groups—WHO's Department of Reproductive Health and Research, the François Xavier Bagnoud Center for Health and Human Rights of the Harvard School of Public Health in the USA, and the Women's Health Project at the University of the Witwatersrand in South Africa—a "manual for training managers in gender and rights in reproductive health" saw the light of day in 2001.

The manual, which is in the form of a 490-page volume titled *Transforming Health Systems: Gender and Rights in Reproductive Health*, is intended for use by institutions wishing to offer health managers training in reproductive health issues that emphasizes women's rights. The manual is part of the WHO department's efforts to ensure that health policies, programmes, and services reflect an effort to redress inequities between women and men, and to protect people's rights with respect to reproductive health.

The manual is in two parts: an introduction on organizing a training course and a curriculum for the course itself. The curriculum comprises six modules on, respectively, gender, determinants of health, reproductive rights, evidence, policy, and health systems. Together, the modules reflect the interconnected nature of these components in a broad socio-economic, cultural, and political context. The main focus of the manual is on reproductive health—specifically: maternal mortality and morbidity, contraceptive technologies, abortion, HIV/AIDS, reproductive tract infections (including sexually transmitted infections), cervical cancer, sexuality, violence against women, and infertility.

Extensive field-testing of the manual has taken place in 13 courses held in five countries—Argentina and China (one course each), Australia and Kenya (three courses each), and South Africa (five courses).

The manual will be distributed through WHO's regional offices and collaborating centres and will be provided, together with technical support, to institutions who have expressed an interest in it. Currently available only in English, the manual is being translated into Mandarin (Chinese) and Spanish, and a CD-ROM version is in preparation.

Annex I
Financial overview for the biennium 2000–2001

In June 2000 the HRP Policy and Coordination Committee approved the Programme's budget and programme of work for 2000–2001[1] totalling US$ 39.8 million. However, income for the biennium amounted to US$ 33.3 million, representing a shortfall of some US$ 6.5 million. Figure I.1 shows the historical trend in the approved HRP biennial budgets and the net income levels over the past six biennia. As can be seen in the figure, HRP's income declined during the period 1992–1999, but the decline was arrested in 2000–2001, with income stabilizing at about US$33–34 million.

Sources of income

Table I.1 shows the sources of contributions received by HRP during the 2000–2001 biennium as well as totals of contributions for each donor for the period 1970–2001.

Three of the four HRP cosponsors, namely the United Nations Population Fund, The World Bank and WHO maintained their substantial support. Income from WHO Member States was also strong, with contributions having been received from 13 of them, including a number of developing countries. This can be viewed as an important indicator that HRP is meeting the needs of the developing countries. Significant contributions were also received during the biennium from foundations, non-governmental organizations, and civil society. The foundations included: The Bill and Melinda Gates Foundation, The David and Lucile Packard Foundation, The Ford Foundation, The William and Flora Hewlett Foundation, The MacArthur Foundation and The Rockefeller Foundation. Contributions were also received from the Wellcome Trust, the Program for Appropriate Technology in Health (PATH), the United Nations Foundation Inc., and the Joint United Nations Programme on HIV/AIDS (UNAIDS). These sources are viewed as a key area for income growth in the future.

In order to strengthen its financial position and to expand into new and emerging areas of research in human reproduction, HRP is working actively to maintain its existing sources of income as well as to seek new ones.

