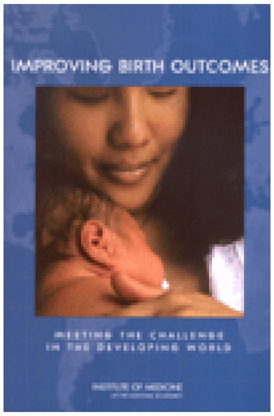

Improving Birth Outcomes: Meeting the Challenge in the Developing World

Judith R. Bale, Barbara J. Stoll, Adetokunbo O. Lucas
Editors, Committee on Improving Birth Outcomes

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IMPROVING BIRTH OUTCOMES

MEETING THE CHALLENGE IN THE DEVELOPING WORLD

Committee on Improving Birth Outcomes
Board on Global Health

Judith R. Bale, Barbara J. Stoll, and
Adetokunbo O. Lucas, *Editors*

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **ELAINE L. LARSON,** Columbia University, New York, New York, and by **ELENA NIGHTINGALE**, National Research Council, Washington, DC. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Acknowledgments

The Institute of Medicine acknowledges the committee for undertaking the development of both this comprehensive report and the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World*.

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PART I

Meeting the Challenge in the Developing World

Executive Summary

The death of a mother, fetus, or neonate is tragic whenever it occurs. While relatively rare in the industrialized world, maternal, fetal, and neonatal deaths occur disproportionately in developing countries, where the vast majority of the 515,000 maternal deaths, 4 million late fetal deaths (beyond 22 weeks' gestation), and 4 million neonatal deaths are conservatively estimated to occur each year. In Eastern Africa, 1 in 11 women dies of pregnancy-related causes, a lifetime risk of maternal death 500 times greater than that faced by women in some industrialized countries. Most maternal, neonatal, and fetal deaths occur between late pregnancy and the end of the first month of the child's life and many are preventable. Yet this important period has received inadequate attention in the health care programs of most countries. This report reviews the evidence on key interventions that could greatly improve birth outcomes[1] in developing countries.

STUDY PURPOSE AND APPROACH

The Centers for Disease Control and Prevention requested that the Institute of Medicine's Board on Global Health undertake a study to exam-

[1]In this report, a successful birth outcome is defined as the birth of a healthy baby to a healthy mother.

ine the steps needed to improve birth outcomes in the developing world. The National Institute for Child Health and Human Development of the National Institutes of Health and the U.S. Agency for International Development joined the sponsorship of the project. The specific charge to the committee was:

Birth outcomes worldwide have improved dramatically in the past 40 years. Yet there is still a large gap between the outcomes in developing and developed countries. This study will address the steps needed to reduce that gap. The study will:

1) review statistics on low birth weight, premature infants, and birth defects;
2) review current knowledge and practices;
3) identify cost-effective opportunities for improving birth outcomes, reducing maternal, infant, and fetal mortality, and supporting families with an infant handicapped by birth problems; and
4) recommend priority research, capacity building, and institutional and global efforts to reduce adverse birth outcomes in developing countries.

The committee will base its study on data and information from several developing countries, and provide recommendations that can assist the Centers for Disease Control and Prevention, the National Institute of Child Health and Human Development of the National Institutes of Health, and the U.S. Agency for International Development in tailoring their international programs and forging new partnerships to reduce the mortality and morbidity associated with adverse birth outcomes.

Initial discussions convinced the committee and the Board on Global Health of the importance and need for a broader study. As a result, the scope of the study was extended from addressing neonatal outcomes to including maternal and fetal outcomes in developing countries. In addition, the discussion of perinatal transmission of HIV/AIDS was expanded to a full chapter. The committee also wrote a companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World.*

To conduct the current study, the Institute of Medicine assembled a committee with broad international expertise in public health, neonatology, obstetrics, genetics, epidemiology, pediatrics, and clinical research. The members of the committee were also chosen for their experience on birth outcomes in a range of developing countries. The committee members are listed at the beginning of the report, and their brief biographies are given in Appendix D.

Many health services offered to pregnant women in developing countries are based on traditions and "common wisdom." Relatively few of these have been *demonstrated* to be effective and safe. The goal of this study is to provide evidence-based recommendations founded on rigorous evaluations. The data for the study were assembled by the committee, consultants, and staff through bibliographic references on related topics and through databases such as Medline, university libraries, and Internet sites of organizations associated with research and services for birth outcomes. Although much of the published information on birth outcomes in developing countries was found in international and national journals and reports, some of the evidence has appeared in local journals, the proceedings of meetings, and unpublished reports. To tap this knowledge base, the committee enlisted experts with recent research or service experience in developing countries. Data and supportive evidence were provided by these experts through workshop presentations and technical consultation on the report chapters (see Appendix A). The framework for the committee's examination of birth outcomes included an overview of epidemiological parameters; a review of the current knowledge base on interventions; and a review of the feasibility, cost, and impact of proposed interventions.

The combined weight of such evidence, the committee believes, has produced an accurate account of the state of knowledge concerning the epidemiology of neonatal and maternal mortality and morbidity and fetal mortality, prevention and care in developing countries, and the capacity of health care systems to provide appropriate prevention and care with limited resources. Evaluation of the evidence base enabled the committee to identify gaps in knowledge and to propose strategies for a research agenda that would fill these gaps. The findings, strategies, and recommendations included in the report were developed from this broad base of evidence; areas are noted in which the data are inadequate to support definitive conclusions.

While the committee explicitly searched for the best evidence available on interventions with the potential to improve birth outcomes, and has built its recommendations on this scientific foundation, a note of caution is in order with regard to the nature and adequacy of the evidence base. The best available evidence is sometimes inadequate for a satisfactory evaluation of the cost and effectiveness of promising health care interventions in developing countries. It is often difficult to generalize the results of studies carried out in developed countries to developing-country settings. The results of an intervention can differ from one setting to another, and the delivery of interventions is likely to vary considerably across settings. Thus the committee's recommendations regarding the effectiveness of certain interventions in different health care systems are informed by expert judgement as well as scientific research. The committee's research recommendations emphasize the importance of research to recognize priority reproductive health problems, identify effective interventions to address these problems, implement the interventions, monitor and assess their effectiveness in diverse settings, and tune them for maximal clinical- and cost-effectiveness.

PRINCIPAL ATTRIBUTES OF THE PROBLEM

The Social, Cultural, and Economic Context

While recognizing the profound influence of social, cultural, and economic factors on birth outcomes and supporting efforts to counteract their negative effects, this study focuses on interventions and health care services that can rapidly reduce maternal, neonatal, and fetal mortality. However, it is clear that to be successful, such interventions must not only be clinically effective, but must take into account the following major influences on birth outcomes.

Poverty

At the individual and the population level, poverty tends to reduce the availability of all types of health services. Populations with high infant mortality generally have low GDP per capita and significant inequalities in income. Women in poverty face higher rates of infectious disease, including malaria, rubella, and HIV/AIDS, that also pose risks to the fetus and neonate. Unhygienic conditions, frequently associated with poverty, increase the risk of maternal and neonatal sepsis. Malnourished mothers are at increased risk for complications and death during pregnancy and childbirth and their infants are more likely to have low birth weight, fail to grow at a normal rate, and have higher rates of disease and death.

Women's education and socioeconomic status

Maternal education, literacy, and overall socioeconomic status are powerful influences on the health of both mother and newborn. Where women's social or economic status is low, maternal mortality tends to be higher. The educational level of women relative to men in a society both determines and is determined by the degree of autonomy and power held by women. Women's educational and socioeconomic status also influence age at marriage and first pregnancy, use of family planning, and the prevalence of domestic violence. Female literacy has been found to be a strong predictor of family size and birth spacing, which in turn strongly affect birth outcome. Female literacy also appears to influence the proportion of physicians and nurses in a population.

Unintended pregnancy

Worldwide estimates indicate that between 100 and 150 million married women want to postpone or stop childbearing, but lack access to family planning services. Other barriers to women's control of their own reproduction include poverty, lack of education, and low social status. A major consequence of the unmet need for family planning is maternal mortality and morbidity—including infertility—due to unsafe abortion. The 20 million unsafe abortions estimated to occur each year, 90 percent in developing countries, result in more than 70,000 maternal deaths. Most of these women live in countries where abortion is illegal.

Maternal age and parity

The following factors have been associated with an increased risk of infant death: a mother older than 35 years; a very young (early adolescent) mother; birth intervals of less than 2 years; and four or more older children. Traditions in many developing countries promote early marriage and frequent childbearing, and many women—due to cultural norms, lack of access to birth control, or both—continue to bear children until they reach menopause. Interpregnancy intervals of less than 6 months may be associated with increased risk of low birth weight. Advanced maternal age has consistently been associated with increased risk for fetal and neonatal deaths, primarily due to chromosomal abnormalities.

Cultural barriers to obstetric and neonatal care

Life-threatening complications for pregnancy and childbirth frequently go unrecognized in developing countries. Pregnancy is widely considered to be a time of well-being; complications may be viewed as fated due to a woman's misbehavior. Where such beliefs prevail, women and traditional birth attendants tend to perceive obstetric complications as supernatural and best treated through traditional means. When women recognize the need for obstetric care, the sometimes well-founded belief that care will be of poor quality may inhibit them from seeking that care. Those who reach an appropriate medical facility may also find that differences in language, behavior, and expectations between a woman experiencing complications and the medical staff limit her access to care.

The invisibility of many fetal and neonatal deaths that occur at home, along with the widespread acceptance of these deaths, poses major barriers to reducing fetal and neonatal mortality. In many cultures, a child's birth is not acknowledged until he or she has survived the first days or weeks of life. Until the critical period of survival has passed, mother and infant may be isolated, which can delay access to medical care if either becomes ill. Such delays are particularly dangerous for mothers and neonates with infections, as their survival often depends on receiving care within hours of the appearance of symptoms.

Adverse Birth Outcomes

Deaths of both mothers and infants are concentrated in the period spanning the onset of labor through the first 28 days postpartum. During those few weeks, most maternal deaths (except those due to unsafe abortion) and almost two-thirds of infant deaths occur. The intrapartum period is the most likely time for late fetuses to die. Labor is also particularly perilous for the fetus in rural areas, where few women receive skilled assistance at childbirth. Neonates are at greatest risk in the 48 hours after birth. For mothers, both periods are of high risk. Half of maternal, late fetal, or neonatal deaths occur in the intrapartum period and the next 48 hours.

Inadequate data on birth outcomes

The true magnitude of death, disease, and injury associated with poor birth outcomes in developing countries has not been established. Countries with the highest estimated maternal, neonatal, and fetal mortality rates also have the lowest registration of births and neonatal deaths; an even lower proportion of fetal deaths are recorded. Several factors contribute to this situation, including the absence of national systems for registration of vital statistics, failure to report deaths that occur in the home, the lack of consistent international definitions of neonatal mortality, and cultural practices that confer "personhood" on infants only after they have survived their first days or weeks. Inadequate data on late fetal deaths are partly responsible for their not being included in calculations of the global burden of disease.

Maternal mortality

Maternal death (death while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by the pregnancy or its management) is a leading cause of death for women between the ages of 15 and 49. Ninety-nine percent of maternal deaths occur in the developing world, where one in four women suffers from an acute or chronic disability related to pregnancy. The five major causes of maternal mortality are hemorrhage, sepsis, unsafe abortion, eclampsia, and obstructed labor. Together these account for more than two-thirds of maternal mortality. Indirect causes of maternal death, which are responsible for approximately 20 percent of maternal mortality, include pre-existing conditions such as malaria and viral hepatitis that are exacerbated by pregnancy or its management.

Neonatal mortality

The greatest risk of childhood death occurs during the neonatal period. About 40 percent of all deaths to children under 5 years of age, and nearly two-thirds of all infant deaths (between birth and 12 months) occur during the neonatal period (the first month of life). Approximately 98 percent of the approximately 4 million neonates who die each year are born in the developing world. The major causes of neonatal death are asphyxia, infection, complications of preterm birth, and birth defects in the early neonatal period (0-6 days); infections cause the majority of late neonatal (7-27 days) deaths. Health services in the antenatal, labor and delivery, and postnatal periods can be refined to prevent or reduce neonatal mortality and severe morbidity, and can be made both accessible and workable in different developing country settings.

Fetal mortality

If, after separation from the mother, a fetus does not breathe or show other evidence of life (beating of the heart, pulsation of the umbilical cord, definite movement of voluntary muscles), the death is classified as fetal rather than neonatal. Antepartum fetal deaths occur before the onset of labor and are associated with a variety of risk factors, including maternal conditions, obstetric complications, and advanced maternal age. Intrapartum fetal deaths, which occur during labor, frequently result from maternal conditions or obstetric complications. With skilled assistance and access to the appropriate level of care, such complications can often be handled successfully. Where skilled health care services are not available and where many deliveries occur at home, as in many developing country settings, the proportion of intrapartum fetal deaths and overall fetal mortality are both much higher. The fetal deaths most amenable to prevention generally occur late in gestation (after 28 weeks) and involve a potentially viable fetus. Late fetal deaths are not included in estimations of the global burden of disease. They are not, therefore, recognized by decision makers for their significant role in that burden.

Health Care Systems

Effective obstetric and neonatal services depend on skilled care at each delivery and, in the case of complicated deliveries, access to good quality referral care. Building this healthcare capacity involves personnel, facilities, equipment, and supplies. Personnel is the most important category, and it is complicated by the shortage of physicians, midwives, and nurses throughout much of the developing world. This shortage is exacerbated by the concentration of skilled staff in urban areas and recruitment of staff, particularly nurses, by developed countries such as the United States and the United Kingdom.

Another challenge to achieving greater population coverage with effective health interventions, including those to reduce maternal and neonatal mortality, is the low level of total health expenditures in developing countries. With the average annual per capita health care expenditure in low-income countries at US$26 in 2002 and only half that amount in the 48 poorest countries, additional funds are clearly necessary to improve birth outcomes and health care in general. Since the 1980s, many countries have undertaken health reforms, including introduction of user charges, delivery of a more focused set of essential health services, and coordination of donors, in an effort to improve the accessibility, equity, quality, and efficiency of services.

Four models of health care are currently provided in communities across the world: Model 1, the most basic, involves home delivery by a nonprofessional; Model 2, home delivery by a professional; Model 3, delivery by a professional in a clinic or hospital with basic essential care; and Model 4, delivery by a professional in a hospital with comprehensive essential care. Model 1 and even Model 2 may not have the capacity to refer complicated cases to a health facility that provides basic or comprehensive essential care (as described in Chapter 2). Experience in developing countries suggests that Model 2 or 3 care is clinically- and cost-effective for uncomplicated deliveries. Model 4 care can be a valuable and cost-effective resource when most of the deliveries are referrals by skilled attendants rather than by patients on their own.