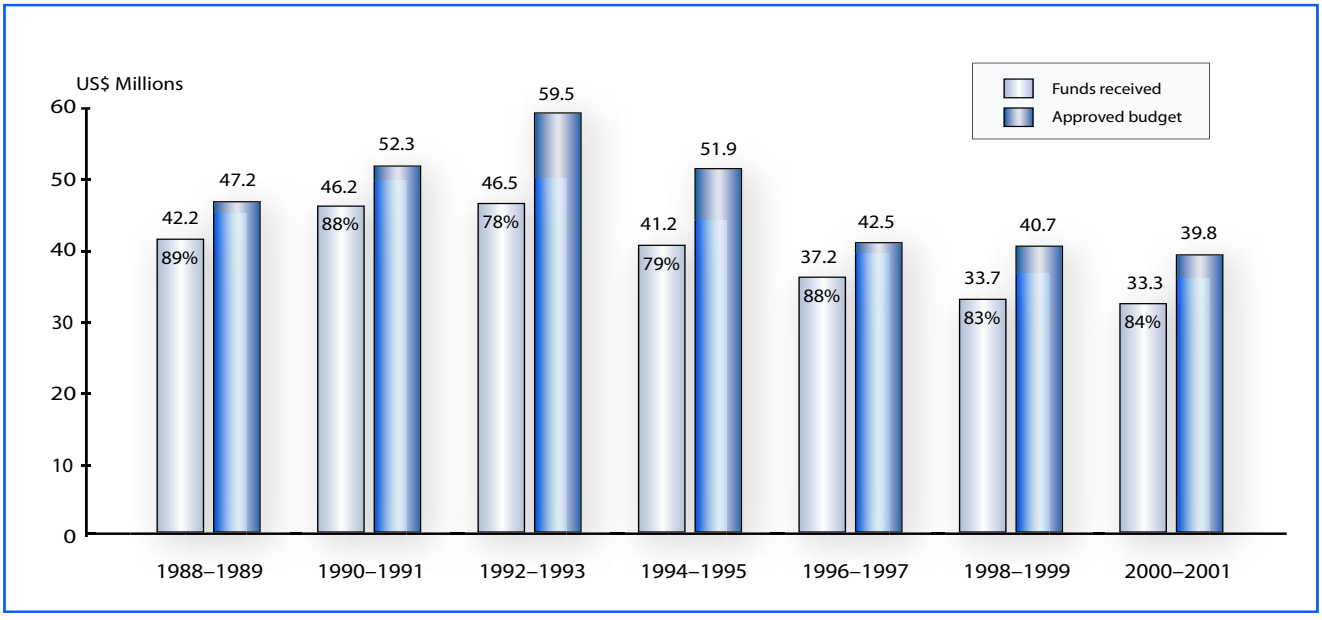


Figure I.1. Funds received in relation to approved budgets during 1988–2001

[1] *HRP Programme Budget 2000–2001* (document No. WHO/CHS/RHR/HRP/99.2)

Table I.1. HRP income, 1970–2001[1] (US$000)

Source	1970-1997	1998	1999	2000	2001	Grand Total
HRP Cosponsors[2] and other UN system agencies						
Joint United Nations Programme on HIV/AIDS	-	12	-	405	150	567
United Nations Development Programme	1 695	-	-	-		1 695
United Nations Population Fund	55 040	3 000	3 000	1 000	2 000	64 040
United Nations Foundation for International Partnerships	-	-	131	105	89	325
The World Bank	24 258	2 500	2 250	2 000	2 000	33 008
World Health Organization [3]	14 476	725	513	1 240	66	17 020
Subtotal Cosponsors and other UN system agencies	*95 469*	*6 237*	*5 894*	*4 750*	*4 305*	*116 655*
National governments						
Argentina	45	-	-	-	-	45
Australia	4 109	-	-	-	-	4 109
Bangladesh	5	-	-	-	-	5
Canada	9 829	282	265	270	253	10 899
Chile	35	-	-	-	-	35
China	820	55	55	-	110	1 040
Cuba	25	-	-	-	-	25
Denmark	29 515	-	-	-	-	29 515
Finland	3 198	151	-	-	-	3 349
France	7	-	-	-	-	7
Germany	15 327	691	519	199	258	16 994
India	729	-	35	35	35	834
Italy	655	-	-	-	-	655
Japan	300	-	-	-	-	300
Kenya	1	-	-	-	-	0.5
Malaysia	1	-	-	-	-	1
Mexico	98	3	4	3	4	112
Netherlands	6 291	538	1 888	1 724	1 726	12 167
New Zealand	27	-	-	-	-	27
Nigeria	60	-	-	-	-	60
Norway	45 864	1 475	1 394	1 228	1 237	51 198
Pakistan	5	-	-	-	-	5
Russian Federation	99	-	-	-	-	99
Spain	-	-	20	-	20	40
Sweden	93 742	1 282	1 180	1 057	1028	98 289
Switzerland	2 907	177	163	146	155	3 548
Thailand	159	40	19	-	20	238
United Kingdom	68 538	2 353	1 587	1 089	-	73 567
United States of America	15 221	2 000	2 250	2 250	2 750	24 471
Subtotal national governments	*297 612*	*9 047*	*9 379*	*8 001*	*7 596*	*331 635*
Foundations and other sources						
Contraceptive Research and Development Program	-	-	28	-	-	28
Family Health International	205	-	-	-	-	205
Ford Foundation	1 084	78	-	-	230	1 392
Bill & Melinda Gates Foundation	-	-	2 000	2 000	2 000	6 000
William and Flora Hewlett Foundation	-	-	150	-	150	300
International Development Research Centre	716	-	-	-	-	716
The John D. and Catherine T. MacArthur Foundation	-	15	-	30	20	65
The Andrew W. Mellon Foundation	360	-	-	-	-	360
Ortho-McNeil Pharmaceutical, Inc.	-	-	5	-	-	5
The David and Lucile Packard Foundation	20	-	20	2 020	-	2 060
Program for Appropriate Technology in Health	156	-	27	5	-	188
Reproductive Health Alliance Europe	-			41	-	41
The Rockefeller Foundation	3 518	20	143	220	-	3 901
The Wellcome Trust	21	18	-	-	25	64
Miscellaneous income[4]	185	4	31	113	2	335
WHO Special Account for Servicing Costs	999	93	93	-	-	1 185
Interest, adjustments and royalties[5]	13 390	380	431	837	980	16 018
Subtotal foundations and other income	*20 654*	*608*	*2 928*	*5 266*	*3 407*	*32 863*
Grand Total	***413 735***	***15 892***	***18 201***	***18 017***	***15 308***	***481 153***

Notes

(1) Source: WHO accounting database.

(2) UNDP, UNFPA, WHO and The World Bank are the Cosponsors of HRP.

(3) The WHO Regular Budget income figure shown for 2000 is the amount allotted for the biennium 2000–2001.

(4) For 2000 includes miscellaneous income ($1,486), support to Associate Professional Officers FB ($58,939), miscellaneous contributions from UNFPA ($46,213), funds in trust FT ($7,000). For 2001, includes miscellaneous income ($ 1,800).

(5) Interest, Adjustments and Royalties for 2000 include savings on unliquidated obligations ($40,009), interest ($442,590) and licensing fees/royalties from Schering ($304,300) and Women's Capital Corporation ($50,000). For 2001, this includes interest ($468,890) and royalties from Schering ($410,915) and Women's Capital Corporation ($100,000).

Annex II
Centres collaborating with HRP during 2000–2001

WHO African Region

Benin
- Centre for Research in Human Reproduction and Demography (CERRHUD), Cotonou
- Network for Research in Reproductive Health (RESAR), Cotonou

Burkina Faso
- MURAZ/OCCGE Centre, Bobo Dioulasso
- Yalgado Ouedraogo, National Medical Centre, Ouagadougou

Cameroon
- Institute for Training and Research in Demography (IFORD), Yaoundé WHO Centre for Research in Human Reproduction, University of Yaoundé, Yaoundé

Côte d'Ivoire
- Reproductive Health Research Unit (CRESARCI), Abidjan

Ghana
- Institute of African Studies, University of Ghana, Legon
- Rural Help Integrated, Bolgatanga

Republic of Guinea
- Reproductive Health Research Unit, Conakry

Kenya
- African Population and Health Research Centre, Nairobi
- Department of Sociology, University of Nairobi, Nairobi
- Development Communication Support Programme, Nairobi
- East and Southern Africa Office, Population Council, Nairobi
- Kenyan Medical Research Institute, Nairobi
- Kenyatta National Hospital Campus, University of Nairobi, Nairobi

Mali
- Reproductive Health Research Unit, Bamako

Mozambique
- Department of Obstetrics, Maputo Central Hospital, Maputo

Nigeria
- African Regional Health Education, University of Ibadan, Ibadan
- College of Medicine, University of Ibadan, Ibadan
- Department of Geography and Planning, University of Jos, Jos
- Department of Preventive Medicine, University of Ibadan, Ibadan
- National Hospital for Women and Children, Abuja
- Teaching Hospital, Ogun State University, Sagamu
- Teaching Hospital, University of Benin, Benin City
- Teaching Hospital, University of Nigeria, Enugu