Complications of childbirth may lead to neonatal, maternal, or fetal death unless each of the following four steps is taken in a timely way: recognizing the problem, making the decision to seek care, reaching an appropriate medical facility, and obtaining the needed care. For many women in developing countries, each step in this pathway is blocked. Similarly, few neonates in the rural areas of developing countries receive medical care. Most obstetric and neonatal complications can be managed successfully if recognized and treated in a timely manner, but only about half of all births in developing countries are assisted by a skilled birth attendant who has been trained to detect and respond to complications. Even when complications are recognized, many women in rural areas lack access to a medical facility with appropriate services. Their way may be barred by the lack of 24-hour, good quality essential services; distance and the lack of affordable transportation; or the cost of needed services. Clearly, successful strategies to improve birth outcomes must not only address the direct causes of maternal, neonatal, and fetal mortality, but must also address their implementation within health care systems.

Three additional neonatal challenges

Three conditions that pose additional challenges to neonatal health in developing countries are low birth weight (LBW), birth defects, and HIV/AIDS. Each is associated with medical, social, and cultural risk factors that affect their incidence and severity in a given setting.

More than 20 million LBW infants are estimated to be born each year. This includes 17 percent of the neonates born in developing countries—nearly three times as many as in developed countries. LBW increases the risk of infant mortality, may lead to problems in infant and child development, and may increase the risk for certain chronic disorders in adulthood.

More than 4 million children are born each year with birth defects.[2] As infant mortality and morbidity due to infectious diseases and birth asphyxia are controlled, the relative contribution of birth defects increases. Risk factors for birth defects that may be higher in developing countries include infectious diseases and nutrient deficiencies in the mother during pregnancy.

HIV/AIDS, a worldwide epidemic, has devastated sub-Saharan Africa and is a serious problem in several other countries. Mother-to-child transmission of HIV produces about 800,000 new HIV infections each year, the vast majority of which occur in developing countries. About one in three children born to HIV-infected mothers in the developing world becomes infected. In developed countries, by contrast, antenatal testing and antiretroviral therapy programs have reduced mother-to-child HIV transmission to about 5 percent.

FINDINGS AND FUTURE STRATEGIES

Policymakers concerned with maternal and child health have long recognized the need to reduce both maternal and infant mortality. While this study recognizes the common ground between these historically separate goals, it also emphasizes the need to address the specific causes of mortality for mother, neonate, and fetus with practical, affordable interventions.

Improving Birth Outcomes Now

The committee's first four recommendations are for implementation now. They are developed in chapters addressing maternal and neonatal mortality, overall health systems, LBW, birth defects, and HIV. The specific recommendations from these chapters are integrated here to provide a

[2] See the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World.*

comprehensive set of priority interventions for each stage of pregnancy. The recommendations are given in priority order.

The committee identified two interventions they considered key to the reduction of maternal, fetal, and neonatal mortality: skilled attendance during labor and delivery, and in the event of complications that cannot be addressed by the birth attendant, timely access to essential care for the mother and/or neonate. While traditional birth attendants provide invaluable physical and emotional support during the birth process, reducing mortality requires that labor and delivery be handled by skilled medical staff, such as a midwife, physician, or nurse. The components of skilled care include clean and safe delivery practices that minimize maternal and neonatal infection, the use of the partograph to monitor the progress of labor, neonatal resuscitation, recognition of complications requiring a higher level of care, along with the capacity to organize a prompt and appropriate referral.

Recommendation 1. Every delivery, including those that take place in the home, should be assisted by a skilled birth attendant (a midwife, physician, or nurse) who has been trained to proficiency in basic techniques for a clean and safe delivery; recognition and management of prolonged labor, infection, and hemorrhage; and recognition and resuscitation of neonates who fail to initiate respiration at birth. Where necessary, the birth attendant should also be prepared to stabilize and swiftly refer the mother and/or neonate to a facility providing essential obstetric and neonatal care (Chapters 2 and 3).[3]

Future significant reductions in maternal, neonatal, and fetal mortality can be achieved if complications in labor and delivery are anticipated and addressed promptly. For example, treatments for hypertensive disease of pregnancy can prevent or minimize the recurrence of life-threatening convulsions; vacuum extraction, use of forceps, and cesarean section can be used to manage obstructed labor; preventive medications and blood transfusion can reduce maternal deaths due to postpartum hemorrhage. Access for the majority of a population to the appropriate level of care also requires strong referral systems that include communication with, and transportation to, referral facilities.

Recommendation 2. Essential obstetric and neonatal care should be accessible to address all complications of childbirth that cannot be managed by a skilled birth attendant. This requires a network of good-quality essential care facilities that provide basic essential obstetric care: administration of antibiotic, oxytocic, and anticonvulsant drugs;

[3]This issue is also discussed in Appendix E, Dissenting Note by Dr. Abhay Bang.

manual removal of the placenta; removal of retained products of conception; and assisted vaginal deliveries. Comprehensive essential obstetric care facilities have the capacity to perform these basic services and also surgery and blood transfusion. Services for essential neonatal care should emphasize the diagnosis and treatment of infection. Access for the majority of a population to the appropriate level of care also requires strong referral systems that include communication with, and transportation to, referral facilities (Chapters 2, 3, and 5).

The postpartum period—particularly the first 48 hours—is, after labor and delivery, the most important time for reducing maternal and neonatal mortality. Many deaths could be prevented through a combination of clean and safe delivery (by a skilled birth attendant, as described above) and prompt diagnosis and treatment of infection during the first month postpartum. Postpartum maternal complications such as hemorrhage require similar prompt treatment. Postpartum care should also provide guidance on infant feeding, thermal control, and clean and safe neonatal care.

Recommendation 3. Postpartum care is critical during the first hours after birth and important throughout the first month. Such care should emphasize: for the mother, the prevention, timely recognition, and treatment of infection, postpartum hemorrhage, and complications of hypertensive disease of pregnancy; and, for the neonate, the prevention, timely recognition, and treatment of infection, thermal control, and promotion and support of early and exclusive breastfeeding[4] (Chapters 2 and 3).

Several effective preconceptional and antenatal services, beginning with family planning, can reduce the risks for maternal, neonatal, and fetal mortality. These services, which can be provided in about five antenatal visits, can also counsel women on risks to a healthy pregnancy, encourage them to plan clean and safe deliveries with skilled assistance, and alert them to recognize and seek appropriate medical assessment of danger signs during pregnancy, labor, and delivery.

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- **Greater access for women and men of reproductive age to family planning services that provide effective contraception along with counseling on the risks for adverse birth outcomes** (Chapter 2).
- **Discouragement of women from childbearing after age 35 to**

[4]See also recommendation 4 with respect to HIV.

minimize the risk of chromosomal birth defects such as Down syndrome (Chapter 7).
- **Immunization against rubella for women before they reach reproductive age** (Chapter 7).
- **Routine and continuous provision of 400 micrograms of folic acid per day for all women of reproductive age** (Chapter 7).
- **Universal iodine fortification of salt (25-50 milligrams of iodine per kilogram of salt)** (Chapter 7).
- **Immunization against tetanus for all women of reproductive age** (Chapter 3).
- **Intermittent prophylactic and early treatment of malaria, especially for primiparae** (Chapters 2 and 6).
- **Early detection and timely management of syphilis and other sexually transmitted diseases, asymptomatic bacteriuria/urinary tract infection, and tuberculosis** (Chapter 3).
- **Counseling of women to limit alcohol consumption during pregnancy** (Chapter 7).
- **Counseling and other forms of support to stop smoking during pregnancy** (Chapter 6).
- **Early detection and timely management of hypertensive disease of pregnancy** (Chapter 2).
- **Early detection and timely management of asymptomatic urinary tract infection** (Chapter 6).
- **Counseling of women and their health care providers on locally relevant teratogenic medications to be avoided during pregnancy** (Chapter 7).
- **In areas where HIV is a public health problem (seroprevalence exceeds 1 percent), antenatal screening for HIV should be provided to women who, after counseling, give their informed consent. Women who test positive should receive antiretroviral prophylaxis to prevent mother-to-child transmission of the virus, along with appropriate counseling on infant feeding options** (Chapter 8).

Certain interventions may be overused or are inappropriate. Cesarean section and episiotomy tend to be overused in some middle-income countries. In settings where good hygiene is not guaranteed, vaginal examination is not appropriate.

Improving Birth Outcomes in the Future

Successful and sustained implementation of the first four recommendations requires the support of an effective health care system. Unfortunately, evaluation of health care systems often relies on studies that are less rigorous than those used to evaluate individual interventions. In addition, health care systems and priorities vary with local mortality rates and the resources available for obstetric and neonatal care. This report, therefore, describes processes by which reproductive and neonatal health care may be strengthened. Key elements of this process include:

- A country strategy, a framework of activities, and the support of key leaders to reduce mortality associated with childbirth.
- Field trials to test locally appropriate models of reproductive and neonatal health care during pregnancy, labor and delivery, and postpartum.
- The strengthening of health care capacity through staff development and reforms, reforms in financing, and reforms in the delivery of effective health services. Staff development involves the training and supervision of skilled birth attendants as well as staff in the clinics and hospitals.
- Surveillance of key birth outcomes to establish a sound database for identifying the priority problems to be addressed.
- Monitoring, evaluation, and action on new and old interventions to tune the interventions and the health system to be clinically- and cost-effective.

The capacity of the health care infrastructure, local health priorities, and resources—personnel and financial—all influence the speed with which maternal, neonatal, and fetal mortality can be reduced. To improve birth outcomes over the long term, strategies need to be advanced at every level, from local communities to international bodies. National public health policy should seek to control preventable risk factors for maternal, neonatal, and fetal mortality, and to coordinate the many institutions and organizations involved in comprehensive reproductive care. The first steps toward developing this important health capacity are to identify the goal, the process by which it can be accomplished, adequate resources, and to gain the support of political and health care leaders who can ensure success.

Recommendation 5. Each country should develop a strategy to reduce maternal, fetal, and neonatal mortality; a framework of activities by which this can be accomplished; and the commitment of health leaders to accomplish these goals (Chapter 5).

The first step in improving maternal, neonatal, and fetal health is the identification of priority outcomes, which must be measured with as much precision as is practical. Surveillance of maternal, neonatal, and fetal mortality and other outcomes can provide the foundation for identifying and evaluating interventions. All outcomes must be clearly defined in order to identify and evaluate interventions that address the distinct causes of mortality for each of these populations.

Recommendation 6. To determine the true burden of disease associated with adverse birth outcomes and measure the effectiveness of interventions to address these problems, basic epidemiological and surveillance data must be collected, analyzed, interpreted, and acted upon. Each country should, as resources permit, incrementally develop complete national demographic data and ongoing surveillance of maternal, neonatal, and fetal mortality and morbidity (Chapter 5).

Health care services can be improved continuously over time by recognizing priorities that need to be addressed, identifying interventions that address them, implementing the interventions, assessing their effectiveness, and tuning them to be more effective.

Recommendation 7. Each country should strengthen its public health capacity for recognizing and implementing interventions that have proven effective in reducing maternal, neonatal and fetal mortality in similar populations. This also involves monitoring and tuning interventions for clinical- and cost-effectiveness in the local setting (Chapter 5).

CONCLUSIONS

Health care services to reduce maternal, neonatal, and fetal mortality—particularly during the period spanning late pregnancy through the first month of a child's life—have shown inadequate improvement in most developing countries. After more than a decade of increased attention to maternal health care in the developing world, maternal mortality rates have not measurably declined. Meanwhile, although significant reductions in mortality rates in children under 5 years have been achieved during the 1990s, neonatal mortality rates, which now account for the majority of infant mortality, have declined far less quickly.

Over the past 15 years, however, researchers have built a significant body of knowledge on pregnancy outcomes in low-resource settings. There is increasing agreement on the interventions most likely to reduce maternal, neonatal, and fetal mortality and recognition that some interventions can benefit all three populations. Mortality rates could approach those in developed countries by effectively implementing strategies already established as effective: skilled attendance at all deliveries; referral of all deliveries with complications to good-quality essential obstetric and neonatal care; and effective antenatal and postpartum maternal and neonatal care. Continued and sustained improvement of birth outcomes, however, will require an investment in the development of effective health care systems. This will require strong health care policies supported by appropriate resources, good collection of basic surveillance data, and the public health capacity to recognize priority interventions and implement them effectively.

1

Introduction

The death of a mother, fetus, or neonate is tragic whenever it occurs. While relatively rare in the industrialized world, maternal, fetal, and neonatal deaths occur disproportionately in developing countries. In some industrialized countries, a woman's lifetime risk of dying as a result of pregnancy in childbirth is 1 in 5,000. In the least-developed countries, a woman's lifetime risk of maternal death is 1 in 11. Overall, developing countries account for the vast majority of the 515,000 maternal deaths (World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001), 4 million fetal deaths (beyond 22 weeks' gestation), and 4 million neonatal deaths that occur each year, according to conservative estimates (Save the Children, 2001). The majority of these deaths are preventable.

The crucial period discussed in this report, from late pregnancy through the first month of the child's life, has received inadequate attention in the health care programs of most countries. Mother-child programs initially focused on infants and younger children at the expense of women's health (Rosenfield and Maine, 1985). The Safe Motherhood Initiative began in 1987 to address this gap in programming. However, after more than a decade of increased attention to maternal health care in the developing world, maternal mortality rates have not measurably declined (Weil and Fernandez, 1999; World Health Organization, 1999; AbouZhar and Wardlaw, 2001). Moreover, the fate of the neonate has been neglected (Lawn et al., 2001; Stoll and Measham, 2001; The Child Health Research Project, 1999). Whereas significant reductions in under-5-year mortality rates and improvements in health indicators such as immunization rates were achieved during the 1990s (United Nations Children's Fund, 2002), neonatal mortality rates, which currently account for half or more of infant mortality, have declined far less quickly (The Child Health Research Project, 1999; Rutstein, 2000).

Over the past 15 years, agencies and researchers working in the field have acquired considerable knowledge about pregnancy and childbirth in low-resource settings. There is increasing agreement on which interventions are most likely to reduce maternal, late fetal, and neonatal mortality. This report reviews the individual—and to a large extent, interdependent—health risks and needs of mothers, fetuses, and neonates and identifies a limited number of interventions to significantly improve birth outcomes[1] in developing countries.

STUDY PURPOSE AND APPROACH

The Centers for Disease Control and Prevention requested that the Institute of Medicine's Board on Global Health undertake a study to examine the steps needed to improve birth outcomes in the developing world. The National Institute for Child Health and Human Development of the National Institutes of Health and the U.S. Agency for International Development joined the sponsorship of the project. The specific charge to the committee is:

Birth outcomes worldwide have improved dramatically in the past 40 years. Yet there is still a large gap between the outcomes in developing and developed countries. This study will address the steps needed to reduce that gap. It will review the statistics of low birth weight and premature infants and birth defects; review current knowledge and practices, identify cost-effective opportunities for improving birth outcomes and supporting families with an infant handicapped by birth problems, and recommend priority research, capacity building, and institutional and global efforts to reduce adverse birth outcomes in developing countries. The committee will base its study on data and information from several developing countries, and provide recommendations that can assist the Centers for Disease Control and Prevention, the National Institute for Child Health and Human Development, and the U.S. Agency for International Development in tailoring their international programs and forging new partnerships to reduce the mortality and morbidity associated with adverse birth outcomes.

[1] In this report, a successful birth outcome is defined as the birth of a healthy baby to a healthy mother.

The initial discussions of this study convinced the committee and the Board on Global Health of the importance and need for a broader study. As a result, the scope of the study was broadened from neonatal outcomes to maternal, neonatal, and fetal outcomes and building capacity in health care systems. In addition, the discussion of perinatal transmission of HIV/AIDS was expanded to a full chapter. The findings and recommendations of this study are intended to assist policymakers, ministries of health, nongovernmental organizations, and academics in developing countries as well as the four sponsors. The committee also wrote a companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World*.

To conduct the studies, the Institute of Medicine assembled a study committee with broad international expertise in public health, neonatology, obstetrics, genetics, epidemiology, pediatrics, and clinical research. The members of the committee were also chosen for their experience on birth outcomes in a range of developing countries. The committee members are listed at the beginning of the report, and their brief biographies are given in Appendix D.

Many health services offered to pregnant women in developing countries are based on traditions and "common wisdom." Relatively few of these have been *demonstrated* to be effective and safe. The goal of this study is to provide evidence-based recommendations founded on rigorous evaluations. The data for the study were assembled by the committee, consultants, and staff through bibliographic references on related topics and through databases such as Medline, university libraries, and Internet sites of organizations associated with research and services for birth outcomes. Although much of the published information on birth outcomes in developing countries was found in international and national journals and reports, some of the evidence has appeared in local journals, the proceedings of meetings, and unpublished reports. To tap this knowledge base, the committee enlisted experts with recent research or service experience in developing countries. Data and supportive evidence were provided by these experts through workshop presentations and technical consultation on the report chapters (see Appendix A). The framework for the committee's examination of birth outcomes included an overview of epidemiological parameters; a review of the current knowledge base on interventions; and a review of the feasibility, cost, and impact of proposed interventions.

The combined weight of such evidence, the committee believes, has produced an accurate account of the state of knowledge concerning the epidemiology of neonatal and maternal mortality and morbidity and fetal mortality, prevention and care in developing countries, and the capacity of health care systems to provide appropriate prevention and care with limited resources. Evaluation of the evidence base enabled the committee to identify gaps in knowledge and to propose strategies for a research agenda that would fill these gaps. The findings, strategies, and recommendations included in the report were developed from this broad base of evidence; areas are noted in which the data are inadequate to support definitive conclusions.

While the committee explicitly searched for the best evidence available on interventions with the potential to improve birth outcomes, and has built its recommendations on this scientific foundation, a note of caution is in order with regard to the nature and adequacy of the evidence base. The best available evidence is sometimes inadequate for a satisfactory evaluation of the cost and effectiveness of promising health care interventions in developing countries. It is often difficult to generalize the results of studies carried out in developed countries to developing country settings. The results of an intervention can differ from one setting to another, and the delivering of interventions is likely to vary considerably across settings. Thus the committee's recommendations regarding the effectiveness of certain interventions in different health care systems are informed by expert judgment as well as scientific research. The committee's research recommendations emphasize the operational research to recognize priority reproductive health problems, identify effective interventions to address these problems, implement the interventions, monitor and assess their effectiveness in diverse settings, and tune them for maximal clinical- and cost-effectiveness.

THE SOCIAL, CULTURAL, AND ECONOMIC CONTEXT

Reproductive health is defined as a condition in which the reproductive process is accomplished in a state of complete physical, mental, and social well-being, not merely as the absence of disease or disorders (Sciarra, 1993). A decade ago, the introduction of this concept raised awareness of the broad social context in which pregnancy and childbirth take place (Donnay, 2000; Sciarra, 1993; Fathalla, 1991). Clearly, health conditions are influenced by the social and political context of countries and communities, which may directly or indirectly contribute to adverse birth outcomes (Tinker, 2000).

While acknowledging the profound influence of sociopolitical factors on birth outcomes and supporting efforts to counteract negative effects, this report focuses on improvements in health care and medical interventions that can produce a more rapid reduction in maternal, neonatal, and fetal mortality. However, it is clear that to be successful, such interventions must be not only clinically effective but also appropriate to the setting in which they are implemented. The following general descriptions of the major social, cultural, and economic influences on birth outcomes are therefore intended to set the stage for the specific discussions of interventions that appear in subsequent chapters of this report, and to place the committee's recommendations within a broader context.

Poverty

Economic factors operating at all levels—from the international to the personal—affect the health status of individuals (Hales et al., 1999). The immediate effects of weak national and local economies on birth outcomes are predictable: limited resources typically reduce the availability of good-quality health services, including obstetric and neonatal care (The Prevention of Maternal Mortality Network, 1992). Family income has been shown to be highly correlated with perinatal mortality in India (Saksena and Srivastava, 1980) and Brazil (Barros et al., 1987), with women from the poorest families having a fetal death rate two to four times higher than that of women from the richest families. A study of 11 Latin American countries found that the late fetal death (stillbirth) rate in free hospitals was nearly twice that in hospitals requiring payment for services (Gadow et al., 1991). And high infant mortality is, not surprisingly, associated with low per capita gross domestic product (GDP) and with income inequalities (Hales et al., 1999). Yet a few countries with low per capita GDP have developed good health services and low infant mortality rates (IMRs). Sri Lanka is a particularly strong example, with a per capita GDP of US$700, a high female literacy rate, and an IMR of 16 per 1,000 live births (Robinson and Wharrad, 2000). Cuba, the poorest country after Haiti in Latin America and the Caribbean, reduced infant mortality from 47 per 1000 live births in 1969 to 19 in 1981 and to 11 in 1990 (Swanson et al., 1995). A program for diagnosis and prevention of genetic diseases was introduced in 4 provinces in 1981 and expanded to include all 14 provinces by 1990.

Infectious disease

Two health problems that profoundly affect birth outcomes—exposure to infectious disease and poor nutrition—are both strongly associated with poverty. At a national level, limited resources for health care restrict prevention and treatment of infectious diseases. Even where health services are available, many women may not be able to afford them. The burden of infectious disease affecting pregnant women is high in developing countries. A strong association has been found between unhygienic conditions, which increase the risk of infection, and maternal and infant mortality (Hertz et al., 1994). HIV infection is a worldwide crisis, but its prevalence and lack of treatment are most significant in developing countries. Other reproductive tract infections associated with poor outcomes, including sexually transmitted diseases (STDs) and vaginal infections, are also highly prevalent in developing countries (National Research Coucil, 1997). Some family planning, antenatal, and maternal and child health clinics in the developing world report that as many as two women in every ten treated are infected with an STD (Cooperative for Assistance and Relief Everywhere, 1997). Moreover, the level of non-STD reproductive tract infections, such as bacterial vaginosis, is thought to be considerably higher than that of traditional STDs among women in developing countries (Bang et al., 1989; National Research Council, 1997; Singh et al., 1995; Younis et al., 1993).

Poverty, low status, racism, social upheaval, and migration all contribute to high-risk sexual behaviors that lead to STDs (Aral and Holmes, 1990). Demographic and social characteristics such as young age, living in a community where women outnumber men (because of war or the lack of local employment), and gender inequality in sexual relationships further compound the risk for STDs. Poverty is associated with additional risk factors for reproductive tract infections: substance abuse, commercial sex, poor access to health care, and young age at the time of first intercourse (National Research Council, 1997).

Nutrition

A healthy diet has long been associated with a successful pregnancy. Malnourished mothers are at increased risk for complications and death during pregnancy and childbirth. In addition, their children are likely to have low birth weight, fail to grow at a normal rate, and have higher rates of disease and early death (Tinker, 2000; United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition, 1994). Poor maternal nutritional status, characterized by low energy intake, low gestational weight gain, low maternal prepregnancy body-mass index (BMI), and short stature, are major contributors to IUGR in developing countries (Allen et al., 1994). A longitudinal study in rural India found that a combination of poverty and a low-quality diet—conditions that tend to occur together—was associated with a significant risk for fetal death (Agarwal et al., 1998).

Women's Education and Socioeconomic Status

Maternal education, literacy, and overall socioeconomic status are powerful influences on the health of both mother and newborn (Biciego and Boerma, 1993; Victora et al., 1992; World Bank, 1993; van Ginneken et al., 1996; Harrison, 1985). Formal and health education of girls can guide women of reproductive age to seek preventive services, increase food intake during pregnancy, reduce tobacco and alcohol use, understand the implications of danger signs during labor and delivery, and seek referral care for obstetric and/or newborn complications. Moreover, the benefits of girls' education extend from one generation to the next, because the children of educated women tend to be healthier and better educated (Hertz et al., 1994).

In particular, female literacy has been found to be a strong predictor of family size and birth spacing, which, as discussed below, strongly affect birth outcomes (Hertz et al., 1994). The gap between female and male literacy in the developing world is significant; in 1990, 18 countries were found to have a female literacy rate less than half that of males (United Nations Children's Fund, 1995). Multiple regression analyses of global data compiled by the United Nations revealed that the combination of GDP and female literacy accounted for 80 percent of the variation in infant mortality rates among 155 countries, and that female literacy appeared to be a factor underlying global variation in the proportion of health personnel (physicians and nurses) in populations (Robinson and Wharrad, 2000).

The educational level of women relative to men in a society both determines and is determined by the degree of autonomy and power of women. These circumstances also influence societal trends (discussed below) in age at marriage and pregnancy, planned or intended pregnancy, and domestic violence. A cross-national analysis of status indicators, such as women's level of education relative to men, age at first marriage, and contraceptive prevalence, showed that all of these factors are in large measure associated with maternal mortality, even after controlling for wealth and economic growth (Shen and Williamson, 1999). Where women's socioeconomic status is low, maternal mortality tends to be higher, and fewer provisions are made for obstetric emergencies (Shen and Williamson, 1999; The Prevention of Maternal Mortality Network, 1992). Gender inequality has also been demonstrated in child mortality rates, nutrition, and health-seeking behavior in developing countries (Institute of Medicine, 1996; Tursz and Crost, 1999).

Unintended Pregnancy

Unintended pregnancy is a global problem with many ramifications that include adverse birth outcomes. Worldwide estimates indicate that between 100 and 150 million married women want to postpone or stop childbearing, but lack access to family planning services (Germain, 2000; Cooperative for Assistance and Relief Everywhere, 1997; Dixon-Mueller and Germain, 1992). If women who want no more children could stop having them, it has been estimated that the number of births would be reduced by an average of 35 percent (4.4 million annually) in Latin America, 33 percent (24.4 million) in Asia, and 17 percent (4 million) in Africa. Maternal and infant mortality would also be expected to decline because many of the prevented pregnancies would have produced high-risk births, or been terminated by unsafe abortion (Sciarra, 1993).

Many barriers, including a lack of quality family planning services, prevent women from controlling their own reproduction. These include poverty, lack of education, and low social status (Germain, 2000). A study based on data from the Demographic and Health Surveys revealed that, because of the combination of a lack of information on family planning, inadequate services, and low literacy, many women do not know enough about the health effects of various contraceptive measures to make informed choices (Bongaarts and Bruce, 1995). In several surveys, women frequently reported that they did not use contraception because of their husband's disapproval (National Research Council, 1997). Although conventional family planning services are available in many developing countries, the contraceptive measures most frequently provided—contraceptive sterilization and intrauterine devices (IUDs)—are inappropriate for adolescents (Germain, 2000).

The most direct consequence of unplanned pregnancy is the estimated 20 million unsafe abortions performed each year (Berer, 2000). About 90 percent of unsafe abortions occur in developing countries (World Health Organization, 1994). Complications from unsafe abortions are thought to cause about 80,000 or more maternal deaths per year (Berer, 2000). The legal status of the procedure is the most important determinant of access to safe abortion. More than 170 million women live in developing countries where most abortions are illegal; these include countries in Central and West Africa, South Asia (other than India), the Middle East, and South America (National Research Council, 1997).

Maternal Age and Parity

Four social factors have been associated with an increased risk of infant death: a mother older than 35; a very young (early adolescent) mother; birth intervals of less than 2 years; and four or more older children (Cooperative for Assistance and Relief Everywhere, 1997). Advanced maternal age has consistently been associated with increased risk for fetal and early neonatal deaths (Nybo Andersen et al., 2000; Murphy et al., 1987; Onadeko et al., 1996; Stanley and Stratton, 1981; Saksena and Srivastava, 1980; Barros et al., 1987). A significant proportion of fetal deaths is caused by chromosomal anomalies, which are more prevalent in the offspring of women older than 35. In some developing countries, many women—due to cultural norms, lack of access to birth control, or both—continue to bear children until they reach menopause, resulting in an increase in the crude prevalence of autosomal trisomies such as Down syndrome. Uterine dysfunction, which can result in obstructed labor (an important cause of maternal, fetal, and neonatal morbidity and mortality), also increases after age 25 (Main et al., 2000).

Young maternal age has been associated with increased risk for early neonatal death (Barros et al., 1987; Saksena and Srivastava, 1980) and infant death (Murphy et al., 1987), but the relationship between young maternal age and fetal death is uncertain (Onadeko et al., 1996; Saksena and Srivastava, 1980). Poor pregnancy outcomes in teenage mothers may result from social and behavioral influences, rather than from a direct biological effect (Hardy et al., 1987), though biological factors may play a role in very young mothers.

Traditions in many developing countries promote early marriage and frequent childbearing. In the least-developed countries, fertility rates exceed five births per woman (United Nations Population Fund, 2002).

Over the years research findings have suggested an association between longer birth intervals of at least 2 years and reduced infant and child mortality. In recent years, there has been a renewed interest in examining the potential association of birth intervals with infant/child/maternal mortality, morbidity, and nutrition status.