Senegal
- Training and Reproduction Health Research Centre, Dakar

South Africa
- Coronation Hospital, University of Witwatersrand, Johannesburg
- Department of Community Health, University of Witwatersrand, Acornhoek
- Department of Obstetrics, University of Natal Medical School, Congella
- Department of Obstetrics, University of Pretoria, Pretoria
- Department of Obstetrics and Gynaecology, Baragwanath Hospital, Johannesburg
- Faculty of Medicine, University of Stellenbosch, Tygerberg
- Frere/Cecilia Makiwane Hospitals, University of Witwatersrand, East London
- Medical Research Council, South African Cochrane Centre, Tygerberg, Cape Town
- Medical Research Council of South Africa, Tygerberg
- Reproductive Health Research Unit, Addington Hospital, Durban
- Reproductive Health Research Unit, Baragwanath Hospital, Bertsham
- South African Institute for Medical Research and Department of Health, Johannesburg
- Women's Health Project, Johannesburg

Uganda
- Department of Obstetrics, Makerere University, Kampala

Institute of Public Health, Makerere University, Kampala
PATH-AYA Uganda, Kampala

United Republic of Tanzania
National Institute for Medical Research, Dar-es-Salaam

Zimbabwe
Department of Obstetrics, University of Zimbabwe, Harare
Human Behaviour Research Centre, Harare

WHO Region of the Americas

Argentina
Centre for Population Studies (CENEP), Buenos Aires
Centre for Studies of the State and Society (CEDES), Buenos Aires
Institute of Biology and Experimental Medicine, Buenos Aires
Rosario Centre of Perinatal Studies (CREP), Rosario

Bolivia
Centre for Research on Socially Appropriate Technology and Capacity Building, La Paz

Brazil
Assis Chateaubriand Maternity School, Fortaleza
Campinas Research Centre for the Control of Maternal and Childhood Diseases (CEMICAMP), Campinas
Centre for Reproductive Biology, Federal University of Juiz de Fora, Juiz de Fora
Department of Social Medicine, University of Pelotas, Pelotas
Federal University of Rio Grande do Sol, Porto Alegre
Institute of Collective Health (ISC), Federal University of Bahia, Salvador
Reprolatina, Campinas
Women, Child, Citizenship and Health, Sao Paulo

Chile
Chilean Institute of Reproductive Medicine (ICMER), Santiago
Clinical Epidemiological Research Unit in Reproduction, Santiago
Department of Obstetrics, Jose Joaquin Aguirre Hospital, Santiago
Faculty of Biological Studies, Catholic University of Chile, Santiago
Faculty of Health Sciences, University of Antofagasta, Antofagasta
Faculty of Medicine, University of Chile, Santiago
Institute for Mother and Child (IDIMI), University of Chile, Santiago
Women and Child Research Institute, Santiago

Colombia
SIS - WOMEN, Bogota
University of Valle, Cali

Costa Rica
University of Costa Rica, San José

Cuba
Eusebio Hernandez Hospital, Havana
Julio Alfonso Hospital, Matanzas
National Institute of Endocrinology, “Cmdte. Fajardo” Hospital, Havana

Guatemala
Education and Research Centre for Rural Areas, Antigua
General San Juan de Dios Hospital, Guatemala City

Mexico
College of Mexico, Mexico City
Department of Reproductive Biology, National Institute of Nutrition, Mexico City
Latin America and the Caribbean Office, Population Council, Mexico City
Mexican Academy for Research and Medical Demography, Mexico City
National Institute of Public Health, Cuernavaca, Morelos

Peru
Institute of Population Studies, Cayetano Heredia National University, Lima
Research and Teaching Multidisciplinary Association, Lima
Research Institute, Cayetano Heredia National University, Lima