Several new studies, some with conflicting findings, have examined the association of longer birth intervals with perinatal and neonatal health. Controlling for demographic and SES variables, and using global data, Rutstein found that birth intervals defined as birth to birth of three to five years are associated with improvements in infant/child survival and nutrition status (Rutstein, 2000). The analysis found that at intervals of two years, infants and children are still at risk. This study was based on data from 18 countries and assessed the outcomes of more than 430,000 pregnancies. Conde-Agudelo analyzed the relationship between pregnancy intervals and perinatal health. The study found that birth intervals of 27–32 months compared to shorter intervals are associated with reduced risk of very preterm and preterm delivery, fetal death, low birth weight, and early neonatal death. This analysis used CLAP data on over 1 million pregnancies (Conde-Agudelo, 2000; Setty-Venugopal and Upadhyay, 2002). Similarly, a recent study by Smith and colleagues based on Scottish data found that a short interpregnancy interval (less than 6 months) was an independent risk factor for extremely preterm birth, moderately preterm birth and neonatal death unrelated to congenital abnormality (Smith et al., 2003). Another study in Sweden has found that short interpregnancy intervals appear not to be causally associated with increased risk of stillbirth and early neonatal death, whereas long interpregnancy intervals were associated with increased risk of stillbirth and possibly early neonatal death (Stephansson et al., 2003).

With respect to the association of birth intervals with maternal mortality and morbidity, only one large-scale analysis has been undertaken. This study (Conde-Agudelo, 2000), using data from the Latin American Center for Perinatalogy and Human Development, found that birth intervals of less than 15 months are associated with increased risk (150 percent) of maternal mortality. Intervals of more than 5 years are associated with increased risk of eclampsia. This study was based on pooled data from 19 countries, with a sample size of just over 450,000 women, and took into account approximately 15 confounding factors.

Cultural Barriers to Obstetric and Neonatal Care

Life-threatening pregnancy and childbirth complications frequently go unrecognized in developing countries. Pregnancy is widely considered to be a time of well-being; complications may be viewed as fated, or even brought on by a woman's misbehavior. Where such beliefs prevail, women and traditional birth attendants tend to perceive obstetric complications as supernatural in origin, and best treated through traditional means (National Research Council, 1997; The Prevention of Maternal Mortality Network, 1992). Because of the expectation of high fetal and neonatal mortality, parents in developing countries may not seek care for their very young offspring. When women and their families recognize the need to seek obstetric or neonatal care, the concern that care will be of poor quality is a barrier to seeking treatment (Ross, 1998; National Research Council, 1997). Those who reach an appropriate medical facility may also find that differences in language, behavior, and expectations between a woman experiencing complications and the medical staff can limit her access to care (The Prevention of Maternal Mortality Network, 1992).

Domestic Violence

Domestic violence is shockingly pervasive, yet hidden in most societies (Bunch 1997; Shaikh, 2000; Jewkes, 2000). A recent global survey of data on the sexual coercion and abuse of women in marriage and other intimate relationships revealed that at least one woman in three has been beaten, coerced into sex, or abused—most often by a member of her family (Germain, 2000). In addition to violating a woman's fundamental rights, such violence may inhibit her use of contraceptives, keep her from seeking health services, or cause her to become infected with a sexually transmitted disease, among other health risks (Germain, 2000). Violence has been linked to increased risk of pregnancy complications, including fetal death, preterm labor, fetal distress, and preterm birth, as well as to teenage pregnancy (Jewkes, 2000; Murphy et al., 2001; Bullock and McFarlane, 1989; Jejeebhoy, 1998; World Bank, 1993; Jewkes et al., 2001).

Natural Disasters and Political Conflicts

In 1999, about one-third of the world's population was affected by floods, earthquakes, and other natural disasters; nearly 14 million people were estimated to be living as refugees and another 20 million displaced within their own countries, largely as a result of political conflict (World Health Organization, 2001). Such crises undoubtedly compound the effects of poverty on maternal, fetal, and neonatal mortality as a result of hardship and suffering, as well as by further limiting access to health care. The magnitude of this problem is poorly documented, however.

Most refugees from armed conflict flee from one developing country to another that can ill afford to provide health care for a refugee population (Southall and Abbasi, 1998). Approximately one-quarter of refugees are women of reproductive age (Jamieson et al., 2000). One of the few studies of pregnancy outcomes among refugee women found that poor outcomes were common in a Burundian refugee camp in Tanzania, with neonatal and maternal deaths accounting for 16 percent of all mortality. More than 22 percent of births to refugees were low birth weight, as compared with the Tanzanian national average of 14 percent (Jamieson et al., 2000). Poor health and birth outcomes have also been shown in Sarajevo (Carballo et al., 1996). As a result of such findings, reproductive health is increasingly recognized as an important component of refugee health. The United Nations High Commissioner for Refugees has stated that "while food, water and shelter remain a priority, reproductive health care is among the crucial elements that give refugees basic human welfare and dignity that is their right" (Marie Stopes International, 1998).

ADVERSE BIRTH OUTCOMES

Inadequate Data on Birth Outcomes

The true magnitude of death, disease, and injury associated with poor birth outcomes in developing countries is not known. Most of the countries with the highest estimated maternal and perinatal mortality rates also have the lowest vital registration coverage (The Child Health Research Project, 1999). Only about one-quarter of the world's births (and if China were excluded, less than 7 percent) are recorded by civil registration systems for the purpose of monitoring maternal mortality (AbouZhar and Wardlaw, 2001). Similarly, the majority of early neonatal deaths and almost all fetal deaths in developing countries—many of which occur at home—are not registered, rendering them invisible to health leaders (Jewkes and Wood, 1998; Lumbiganon et al., 1990; McCaw-Binns et al., 1996). This situation is further complicated by a lack of consistent international definitions of neonatal mortality and by local cultural practices regarding the recognition of early deaths (Jewkes and Wood, 1998; Lumbiganon et al., 1990). In some settings, for example, children are not named nor are their births recognized until after they have survived for up to 40 days (Lawn et al., 2001; Stoll and Measham, 2001). As a result of all of these factors, pregnancy- and birth-related mortality in developing countries are almost certainly underestimated.

Maternal, Fetal, and Neonatal Mortality

Deaths of both mothers and infants are most frequent during the period spanning the onset of labor through the first 28 days postpartum. Within those few weeks, most maternal deaths (except those due to unsafe abortion) and almost two-thirds of infant deaths occur (World Health Organization, 1999; Li et al., 1996). Labor is also perilous for the fetus, particularly in rural areas of developing countries, where few women receive skilled assistance at childbirth. In these settings, intrapartum fetal mortality is high.

Maternal mortality

Complications of pregnancy and childbirth are a leading cause of death and disability among women of reproductive age (15–49 years) in developing countries (Weil and Fernandez, 1999). Globally, more than 70 percent of maternal deaths result from one of five causes (in decreasing order of importance): hemorrhage, sepsis, unsafe abortion, eclampsia, and obstructed labor. Approximately 20 percent of maternal deaths are caused by preexisting conditions that are worsened by pregnancy or its management. Examples include viral hepatitis and HIV/AIDS (World Health Organization, 1999).

Neonatal mortality

The principal direct causes of neonatal death are infectious diseases, birth asphyxia, birth defects, and the sequelae of preterm birth and intrauterine growth restriction. During the early neonatal period (0–7 days), the major causes of death are asphyxia, infection, complications of preterm birth, and birth defects; infections cause most late neonatal deaths (8–28 days) (Lawn et al., 2001). More than 20 percent of children born in developing countries acquire an infection during the neonatal period, which results in 30 to 40 percent of all neonatal deaths (Stoll, 1997).

Fetal mortality

The fetus is particularly vulnerable to adverse influences during the early stages of development. Certain nutritional, infectious, and other environmental factors can be successfully adjusted but many causes are not easily addressed. Late fetal deaths (more than 28 weeks' gestation) include intrapartum and antepartum fetal deaths. Intrapartum deaths predominate in settings where fetal mortality is highest. They typically follow complications of labor and delivery and are more easily prevented than antepartum fetal deaths, which occur before the onset of labor (Sheiner et al., 2000). Antepartum fetal deaths are associated with risks such as maternal conditions, obstetric complications, and advanced maternal age (Conde-Agudelo et al., 2000; Sheiner et al., 2000; Ananth et al., 1999; Seoud et al., 2002).

Linking the Mother, Fetus, and Neonate

Many risk factors affecting the outcomes of mother, fetus, and neonate overlap. The main medical causes of death and disability among neonates (including infection, asphyxia, preterm birth, and intrauterine growth restriction) are associated with poor maternal health and nutritional status (Koblinsky et al., 2000). For example, women in developing countries who give birth to growth-restricted neonates may themselves have been growth-restricted infants and been undernourished since childhood (Ramakrishnan et al., 1999). Chronic maternal infections, such as malaria, further increase the risk of growth restriction.

More directly, poor management of labor and delivery can cause maternal or neonatal infection, exacerbate obstetric complications such as hemorrhage, prolonged and obstructed labor, and hypertensive disease of pregnancy and increase the risk of fetal or neonatal asphyxia. A mother's death is associated with markedly reduced survival of her children, especially infants and daughters of any age (World Health Organization, 1998). The important link between the health of mother and baby should be recognized with combined efforts to improve maternal, fetal, and neonatal health (Stoll and Measham, 2001).

Access to Care

Complications of childbirth may lead to neonatal, maternal, or fetal death if any of the following four steps is not taken in a timely way: recognizing the problem, making the decision to seek care, reaching an appropriate medical facility, and obtaining the needed care (Lawn et al., 2001; Thaddeus and Maine, 1994). For many women in developing countries, each step in this pathway is blocked. Most obstetric and neonatal complications can be managed successfully if recognized and treated in a timely manner, but only about half of all births in developing countries occur under the care of a birth attendant trained to recognize and respond to complications (World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001). If a skilled birth attendant is not present at labor and delivery, complications may not be recognized—

and even if they are, many women in rural areas lack access to a medical facility with good quality obstetric services (World Health Organization, 1998). Their way may be barred by the lack of 24-hour, good-quality essential services and the lack of affordable transportation, lack of recognition of the need for skilled medical care, or the cost of needed services. Or, having reached a medical facility, they may receive inappropriate care due to inadequate staffing, training, or medical supplies. Similarly, few neonates in the rural areas of developing countries receive medical care (Bang et al., 2001).

Building accessible, acceptable, cost-effective health services capable of improving birth outcomes will require appropriate models of health care, national leadership, and support at all levels, from individual communities to international collaborations. Surveillance of maternal, fetal, and neonatal mortality is needed to establish the magnitude of the problem and support the identification and evaluation of interventions to improve birth outcomes.

Three Additional Neonatal Challenges

This report includes discussions of three conditions that pose additional challenges to neonatal health in developing countries: low birth weight (LBW), birth defects, and HIV/AIDS. Each is associated with medical, social, and cultural risk factors that influence its prevalence and severity. In that sense, these conditions can be viewed not simply as isolated causes of neonatal death but as embodiments of the broad range of circumstances that contribute to poor birth outcomes in developing countries.

Data on the worldwide prevalence of LBW (birth weight of <2500 grams) are limited. Estimates based on UNICEF and WHO data for 1995-1999 indicate that 20.4 million LBW infants were born each year (Save the Children, 2001). WHO estimates that LBW affects 17 percent of neonates in developing countries and 6 percent in developed countries (Save the Children, 2001). An infant may be LBW as a result of either intrauterine growth restriction (IUGR) or preterm delivery (<37 weeks). Where LBW rates are highest, the proportion of LBW due to IUGR is also highest (World Health Organization, 1995). IUGR increases the risk of fetal and infant mortality, can negatively affect health and development during infancy and childhood, and may increase the risk of developing certain chronic diseases during adulthood (Barker, 1992; Leon, 1998; Woelk et al., 1998).

More than 4 million children are born each year with birth defects. As infant mortality and morbidity are reduced through the control of infectious diseases, birth asphyxia, and other causes, the relative contribution of birth defects to the burden of disease in developing countries is expected to increase. Risk factors for birth defects that may be higher in developing countries include infectious diseases and nutrient deficiencies (Van Allen and Hall, 1996; Population Reference Bureau, 2002).

Worldwide, half of HIV-infected adults are women, mostly of child-bearing age (Joint United Nations Programme on HIV/AIDS, 2002) who can transmit HIV to their children in utero, during childbirth, or through breastfeeding. Mother-to-child transmission results in an estimated 800,000 new HIV infections each year (Mofenson, 1997; Joint United Nations Programme on HIV/AIDS, 2002). In sub-Saharan Africa and other regions with high HIV prevelance, about one in three children born to mothers with HIV become infected (Brocklehurst, 2002; De Cock et al., 2000); by contrast, vertical transmission of HIV in developed countries can be reduced to less than 5 percent through antenatal HIV testing and antiretroviral therapy (Carneiro et al., 2001; Bulterys and Fowler, 2000).

Child Survival and Safe Motherhood

Leaders and policymakers concerned with maternal and child health have long emphasized the need to reduce both early childhood mortality and, more recently, maternal mortality. A brief history of the two major initiatives toward these goals—those in child survival and safe motherhood—is provided here, as this study recommends building on their successes. This report highlights the common ground between these historically separate initiatives and recognizes the interdependence of maternal and child health during pregnancy, childbirth, and early infancy. It also emphasizes the fates of the fetus and neonate, which have been largely overlooked by child and maternal health programs.

The Child

Before the 1980s, international health care programs emphasized primary health care for a broad range of ages, diseases, and levels of clinical care. A shift in the early 1980s toward strategies targeting diseases that caused the highest percentage of death and illness and for which effective prevention and treatment measures existed, and toward populations with disproportionately high mortality rates, resulted in an increased flow of health resources to children and infants (Murphy et al., 1997). Under this approach, and aided by overall improvements in sanitation and access to health care, under-5 child mortality declined by more than one-third in two decades beginning in the late 1970s (Tulloch, 1999).

Amid these gains, however, it became clear that child health programs needed to go beyond single diseases and address the overall health of the child. The child survival initiative focused at first on growth monitoring, oral rehydration, breastfeeding, and immunization, then expanded to encompass food, female education, and family planning (United Nations Children's Fund, 1997). WHO, working with UNICEF and other agencies, institutions, and individuals, also developed a strategy for the combined treatment of major childhood illnesses in children under 5 known as Integrated Management of Childhood Illness (IMCI) (Tulloch, 1999). The IMCI strategy includes a basic set of prevention, early diagnosis, and treatment measures for acute respiratory infections (ARI), diarrhea, measles, malaria, and malnutrition (Pan American Health Organization, 1999; Tulloch, 1999). A community component of the program coordinates efforts to promote child health and assists families in caring for sick children at home (Pan American Health Organization, 1999). Although IMCI began in 1995 and is underway in more than 41 countries (World Health Organization, 1997), published trials have yet to demonstrate the effectiveness of IMCI measures in reducing child mortality.

Although infant mortality has decreased along with mortality of under-5-year-olds, most gains have been made among children of more than 2 months of age. Since its outset, IMCI has addressed few of the major causes of neonatal and fetal mortality. The most recent guidelines on the integrated management of pregnancy and childbirth include health priorities for infants as young as one week (Gupta et al., 2000). However, these guidelines do not address the major causes of mortality for neonates in the first week of life, nor do they address fetal mortality.

The Mother

In 1985, Rosenfield and Maine published an influential article entitled "Where is the 'M' in MCH?" They asserted that the problem of pregnancy-related deaths in developing countries had been neglected by maternal and child health (MCH) care. To focus on the problem of maternal deaths, the Safe Motherhood Initiative was launched at a Nairobi conference in 1987. Partners in the initiative included UNICEF, the United Nations Development Program (UNDP), the United Nations Population Fund, the World Bank, WHO, the International Planned Parenthood Federation, and the Population Council. Together these agencies set an ambitious goal of reducing maternal mortality worldwide by 50 percent within a decade. They proposed meeting this goal by implementing an integrated approach to maternal health care within primary care, with an emphasis on care and education at the community level (World Health Organization, 1998).

While the Child Survival Initiative through the United States Agency for International Development (USAID) has a specific focus, safe motherhood issues are much broader, encompassing family planning, antenatal care, clean and safe delivery, essential obstetric care, basic maternity care, primary health care, and equity for women. Within numerous maternal and child health care programs, this lack of a strategic focus has contributed to the lack of progress toward reducing maternal mortality (Maine and Rosenfield, 1999; Weil and Fernandez, 1999). Additional reasons include the pursuit of some strategies that proved ineffective (such as large-scale training of traditional birth attendants and the focus on antenatal screening alone to identify high-risk pregnancies) and a lack of political commitment and resources (World Health Organization, 2000). It is important to note, however, that the measurement of maternal mortality has improved in recent years, so direct comparisons cannot be made between today's more accurate estimates and previous underestimates of this indicator (as discussed above) (AbouZhar and Wardlaw, 2001).

Recognizing the importance of integrating maternal and neonatal care, WHO introduced the Mother-Baby Package, a cluster of interventions including family planning to prevent unwanted and mistimed pregnancies, basic maternity care for all pregnancies, special care for the prevention and management of complications during pregnancy, and delivery and postpartum care for mother and newborn (World Health Organization, 1998). In 2000, drawing on the research findings and evaluations of the safe motherhood initiative, WHO launched a 5-year program, the Making Pregnancy Safer initiative. This initiative stresses specific health sector actions, including family planning, antenatal care, the presence of a skilled attendant at every birth, referral centers providing good-quality obstetric services, and basic postpartum care (World Health Organization, 2000). These interventions focus on essential care during pregnancy and childbirth, and bring attention to the fetus and neonate.

The (Missing) Neonate and Fetus

Increasing numbers of children are surviving their first year, but these gains have mostly favored infants of more than a month, and certainly more than a week old (The Child Health Research Project, 1999). Based on data from the Demographic and Health Surveys from 1986 through 1998, approximately two-thirds of under-5 deaths in developing countries occurred to infants (less than 1 year old); among these infants, nearly two-thirds were neonates (less than 1 month old); and among these neonates, nearly two-thirds were less than 1 week old (World Health Organization, 1996). These figures approximate recent estimates by WHO based on data from 1995, which indicate that neonatal mortality accounts for nearly 60 percent of infant mortality (Save the Children, 2001). The importance of reducing neonatal and fetal mortality has only recently begun to be acknowledged, however. Very few field programs have addressed the neonate and estimates of the global burden of disease do not include late fetal deaths as a component of the burden.

Early steps are being taken toward an initiative that would specifically target neonatal and fetal mortality (The Child Health Research Project, 1999; Save the Children, 2000, 2003). Recent grants from the Bill and Melinda Gates Foundation support international programs directed at improving neonatal health, including UNICEF's maternal and neonatal tetanus immunization program and the Saving Newborn Lives Initiative coordinated by Save the Children (Save the Children, 2001; Gates Foundation, 2003). This report recommends cost-effective interventions already shown to reduce neonatal and fetal mortality. Such interventions can be added to or emphasized in existing maternal and child health programs, but it will also be necessary to expand the current focus of the child survival and safe motherhood initiatives to fully recognize and address the issue of improving neonatal health.

ORGANIZATION OF THE REPORT

This report is organized in four parts. The Executive Summary and this introduction constitute Part I. Part II examines—in separate chapters—strategies to improve birth outcomes for mothers (Chapter 2) and neonates (Chapter 3) and to reduce the number of fetal deaths (Chapter 4). Chapters 2 and 3 examine the major causes of mortality and morbidity for mothers and neonates and present findings and interventions to reduce these adverse outcomes. Because the same risk factors underlie many late fetal and early neonatal deaths, and the great majority of them are directly related to the mother's health during pregnancy and her access to skilled attendance and emergency care in the event of complications, it can be assumed that late fetal mortality would decline significantly if the interventions recommended in Chapters 2 and 3 were implemented. For this reason, the discussion of fetal outcomes follows those of the mother and neonate. Chapter 4 also describes the need for systems to recognize and report fetal deaths, an important first step toward identifying further interventions to reduce fetal mortality.

To have the maximum impact on birth outcomes, the interventions recommended in Part II must be implemented within effective health care systems. Part III (Chapter 5) describes the major health care delivery issues related to pregnancy, childbirth, and the neonatal/postpartum period and addresses the implementation of recommended interventions within health care systems and maternal and child programs. Part IV focuses on LBW (Chapter 6), birth defects (Chapter 7), and HIV/AIDS (Chapter 8), three important specific causes of neonatal mortality and morbidity in developing countries. The committee's findings and recommendations are presented with contextual information in the Executive Summary and the recommendations are highlighted in a box in chapter 9 along with concluding comments.

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PART II

Addressing Maternal, Neonatal, and Fetal Mortality and Morbidity

**Summary of Findings:
Reducing Maternal Mortality and Morbidity in
Developing Countries**

- More than half a million women, 99 percent of them in developing countries, die each year from pregnancy-related causes, a leading cause of death among women ages 15-49. The estimated lifetime risk of maternal mortality in some developing countries, where 1 in 11 women die as a result of pregnancy or childbirth, is 500 times that in some developed countries.

- The five most significant direct causes of maternal mortality—hemorrhage, sepsis, unsafe abortion, hypertensive disease of pregnancy, and obstructed labor—together account for about two-thirds of all maternal deaths. Indirect causes, including preexisting conditions exacerbated by pregnancy, account for about 20 percent of maternal mortality.

- With many maternal deaths occurring at home during childbirth, it is difficult to assemble clear epidemiological evidence that skilled attendance at delivery reduces maternal mortality. However, the overall association of skilled attendance with reduced maternal mortality, coupled with a knowledge of strategies that a skilled birth attendant can use to reduce both the incidence of complications and their severity constitute sufficient grounds to recommend that a skilled attendant assist every birth.

- Significant reductions in maternal (as well as fetal and neonatal) mortality can be achieved if complications of childbirth are anticipated and addressed promptly by referral to a facility with the appropriate level of good-quality obstetric care. Access to higher-level care also requires a strong referral system that includes communication with, and transport to, referral facilities.

2

Reducing Maternal Mortality and Morbidity

According to recent estimates, each year more than 500,000 women between the ages of 15 and 49 die of causes related to pregnancy and childbirth—a leading cause of death among women in that age group (Hill et al., 2001; World Health Organization, 1999; Murray and Lopez, 1997; Weil and Fernandez, 1999). Almost all maternal deaths (99 percent) occur in the developing world (World Health Organization and United Nations Children's Fund, 1996; AbouZahr et al., 1996), and more than half occur in Africa (Hill et al., 2001). The vast majority of these deaths are preventable. Researchers also estimate that more than 40 percent of pregnant women experience obstetric disorders that are not immediately fatal (Weil and Fernandez, 1999). Approximately 15 percent of all births are complicated by a potentially fatal condition that requires emergency care (World Health Organization, 1999).

When mothers are malnourished or ill, or when they receive inadequate maternity care, their children also face high risks of disease and death (Tinker, 2000). Tinker (1997) estimates that 30 to 40 percent of infant deaths (1.5-2.5 million) could be averted by maternal interventions alone. This burden of death and illness is borne not only by women and their children, but also by the families and communities that depend upon them (Royston and Armstrong, 1989). For women of child-bearing age (15-44), maternal disorders are the leading causes of death, accounting for almost 16 percent of deaths in this age group (Murray and Lopez, 1997).

According to the International Classification of Diseases (ICD)-10 definition, maternal death is "the death of a woman while pregnant or within

42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes" (World Health Organization, 1999). The most frequently cited measure of maternal mortality, known as the maternal mortality ratio (sometimes mistakenly referred to as a "rate"), is the number of maternal deaths in a population that occur during a given year per 100,000 live births. This number, which represents the risk associated with a single pregnancy, differs by a factor of more than 100 between the highest- and lowest-mortality settings and varies widely among developing countries (see Tables 2-1a and 2-1b) (World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001).

Another useful measure of maternal mortality is lifetime risk—the odds that a woman in a given population will die as a result of pregnancy. In Eastern Africa, as many as 1 woman in 11 dies of pregnancy-related causes, as compared with as few as 1 in 4000 in Western Europe and 1 in 3,500 in North America (World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001). Table 2-1a lists regional and global estimates of the maternal mortality ratio, total annual maternal deaths, and lifetime risk of maternal death. It is important to note that these numbers represent crude estimates at best, since in the regions where the problem of maternal mortality is most acute, it is least likely to be measured accurately (World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001; World Health Organization, 1999). The same caveats apply to estimates of maternal morbidity, which has been reported to occur in up to 30 women for every 1 woman who dies from maternal conditions (Donnay, 2000). In the developing world, one in four women suffers from acute or chronic disability related to pregnancy (Donnay, 2000; World Bank, 1999). Surveillance of maternal mortality, along with other pregnancy and birth outcomes, is discussed in detail in Chapter 5.

CAUSES OF MATERNAL MORBIDITY AND MORTALITY

The five most important direct causes of maternal mortality in developing countries are hemorrhage, sepsis, unsafe abortion, eclampsia, and obstructed labor (Figure 2-1). Together these causes account for more than two-thirds of maternal mortality in the world. Indirect causes of maternal death, which are responsible for approximately 20 percent of maternal mortality worldwide, include preexisting conditions such as malaria and viral hepatitis that are exacerbated by pregnancy or its management (World Health Organization, 1999).

TABLE 2-1a Maternal Mortality Ratio, Maternal Deaths, and Lifetime Risk of Maternal Death: World and Regional Estimates (UNICEF classification of countries used [see Table 2-1b].)

	Maternal Mortality Ratio[1]	Maternal Deaths Annually	Lifetime Risk of Maternal Death 1 in:
World Total	400	515,000	75
More Developed Countries	21	2,800	2,500
Less Developed Countries	440	512,000	60
Least Developed Countries[2]	1,000	230,000	16
Africa	1,000	273,000	16
Eastern	1,300	122,000	11
Middle	1,000	39,000	13
Northern	450	20,000	49
Southern	360	4,500	65
Western	1,100	87,000	13
Asia*	280	217,000	110
Eastern	55	13,000	840
South-central	410	158,000	55
Southeastern	300	35,000	95
Western	230	11,000	95
Europe	28	2,200	2,000
Eastern	50	1,600	1,100
Northern	12	140	3,900
Southern	12	170	5,000
Western	14	280	4,000
Latin America and Caribbean	190	22,000	160
Caribbean	400	3,100	85
Central America	110	3,800	240
South America	200	15,000	150
Northern America	11	490	3,500
Oceania*	260	560	260
Australia and New Zealand	8	25	5,500
Melanesia	310	560	60
Micronesia	—	—	—
Polynesia	33	5	700

[1]Maternal deaths per 100,000 live births.
[2]Subset of less developed countries.
*Australia/New Zealand and Japan have been excluded from the regional totals but are included in the total for developed countries.

SOURCE: World Health Organization, United Nations Children's Fund, United Nations Population Fund, 2001.

TABLE 2-1b Countries Grouped by UNICEF Regions

Industrialized countries

Andorra; Australia; Austria; Belgium; Canada; Denmark; Finland; France; Germany; Greece; Holy See; Iceland; Ireland; Israel; Italy; Japan; Liechtenstein; Luxembourg; Malta; Monaco; Netherlands; New Zealand; Norway; Portugal; San Marino; Slovenia; Spain; Sweden; Switzerland; United Kingdom; United States of America.

Developing countries

Afghanistan; Algeria; Angola; Antigua and Barbuda; Argentina; Armenia; Azerbaijan; Bahamas; Bahrain; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; Brazil; Brunei Darussalam; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde, Central African Republic; Chad; Chile; China; Colombia; Comoros; Congo; Congo, Democratic Republic of; Cook Islands; Costa Rica; Côte d'Ivoire; Cuba; Cyprus; Djibouti; Dominica; Dominican Republic; Ecuador; Egypt; El Salvador; Equatorial Guinea; Eritrea; Ethiopia; Fiji; Gabon; Gambia; Georgia; Ghana; Grenada; Guatemala; Guinea; Guinea-Bissau; Guyana; Haiti; Honduras; India; Indonesia; Iran; Iraq; Israel; Jamaica; Jordan; Kazakhstan; Kenya; Kiribati; Korea, Democratic People's Republic; Korea, Republic of; Kuwait; Kyrgyzstan; Lao People's Democratic Republic; Lebanon; Lesotho; Liberia; Libyan Arab Jamahiriya; Madagascar; Malawi; Malaysia; Maldives; Mali; Marshall Islands; Mauritania; Mauritius; Mexico; Micronesia, Federated States of; Mongolia; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Niue; Oman; Pakistan; Palau; Panama; Papua New Guinea; Paraguay; Peru; Philippines; Qatar; Rwanda; Saint Kitts and Nevis; Saint Lucia; Saint Vincent/ Grenadines; Samoa; Sao Tome and Principe; Saudi Arabia; Senegal; Seychelles; Sierra Leone; Singapore; Solomon Islands; Somalia; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syria; Tajikistan; Thailand; Togo; Tonga; Trinidad and Tobago; Tunisia; Turkey; Turkmenistan; Tuvalu; Uganda; United Arab Emirates; United Republic of Tanzania; Uruguay; Uzbekistan; Vanuatu; Venezuela; Viet Nam; Yemen; Zambia; Zimbabwe.