United States of America
Department of Communication, Cornell University, Ithaca, NY
Department of Comparative Medicine, University of Tennessee, Knoxville, TX
Department of Family Practice and Community Health Program in Human Sexuality, University of Minnesota Medical School, Minneapolis, MN
Family Health International, Research Triangle Park, NC
IPAS, Chapel Hill, NC
Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
Marine Biological Laboratory, Woods Hole, MA
Obstetrics/Gynaecology and Reproductive Sciences, Magee Womens Hospital, Pittsburgh, PA
Peninsula Laboratories, San Carlos, CA
Rollins School of Public Health, Emory University, Atlanta, GA
Sylvester Comprehensive Cancer Center, Miami, FL

The Ohio State University Research Foundation, Columbus, OH

WHO Eastern Mediterranean Region

Egypt

Egyptian Fertility Care Society, Cairo
Faculty of Medicine, Assiut University Hospital, Assiut
Social Planning, Analysis and Administration Consultants, Cairo

Islamic Republic of Iran

National Research Centre of Medical Sciences, Tehran

Pakistan

Maternal and Child Welfare Association of Pakistan (MCWAP), Lahore
The Asia Foundation, Islamabad

Saudi Arabia

Department of Obstetrics, King Khalid National Guard Hospital, Jeddah

Sudan

Faculty of Medicine, University of Khartoum, Khartoum

Syrian Arab Republic

Reproductive Health Department, Ministry of Health, Damascus

Tunisia

National Office for Family and Population, Tunis

WHO European Region

Armenia

Armenian Research Centre for Maternal and Child Health Protection, Yerevan

Belgium

Department of Microbiology, Institute of Tropical Medicine, Antwerp

Croatia

Center for Education and Counselling of Women, Zagreb

France

ANRS/INSERM, University of Victor Segalen, Bordeaux
IDEA/AMP General Secretariat, Marnes-la-Coquette
International Agency for Research on Cancer, Lyon

Georgia

Zhordania Institute of Human Reproduction, Tbilisi

Hungary

Albert Szent-Gyorgyi Medical and Pharmaceutical Centre, Szeged
Department of Obstetrics, University Medical School of Szeged, Szeged
University Medical School of Debrecen, Debrecen

Israel

Department of Sociology, Bar-Ilan University, Ramat-Gan
Tel Aviv University, Tel Aviv

Italy

Department of Clinical Physiopathology, University of Florence, Florence
Department of Obstetrics and Gynaecology, University of Bologna, Bologna

Latvia

Department of Obstetrics, Medical Academy of Latvia, Riga
Family and Sexual Health Center, Riga

Netherlands

Department of Obstetrics and Gynaecology and Reproductive Medicine, Leiden University Medical Centre, Leiden

Poland

Institute of Philosophy and Sociology of the Polish Academy, Warsaw

Romania

East European Institute of Reproductive Health, Targu-Mures
Ministry of Health, Bucharest

Slovenia

Department of Obstetrics and Reproductive Medicine, University Medical Centre, Ljubljana

Sweden

Department of Medical Cell Biology, Biomedical Center, Uppsala
Department of Women and Child Health, Karolinska Hospital, Stockholm

Switzerland

Council for International Organizations of Medical Sciences, Geneva
Department of Obstetrics and Gynaecology, University Hospital of Geneva, Geneva
International Network on Control of Gynaecological Cancers (INCGC), University Hospital of Geneva, Geneva

Turkey

Faculty of Medicine, Marmara University, Istanbul
Institute of Child Health, University of Istanbul, Istanbul
Medical Faculty, Hacettepe University, Ankara

United Kingdom of Great Britain and Northern Ireland

Cancer Epidemiology Unit, Imperial Cancer Research Fund, Oxford
Department of Endocrinology, University of Manchester, Manchester
Department of Social Statistics, University of Southampton, Southampton
Institute of Cancer Research Fund, Royal Cancer Hospital, Sutton
Institute of Health Sciences, Magpie Trial Coordinating Centre, Headington, Oxford
Liverpool School of Tropical Medicine, Liverpool
London School of Hygiene and Tropical Medicine, London

Yugoslavia

Department of Obstetrics, Clinical Center Novi Sad, Novi Sad

WHO South-East Asia Region

Bangladesh

Bangladesh Institute of Research for Promotion of Essential and Reproductive Health Technologies, Dhaka
Bangladesh Rural Advancement Committee, Dhaka