Least developed countries

Afghanistan; Angola; Bangladesh; Benin; Bhutan; Burkina Faso; Burundi; Cambodia; Cape Verde; Central African Republic; Chad; Comoros; Congo, Democratic Republic of; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gambia; Guinea; Guinea-Bissau; Haiti; Kiribati; Lao People's Democratic Republic; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Mozambique; Myanmar; Nepal; Niger; Rwanda; Samoa; Sao Tome and Principe; Sierra Leone; Solomon Islands; Somalia; Sudan; Togo; Tuvalu; Uganda; United Republic of Tanzania; Vanuatu; Yemen; Zambia.

SOURCE: World Health Organization, 2001.

Hemorrhage

Hemorrhage—primarily postpartum hemorrhage (PPH)—is the leading contributor to maternal mortality worldwide, causing about 24 percent of all maternal deaths (World Health Organization, 1999). In some regions, such as certain Chinese provinces, hemorrhage is reported to account for nearly half of all maternal deaths (Kwast, 1991a). In Indonesia, excessive postpartum bleeding (self-reported) occurs in 7 percent of live births (Central Bureau of Statistics et al., 1995).

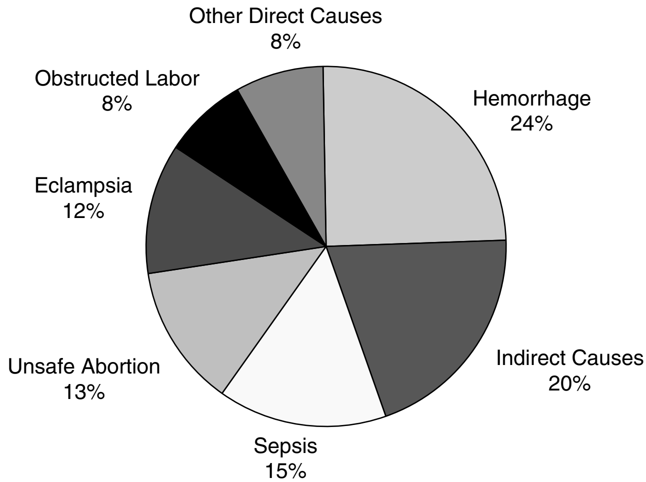


FIGURE 2-1 Global estimates of the causes of maternal deaths.
SOURCE: World Health Organization, 1999.

PPH is the excessive loss—usually of 500 milliliters or more—of blood from the genital tract within 24 hours of delivery (World Health Organization, 1998). If uncontrolled, hemorrhage can quickly lead to shock and death, which generally occurs within 7 days of childbirth. Because of the difficulty of measuring blood loss, a more practical definition of PPH is any blood loss that causes a physiological change such as low blood pressure that threatens a woman's life (McCormick et al., 2002). Immediate PPH is most commonly due to uterine atony, inadequate contraction of the uterus, and a retained placenta or placental fragments (McCormick et al, 2002). Other causes include damage to the genital tract such as cervical tears, perineal lacerations, and episiotomy. Even relatively mild PPH can aggravate existing anemia caused by poor nutritional intake of iron and folate, hookworm infestation, malaria, or repeated short birth intervals. Women who survive hemorrhage frequently suffer from chronic anemia.

Severe anemia, common in developing countries, contributes to high mortality from postpartum hemorrhage. Delivery at home without a skilled birth attendant can result in long delays in obtaining emergency treatment. When the first measures such as use of drugs to stop the bleeding or bimanual compression of the uterus are not taken or are not effective, uterine artery ligation or hysterectomy may be needed, both of which require access to comprehensive essential care services that may involve significant expense and travel. When blood transfusions are required, women are exposed to the risk of infection with HIV, hepatitis B, C, and D, malaria, syphilis, cytomegalovirus, and other agents if blood supplies are unscreened and unsafe.

INFECTIONS[1]

Sepsis

The second leading cause of maternal mortality, sepsis, is estimated to cause 15 percent of all maternal deaths worldwide (World Health Organization, 1999). Puerperal infections are caused by transfer of an infectious agent from the cervix or vagina to the uterus during labor or pelvic examination or by transfer of bacteria from skin, nostrils, and perineum by contaminated fingers or instruments (AbouZahr et al., 1998). The risk of puerperal sepsis is higher for women with sexually transmitted and other infections, premature rupture of membranes, retained products of conception, diabetes, cesarean or other operation, postpartum hemorrhage, anemia, poor nutritional status, history of previous complications of labor, and poor infection control.

The most common sign of puerperal infection is fever, but a small percentage of women with postpartum fever may have an infection at another site or no infection. Coupled with the unavailability and inappropriate use of effective antibiotics, relatively minor puerperal infections can rapidly become life-threatening. Women who survive puerperal sepsis are frequently left to cope with chronic ill health due to pelvic pain, dysmenorrhoea, menorrhagia, and/or infertility (AbouZahr et al., 1998). Information on the incidence and outcome of puerperal sepsis is limited because the majority of women in developing countries deliver at home or are in a clinic or hospital only briefly.

Malaria

More than 40 percent of the world's population lives in malarious areas, and 90 percent of the estimated 300 to 500 million malaria cases occur in sub-Saharan Africa (United Nations Children's Fund, 2000). Malaria in pregnancy has serious health consequences for the newborn, as well as for the mother (see Chapters 3 and 6). Women are more susceptible to malaria infection during pregnancy, but this susceptibility decreases with

[1]Perinatal transmission of HIV/AIDS is addressed in Chapter 8. Primary infection of women with HIV/AIDS and infection with tuberculosis, while important, are outside the scope of this report on birth outcomes.

successive pregnancies (Duffy and Fried, 1999; Miller and Smith, 1998; Brabin, 1983). Where malaria is endemic, adults rarely experience severe illness; however, pregnant women in these populations are at increased risk for high parasitemias and anemia (Miller and Smith, 1998; Diagne et al., 1997). In areas of low malarial transmission, immunity is low, and infection during pregnancy can cause severe disease, including fever and central nervous system complications (Steketee et al., 1996a). HIV infection appears to interfere with the maintenance of pregnancy-specific immunity acquired during first and second pregnancies, placing HIV-positive multigravidae in endemic areas at increased risk for the clinical consequences of malaria (Steketee et al., 1996b; Verhoeff et al., 1999).

Viral hepatitis

Viral hepatitis is the most common cause of liver disease during pregnancy (Pastorek, 1993). The disease, which is caused by several diverse types of virus, is endemic in many regions of Asia, Africa, the Middle East, and Central America where sanitation practices are inadequate (Michielsen and Van Damme, 1999). One form of the disease, hepatitis E, is of greatest concern during pregnancy because of its reported mortality rate of up to 25 percent among pregnant women, compared with a rate of less than 1 percent among the general population (Skidmore, 1997; Aggarwal and Krawczynski, 2000). Pregnant women who contract hepatitis E during the third trimester appear highly susceptible to developing a fulminant infection. Even when the mother escapes liver failure, this infection often causes a fetal death (Michielsen and Van Damme, 1999).

Unsafe Abortion

WHO estimates that about one-quarter of all pregnancies end in abortion, a total of 50 million per year. Of these abortions, an estimated 20 million are performed with unsafe methods, by untrained providers, or by the woman herself (Berer, 2000). About 90 percent of unsafe abortions worldwide occur in developing countries (World Health Organization, 1994a), but there is substantial regional variation in abortion-related mortality, as shown in Figure 2-2. In some areas of Africa, where unsafe abortion exacts the highest death toll, it has been found to contribute to between 20 and 50 percent of maternal mortality (Rogo et al., 1999; Benson et al., 1996; Okonofua, 1997).

Unsafe abortion can lead to a variety of complications, including sepsis, hemorrhage, genital and abdominal trauma, tetanus, perforated uterus, and poisoning from abortifacient medicines (Maine et al., 1994; Bernstein and Rosenfield, 1998; Brabin et al., 2000; Rochat and Akhter, 1999). These

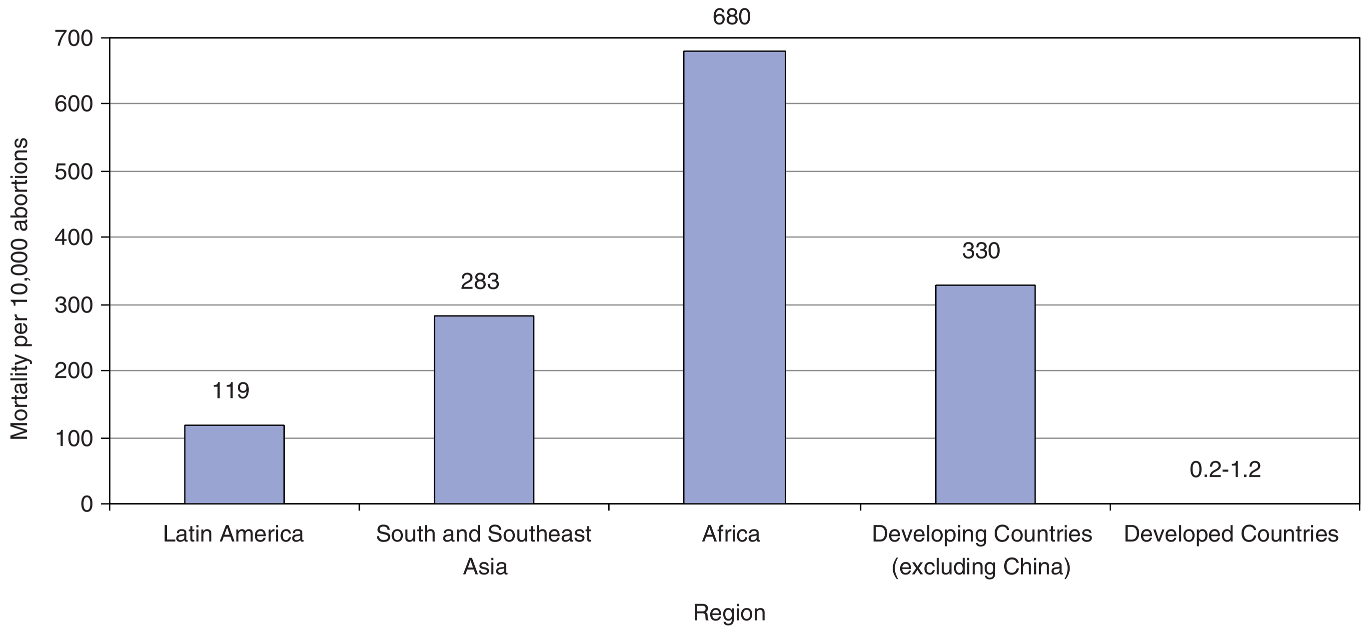


FIGURE 2-2 Global estimates of maternal mortality due to unsafe abortion.
SOURCE: Wulf, 1999.

complications have been estimated to result in at least 70,000 maternal deaths per year, accounting for at least 13 percent of all maternal mortality (Bernstein and Rosenfield, 1998; Maine et al., 1994). Moreover, the treatment of abortion complications consumes a disproportionate share of limited health care resources in developing countries (AbouZahr and Ahman, 1998). For example, in Bolivia in the late 1980s, treatment of abortion complications was reported to consume 60 percent of national spending for obstetric and gynecological care (Maine et al., 1994).

Hypertensive Disease of Pregnancy

Eclampsia is estimated to cause approximately 12 percent of all deaths due to pregnancy-related causes in developing countries (World Health Organization, 1999). A review of hospital-based studies on maternal mortality associated with hypertensive disorders in Africa, Asia, Latin America, and the Caribbean revealed similar rates—between 10 and 15 percent of all maternal deaths—among all regions. In Pakistan, where maternal mortality due to eclampsia has reached an estimated 500 deaths per 100,000 live births, a hospital-based study showed eclampsia to occur in 1 of every 60 deliveries (Jamelle, 1997). Several studies suggest that mortality associated with hypertensive disease of pregnancy is more difficult to prevent than deaths due to other pregnancy-related causes (Duley, 1992; Moodley, 1990; Loudon, 1991).

Obstructed Labor

Obstructed labor is estimated to cause 8 percent of all maternal deaths and also presents serious risks for the fetus and neonate (World Health Organization, 1999). Its incidence varies widely and is particularly high where levels of nutrition are poor and early marriage is common (Kwast, 1992; Konje and Ladipo, 2000). Obstructed labor can often be anticipated, as it is caused by mechanical factors. Women whose growth has been stunted by malnutrition or untreated infection or who bear children before pelvic growth is complete are at greatest risk for cephalopelvic disproportion, disproportion between the size of the infant's head and the bony birth canal, which is the main cause of obstructed labor; fetal malpresentation is another, less common cause (Kwast, 1992).

Prolonged obstructed labor may produce injuries to multiple organ systems, such as vesico-vaginal or recto-vaginal fistulae, and is associated with increased risk of sepsis, hemorrhage, and uterine rupture (Arrowsmith et al., 1996; Konje et al., 1992). In the developing world, women who suffer physical injuries with long-term sequelae resulting from prolonged obstructed labor may also face serious social problems, such as divorce;

exclusion from religious and other social activities; and ultimately, worsening poverty and malnutrition (Arrowsmith et al., 1996).

INTERVENTIONS

The Safe Motherhood Initiative was launched in 1987 as an interagency, international partnership intended to raise awareness of the scope and consequences of poor maternal health in developing countries and provoke action to address the issue of maternal mortality. Through these efforts, access to safe pregnancy and childbirth is beginning to be viewed not just as a public health concern, but as a human right (Thompson, 1999). Yet after more than a decade of increased attention to maternal deaths in the developing world, maternal mortality ratios are essentially unchanged (World Health Organization, United Nation's Children's Fund, 1996). This outcome, which stands in stark contrast to the success of the Child Survival Initiative, resulted in part from a lack of strategic focus in the Safe Motherhood Initiative (Maine and Rosenfield, 1999; Weil and Fernandez, 1999). See Chapter 1 for a discussion of the history of the Safe Motherhood and Child Survival Initiatives.

Maternal health has yet to be perceived as a global priority (Graham, 2002). It is estimated that maternal health services account for 5 to11 percent of total donor contributions to the health sector in developing countries, and 4 to 12 percent of domestic health expenditure (Borghi, 2001). Today the challenge is to provide essential maternal care, consisting of interventions that are most likely to reduce maternal deaths and promote maternal health. Many such interventions, described in the remainder of this chapter, are known to improve fetal and neonatal survival as well, as depicted in Figure 2-3.

Interventions Involving Behavioral Change

Reducing risks for maternal, neonatal, and fetal mortality frequently involves behavioral changes for women. While such changes are often difficult to achieve, they can be facilitated with information about pregnancy, risks, and healthy behaviors (Harrison, 1997). Some examples of behavioral changes in women that are discussed in this report include not reproducing after age 35; eating a healthy diet; limiting or avoiding alcohol consumption; stopping smoking; using a bednet to protect against malaria; arranging for a skilled birth attendant at labor and delivery; and recognizing and acting promptly on signs of a complicated delivery.