India

All India Institute of Medical Sciences, New Delhi
Christian Medical College and Vellore Hospital, Vellore
Clinical Epidemiological Unit, Government Medical College, Nagpur
Institute for Research in Reproduction, Parel, Mumbai
MAMTA, Health Institute for Mother, New Delhi
S.A.T. Hospital, Department of Obstetrics and Gynaecology, Trivandrum Swaasthya, New Delhi
Talking About Reproductive and Sexual Health Issues (TARSHI), New Delhi
The Sangath Society for Child Development and Family Guidance, Goa

Indonesia

Atma Jaya Catholic University of Indonesia, Jakarta
Department of Obstetrics, University of Indonesia, Jakarta
Department of Obstetrics and Gynaecology, Haji Adam Malik Hospital, Medan
Faculty of Medicine, University of Andalas, Padang
Indonesian Society of Andrology, Bagian Biologi Medikj, Padang
National Family Planning Coordinating Board (BKKBN), Jakarta
Reproductive Health Research Centre, Airlangga University, Surabaya
West Indonesian Reproductive Health Development Centre, Jakarta

Lao People's Democratic Republic

Faculty of Medical Sciences, National University of Laos, Vientiane
Institute of Maternal and Child Health, Vientiane
Mother and Child Health Centre, Ministry of Health, Vientiane

Mongolia

State Research Centre for Maternal and Child Health and Human Reproduction, Ulaanbaatar

Myanmar

Department of Health, Ministry of Health, Yangon
Department of Medical Research, Epidemiology Research Division, Yangon
Department of Medical Research, Ministry of Health, Yangon

Nepal

Center for Research on Environment, Health and Population Activities, Kathmandu
Institute of Medicine, Tribhuvan University, Kathmandu

Sri Lanka

Department of Geography, University of Ruhuna, Matara
Faculty of Medicine, University of Colombo, Colombo
Faculty of Medicine, University of Kelaniya, Ragama

Thailand

Bureau of Health Promotion, Ministry of Public Health, Nonthaburi
Chiang Mai University Research Institute for Health, Chiang Mai
Department of Obstetrics, Chulalongkorn University, Bangkok
Department of Obstetrics, Siriraj Hospital, Bangkok
Faculty of Medicine, Chiang Mai University, Chiang Mai
Faculty of Medicine, Khon Kaen University, Khon Kaen
Faculty of Medicine, Prince of Songkla University, Hat Yai
Institute for Population and Social Research, Mahidol University, Nakorn Prathom
Population Council, Bangkok

WHO Western Pacific Region

Australia

Australian National University Demography Programme, RSSS, Canberra
Australian National University Health Transition Centre, Canberra
Australian National University Research School of Biological Sciences, Canberra
Department of Biological Sciences, The University of Newcastle, Callaghan
Monash University Centre for Women's Health Research, Clayton

Prince Henry's Institute of Medical Research, Clayton

China

Beijing Obstetrics and Gynaecology Hospital, Beijing
Department of Science, State Family Planning Commission, Beijing
Family Planning Research Institute of Guangdong, Guangzhou
Family Planning Research Institute of Sichuan, Chengdu
Institute for Health Sciences, Kunming Medical College, Kunming
Institute of Sociology, Yunnan Academy of Social Sciences, Kunming
International Peace Maternity and Child Health Hospital, Shanghai
Jiangsu Family Planning Research Institute, Nanjing
National Research Institute for Family Planning, Beijing
Peking Union Medical College Hospital, Beijing
Ren Ji Hospital, Shanghai Second Medical University, Shanghai
Shanghai Institute of Planned Parenthood Research, Shanghai
Sociology Department, Renmin University of China, Beijing
Tianjin Municipal Research Institute for Family Planning, Tianjin
Zhong Shan Hospital, Shanghai Medical University, Shanghai

Hong Kong

Queen Mary Hospital, University of Hong Kong, Hong Kong

Malaysia

Faculty of Medicine, University of Malaya, Kuala Lumpur
International Council on Management of Population Programmes, Ampang

Philippines

Clinical Epidemiology Department, Office of Education and Research, Quezon City

Republic of Korea

Department of Preventive Medicine, Catholic University of Taegu-Hyosung, Taegu

Viet Nam

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