Strategies that improve birth outcomes in monitored clinical trials may fail when introduced into large, unmonitored populations if compliance with the intervention is inadequate. As a result, the recommendations in

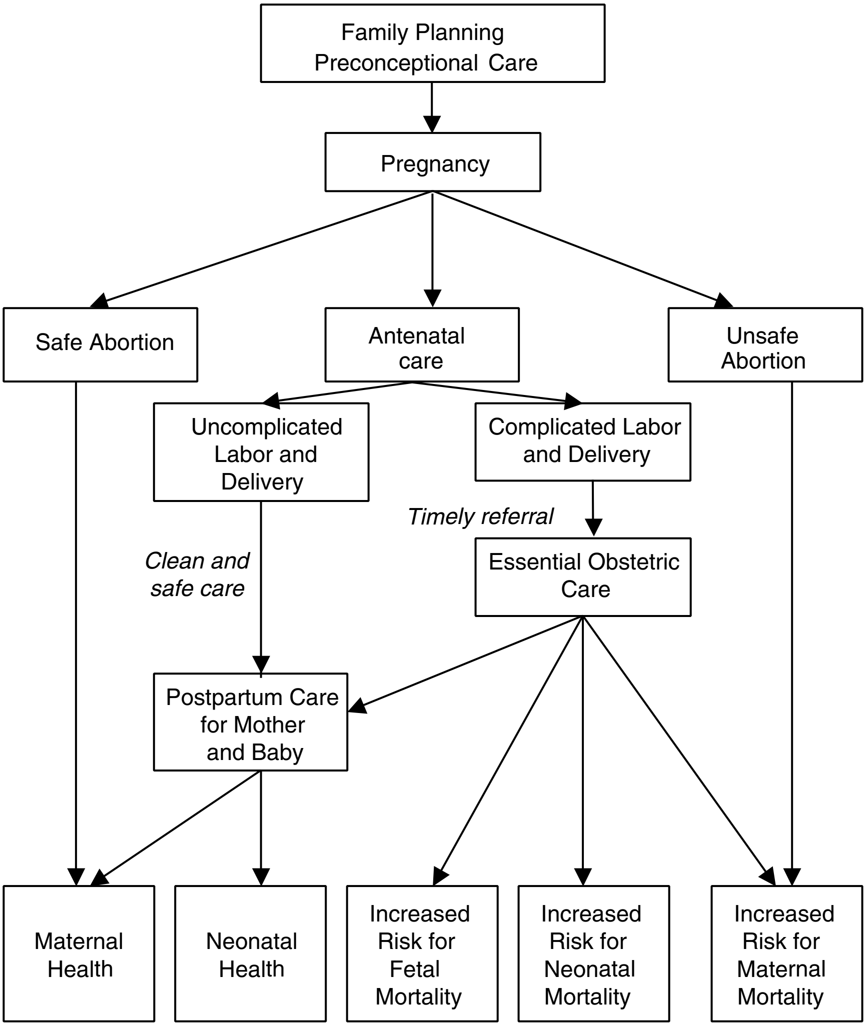


FIGURE 2-3 Health care decisions for improved birth outcomes.

this report focus on strategies that have proven effective in both clinical trials and in large comparable populations. Research that identifies additional strategies for encouraging healthy behaviors can contribute significantly to the success of health interventions that rely on patient compliance over time. Such efforts might involve education of women through campaigns and advice or counseling during antenatal care. They might also involve the development and showing of movies that initiate changes in social behaviors.

Antenatal Care

Many antenatal interventions have been shown to reduce neonatal morbidity and mortality (Bergsjo and Villar, 1997); however, evidence for the effectiveness of antenatal care in reducing maternal mortality (and to a lesser extent, morbidity) is less compelling (McDonagh, 1996). Therefore the main discussion of antenatal care will be presented in Chapter 3 of this report, which concerns the neonate.

It is widely accepted that screening pregnant women to identify those at risk for obstetric complications is not a replacement for skilled care during labor and delivery. More maternal deaths occur in the much larger group of low-risk women. As a result, antenatal care will not necessarily prevent complications from occurring (Maine and Rosenfield, 1999). This was demonstrated in a study in Gambia in the early 1980s in which a relatively high standard of antenatal care was not able to identify the specific risk factors that could predict which women were more likely to experience fatal complications (Greenwood et al., 1987). In addition, those who did experience complications were often located too far from a competent medical facility to receive treatment. As a result, maternal mortality remained extremely high at 2,000 deaths per 100,000 live births (Greenwood et al., 1987).

Where adequate medical care is available, however, certain antenatal interventions appear to be effective in reducing adverse maternal outcomes (Carroli et al., 2001; Villar and Bergsjo, 1997). These include the recognition and treatment of hypertensive disease of pregnancy, detection and treatment of asymptomatic bacteriuria, and external cephalic version at term (to prevent obstructed labor) (Carroli et al., 2001; Villar and Bergsjo, 1997); more controversial are antenatal interventions to prevent maternal anemia and other forms of nutritional supplementation. In addition to the potential for reducing specific causes of maternal morbidity and mortality, antenatal care can also encourage birth preparedness and the use of skilled assistance in labor and delivery.

Recognition of hypertensive disease in pregnancy

A variety of symptoms may occur in women with pre-eclampsia, including headache, edema, visual disturbance, abdominal pain, and nausea. Any of these symptoms warrants a blood pressure check and screening for proteinuria (Walker, 2000). Recording of blood pressure at every antenatal visit is recommended so that hypertensive disease in pregnancy can be recognized and treated before symptoms develop and to prevent eclampsia. A dipstick test for proteinuria is also recommended at the first visit for all women and at subsequent visits for all nulliparous women and those with previous preeclampsia or hypertension (Villar and Bergsjo, 1997). Antihypertensive treatment for women with mild to moderate hypertension during pregnancy remains controversial (Magee and Duley, 2001). The management of hypertensive disease in pregnancy is addressed in a subsequent section.

Detection and treatment of asymptomatic bacteriuria

Routine screening for and treatment of asymptomatic bacteriuria has been shown to be cost-effective (Rouse et al., 1995). Antibiotic treatment prevents pyelonephritis and may also reduce the risk of preterm delivery (Smaill, 2001).

Prevention and treatment of malaria

Pregnant women who live in malaria-endemic areas need access to prevention and/or treatment of malaria and associated anemia. The Cochrane Library has reviewed trials on the effectiveness of prompt treatment of malaria infection, prophylaxis with antimalarial drugs to prevent parasitemia, and reduced exposure to infection by using insecticide-impregnated bednets (Garner and Gülmezoglu, 2000). Prophylaxis with antimalarials is clearly associated with a reduced frequency of disease—lower antenatal parasitemia, lower malarial infection, less anemia, and fewer episodes of fever, and fewer low birth weight infants and preterm births. A recent study in the Gambia (Okoko et al., 2002) adds to the Cochrane review, findings in Ghana published 20 years earlier (McGregor et al., 1983), and findings in other African settings (Garner and Brabin, 1994; Steketee et al., 2001) that intermittent preventive treatment with antimalarials confirms these findings. Intermittent preventive treatment has several advantages: it is easier to sustain over time, more cost-effective, and less likely to cause resistance to antimalarial drugs. The 20th WHO Expert Committee Report recommends an effective one-dose regimen for women in malaria-endemic areas who are in their first and second pregnancies (Steketee, 2002). Sulfadoxine-pyrimethamine is effective in a single dose to semi-immune women, is not bitter, and is relatively well tolerated. In non-African settings where malaria transmission is lower and *Plasmodium vivax* and multidrug resistant *P. falciparum* coexist, finding an appropriate drug regimen is more difficult (Steketee, 2002).

Although insecticide-impregnated bednets have been shown to reduce malaria infection and death among children (Binka et al., 1997; Lengeler, 2000), and are provided free of charge to pregnant women in Kenya (Guyatt et al., 2002), their effectiveness in preventing malaria among pregnant women has not been established. Further studies of bednets are warranted as bednet use requires considerable effort to maintain good adherence and requires resources, yet has significant potential for pregnant women.

Prevention of anemia

Based on data from 1988, WHO estimates that 55 percent of all pregnant women living in developing countries and 18 percent of those in developed countries have anemia, defined as a blood hemoglobin concentration of less than 11 grams per deciliter (World Health Organization, 1992). The effects of anemia on maternal mortality are less well understood. Reports from India, Kenya, Nigeria, and Malawi identify anemia as the underlying cause of 8 to 16 percent of maternal deaths (AbouZahr and Royston, 1991). WHO estimates that one-tenth of maternal mortality in developing countries is atttributable to iron deficiency (World Health Organization, 2002a). Another study concludes that a significant body of causal evidence exists to suggest maternal mortality from severe anemia (Stoltzfus, 2001).

On the other hand, a critical review of existing research in this area concluded that the data available are inadequate for determining the contribution of maternal anemia to maternal mortality (Allen, 2000).

Many factors may predispose a pregnant woman to become anemic, and their relative importance varies by geographic area and by season (van den Broek and Letsky, 2000). The common causes include nutritional deficiencies—iron, folate, and less often vitamin B12; blood loss (childbirth, hookworm infestation); infections (malaria, HIV/AIDS); and genetic defects (sickle cell, α- and β-thalassemias, and some metabolic disorders). In the developing world, nutritional iron deficiency appears to be the predominant cause of anemia; other important causes include malaria and hookworm infection, as well as other micronutrient deficiencies (Guidotti, 2000; van den Broek and Letsky, 2000).

Guidelines for developing countries compiled by WHO, UNICEF, and the International Nutritional Anemia Consultative Group recommend that all pregnant women receive 60 mg of elemental iron and 400 micrograms of folic acid daily to reduce the prevalence of severe maternal anemia (van den Broek, 1998). The guidelines also advise prophylaxis against malaria and hookworm for anemic women in areas where these infections are common. Although iron supplementation can prevent low hemoglobin at birth and at 6 weeks postpartum, there is inconclusive evidence of a beneficial effect on pregnancy outcomes for either mother or child (Mahomed, 2002; Sloan et al., 2002). A multicenter, double-blind, randomized trial in Mexico observed a greater increase in hemoglobin levels in women receiving a daily supplement of both iron (80 milligrams) and folate (370 milligrams) than of iron alone, but did not measure an impact on birth outcomes (Juarez-Vazquez et al., 2002). Rigorous trials need to examine more successful strategies for supplementing iron consumption in communities where iron deficiency is common and anemia is a serious health problem (Mahomed, 2002).

Vitamin A supplementation

Studies conducted in Nepal indicate that vitamin A or β-carotene supplementation may reduce morbidity and mortality in pregnant women related to night blindness, nausea, and length of labor (Christian et al., 2000a, 2000b; West et al., 1999).

Nutritional interventions

Widespread maternal malnutrition in developing countries has created a demand for nutritional interventions. As noted in Chapter 1, malnourished mothers are at increased risk for complications and death during pregnancy and childbirth. In addition, their children tend to have low birth weight, fail to grow at a normal rate, and have higher rates of disease and early death (Tinker, 2000; United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition, 1994). Evidence is insufficient, however, with regard to the clinical efficacy and cost-effectiveness of nutritional supplementation designed specifically to prevent maternal morbidity and mortality, particularly in comparison with other interventions (Ladipo, 2000; Kulier et al., 1998; Rush, 2000). There is some concern that nutritional programs divert resources from interventions that could be more effective in reducing maternal mortality and morbidity (Rush, 2000). While it has been noted that past improvements in nutrition in Western Europe had little effect on maternal mortality, these women were not as malnourished as the target populations for contemporary nutritional programs (Loudon, 2000).

Prenatal counseling to recognize signs of complications

Since every pregnant, delivering, or postpartum woman is at risk for serious, life-threatening complications, an important goal of antenatal care in developing countries should be to teach women and their families to recognize signs of obstetric complications and respond promptly (Akalin and Maine, 1995). Signs and symptoms of pregnancy and labor complications are not always recognized as causes for concern. In rural West African communities, for example, symptoms such as swelling of the feet (a possible sign of pre-eclampsia), late-term spotting or bleeding (a sign of antepartum hemorrhage), and long labors are not viewed as potential medical emergencies (The Prevention of Maternal Mortality Network, 1992).

Prenatal counseling to use a skilled birth attendant

Antenatal care can also contribute to successful pregnancy outcomes by encouraging women to obtain skilled care for labor and delivery. According to WHO estimates, more than half of all women give birth without the assistance and supervision of a skilled birth attendant (World Health Organization, 1997). A study of 300 women from low- and middle-income families in urban India showed that those who received a relatively high level of antenatal care were four times more likely than those who had little or no antenatal care to deliver with a skilled attendant (Bloom et al., 1999). Antenatal care providers can help women and their families find a place to give birth, a skilled attendant, and the essential items necessary for a clean delivery. Planning for delivery should also anticipate complications and the need for referral to an appropriate medical facility with the appropriate level of good quality essential obstetric care. It may involve transport arrangements, emergency funds, a family member to accompany the woman and assist in decisionmaking.

Skilled Attendance at Childbirth

There are two important challenges to achieving a significant reduction in maternal mortality: obtaining skillful services from the birth attendant at labor and delivery and access to higher level obstetric care in the event of complications (Weil and Fernandez, 1999; Koblinsky et al, 1999). Meeting these challenges requires competent health professionals as well as an environment in which they can perform effectively (Graham et al, 2001). This section discusses the evidence for the use of a skilled birth attendant during childbirth.

According to a comprehensive definition of the "skilled birth attendant" given in a 1999 joint statement by WHO, the United Nations Fund for Population Activities (UNFPA), UNICEF, and the World Bank (World Health Organization, 1999), a skilled birth attendant is a person with midwifery skills, such as a midwife, nurse, or physician, who has been trained to proficiency in the skills necessary to manage normal labor and delivery. A skilled attendant recognizes the onset of complications, performs essential interventions, starts treatment, and supervises the referral of mother and baby for interventions that are beyond their competence or not possible in the particular setting. More detailed information on the essential competencies of a skilled birth attendant is given in Appendix C.

There are major differences worldwide and among developing countries in the proportion of deliveries with skilled attendance, the quality of that attendance, the proportion of deliveries that take place in health facilities, and the quality of services in these facilities. There are also important differences in the risks for maternal and neonatal mortality in different settings. In some urban areas of developing countries and in all developed countries, most childbirth takes place in a hospital attended by a physician or midwife. In developing-country urban areas, childbirth may also take place in the home with or without medically trained attendants or in a health clinic with a nurse or physician. In rural areas of the developing world, most childbirth takes place at home, generally without skilled birth attendance, and often with poor access to medical care.

What is the evidence that skilled attendance at childbirth reduces mortality?

For an issue as important as the role of skilled attendance, it might be assumed that randomized, controlled trials would have been undertaken in a range of low- and middle-income settings. Such rigorous trials are particularly challenging (Safe Motherhood Inter-Agency Group, 2000), however, and have not been done. The appropriate outcomes—maternal, neonatal, and fetal mortality—are able to be measured, but since maternal mortality is a relatively rare event, obtaining an accurate estimate of the effectiveness of skilled attendance at childbirth on reducing maternal mortality would require a very large population study. The individual follow-up of each pregnancy adds an additional complication to a very large trial (compared with simpler interventions such as mass vaccination). Such a trial may also have ethical issues involving the withholding of skilled birth attendance from a population of women who are serving as controls in the trial. The result of the cost and complexity of conducting a rigorous trial is that only now—in 2003—is the first discussion of rigorous studies, possibly randomized, controlled trials (RCTs), underway by Initiative for Maternal Mortality Programme Assessment (IMMPACT). It is anticipated that this program will address measurements of maternal, neonatal, and fetal mortality, will undertake rigorous trials on the effectiveness of different strategies to reduce mortality and severe morbidities during childbirth, and that these assessments will include the impact of skilled attendance. There are serious difficulties to be addressed, such as how to randomize the women who are delivering to trained and untrained attendants. Although rigorous cause and effect data are not available, the committee has reviewed the wide range of less rigorous data that are currently available in order to address this important issue. In the committee's judgment, skilled birth attendance has the best evidence so far for reducing maternal and neonatal mortality.

Historical trends

Maternal mortality in 1870 in much of what is now the developed world exceeded 600 per 100,000 live births, a figure comparable with current maternal mortality ratios in many developing countries (Safe Motherhood Inter-Agency Group, 2000). Significant reductions in maternal mor-

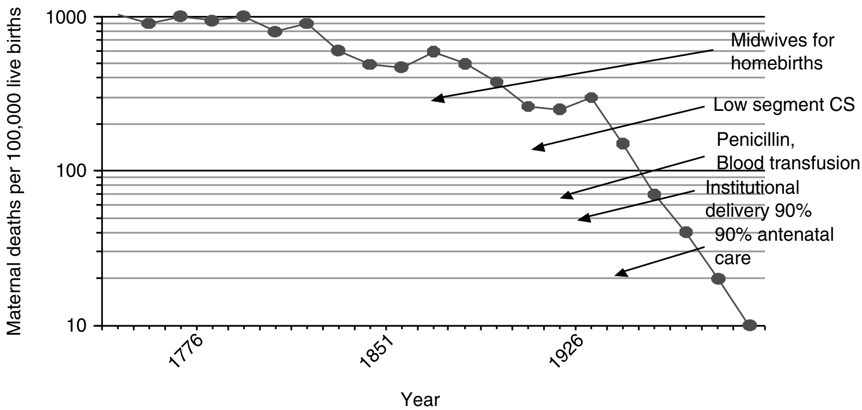


FIGURE 2-4 Maternal mortality in Sweden 1751-1980.
NOTES: CS is cesarean section.
SOURCE: Högberg et al., 1986.

tality were accomplished first in northwestern Europe (Sweden, Norway, Denmark, and the Netherlands) in the mid- to late-19th century, and several decades later in Britain and the United States (Loudon, 2000). In the mid-18th century, policy-makers in Sweden concluded—on the basis of newly collected vital statistics—that maternal mortality could be greatly reduced if all births were attended by qualified midwives (Högberg et al, 1986). The country actively recruited and trained midwives, and, over the course of more than a century, developed a cadre of largely autonomous midwives who worked under the supervision of local physicians (Van Lerberghe and De Brouwere, 2001). Between 1860 and 1900, the percentage of deliveries in Sweden attended by certified midwives increased from 40 to 78 percent, while the maternal mortality rate declined by more than 40 percent (Van Lerberghe and De Brouwere, 2001). This was in marked contrast to the United States, where skilled birth attendance was not promoted and maternal mortality remained at 800 per 100,000 live births (Van Lerberghe and De Brouwere, 2001). Figure 2-4 shows the decrease in maternal mortality in Sweden between 1870 and 1900 considered (but not proven) to be due to the effectiveness of skilled attendance at childbirth. It also shows a second phase of decreasing maternal mortality for about 30 years beginning in 1937, which is considered to be the result of a series of medical advances—cesarean section, penicillin, blood transfusion, institutional delivery, and antenatal care.

Epidemiological trends

National percentages of childbirths assisted by a skilled birth attendant are shown with corresponding maternal mortality ratio (MMR) and infant mortality rate[2] (IMR) data in Figures 2-5 and 2-6 respectively. Similar data are given by region in Table 2-2. Both MMRs and IMRs tend to be lowest where most women give birth with a skilled attendant. In settings where a typical birth takes place at home, not attended by a skilled birth attendant (World Health Organization, 1997), MMRs and IMRs tend to be highest. The associations of skilled care with reduced maternal and infant mortality appear to be strong. Again caution is appropriate in drawing inferences about causality from these associations as other factors could also be involved. In assessing the reliability of the data, it is necessary to consider the problems involved in estimating maternal and neonatal mortality and coverage by skilled attendants. The definition of skilled attendant may vary with country and setting, the effectiveness of attendants varies with their support in terms of supplies and equipment, access to strong referral facilities, their abilities at convincing patients to be referred and accomplishing that in time to influence the outcome, and their oversight and continuing training. The data available aggregates skilled care provided by physicians, nurses, and midwives, which may distort the results that would be observed for midwives alone. Finally, measurement of the association of skilled attendance with neonatal, not infant mortality—almost two-thirds of which is neonatal—would be more specific and therefore more accurate.

Provision of clinical strategies during childbirth

Clinical strategies to address childbirth and its complications are identified in Chapters 2 to 4 of this report. Providing a skilled birth attendant during childbirth who has the knowledge and experience to use certain strategies when they are needed is a key step to reducing mortality and severe disability in childbirth. The second key strategy is provision of good-quality obstetric care for complicated deliveries. For many, childbirth proceeds normally and attendants can focus on the provision of safe and hygienic care and guidance to new mothers on their care and the care of their infants. However, most complications of childbirth cannot be predicted and, when they occur, having a skilled attendant at the delivery is generally the only safe way to provide life-saving clinical strategies. An alternative strategy is to provide broad access to basic or comprehensive essential obstetric care. This is more realistic in urban than rural areas. However, even when higher-level care is

[2]Infant mortality data are used because neonatal mortality data are not available. Neonatal mortality accounts for nearly two-thirds of infant mortality.

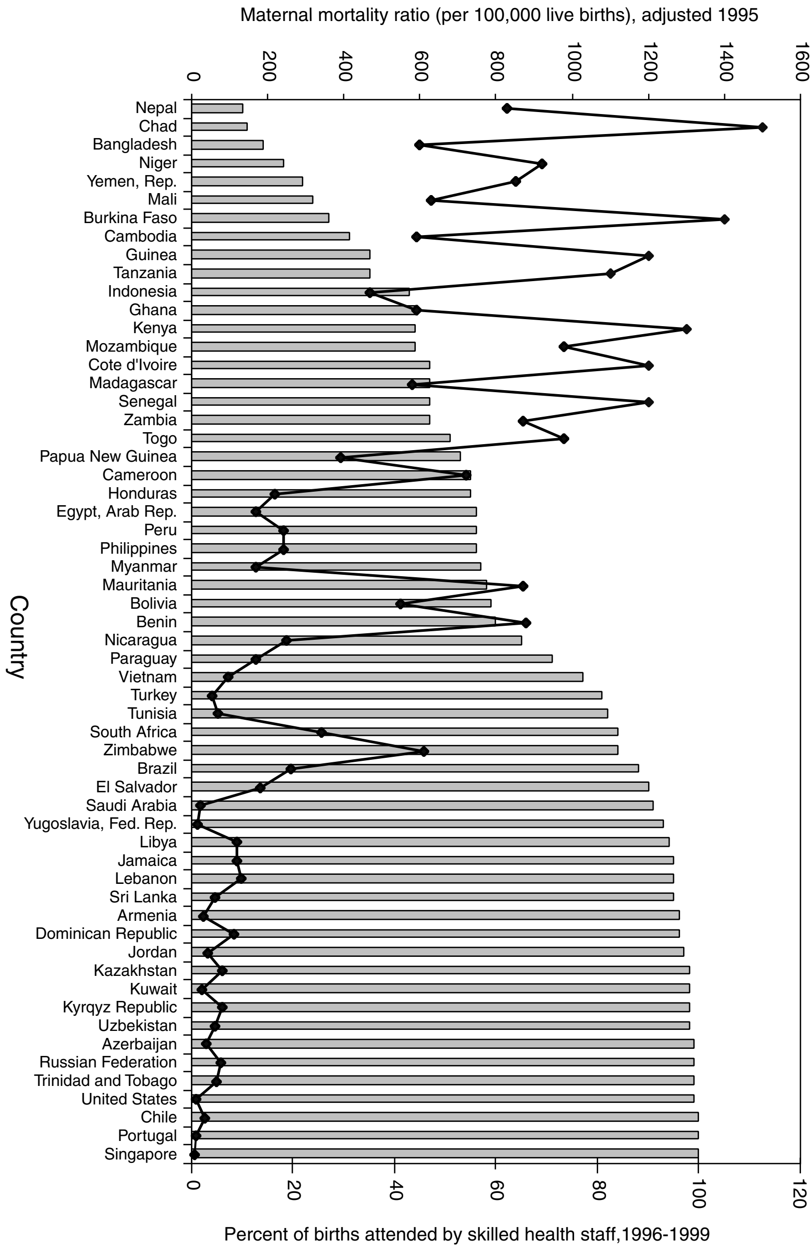


FIGURE 2-5 Association of maternal mortality ratio and delivery by a skilled birth attendant.
NOTES: Bars: Percent of births with skilled attendance. Line: Maternal mortality rate.
SOURCE: World Bank, 2002.

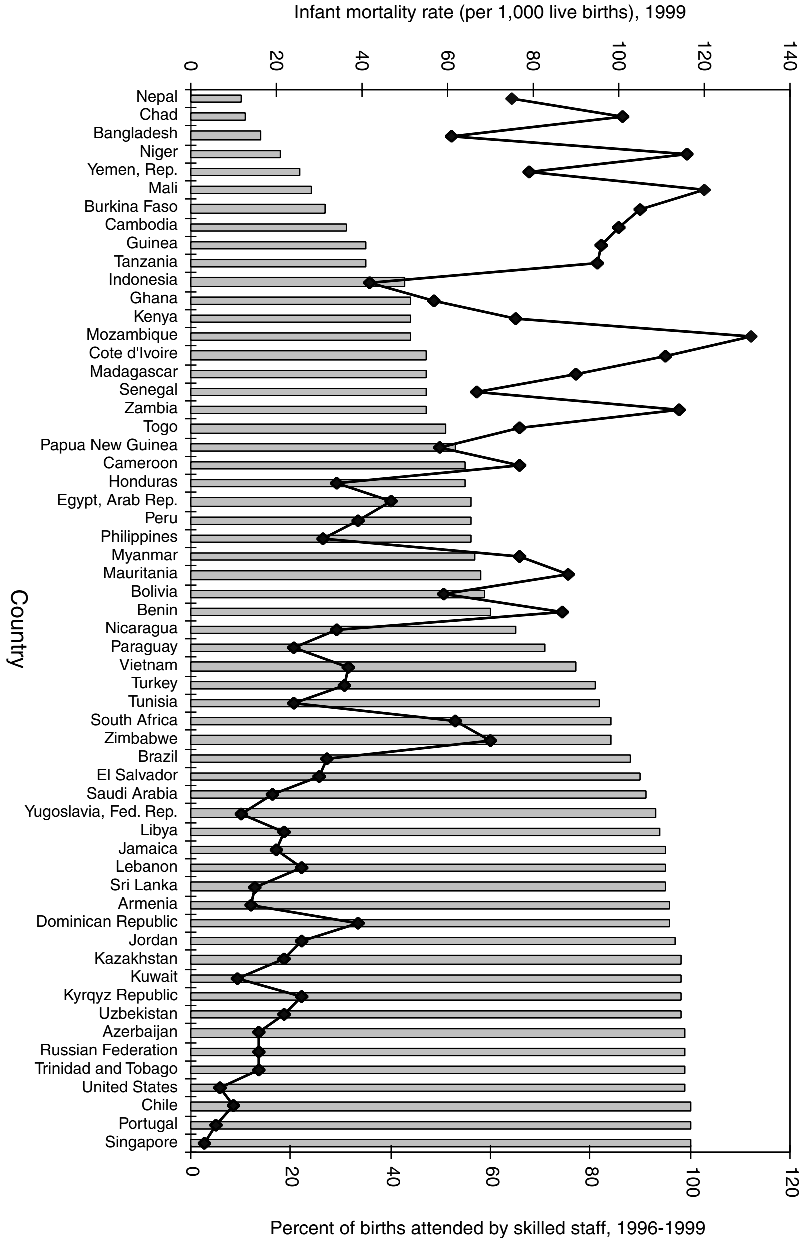


FIGURE 2-6 Association of infant mortality rates and delivery by a skilled birth attendant.
NOTES: Bars: Percent of births with skilled attendance. Line: Infant mortality rate.
SOURCE: World Bank, 2002.

TABLE 2-2 Maternal and Neonatal Mortality Compared with Rates of Skilled Care and Use of Health Facilities for Childbirth

Region	Maternal Deaths per 100,000 live births (1990)	Neonatal Deaths per 1,000 live births (2001)	Deliveries with Skilled Attendant at Delivery (%) (1996)	Deliveries in Health Facilities (%) (1996)
World	430	31	57	46
Developed	27	5	99	98
Less developed	480	34	53	40
Africa	870	42	42	36
Eastern	1,060	41	34	32
Middle	950	39	42	41
Northern	340	32	63	39
Southern	260	18	79	76
Western	1,020	54	34	32
Asia	390	34	53	37
Eastern	95	20	86	54
South-central	560	46	34	26
Southeastern	440	24	53	33
Western	320	22	68	57
Europe	36	6	98	97
Eastern	62	9	NA	NA
Northern	11	4	NA	NA
Southern	14	5	NA	NA
Western	17	3	NA	NA
Latin America/ Caribbean	190	17	75	71
Caribbean	400	19	71	70
Central America	140	13	65	58
South America	200	18	80	78
North America	11	4	99	99

NA: Data not available.
SOURCES: World Health Organization, 1996, 1997; Save the Children, 2001.

very readily accessible, the birth attendant must first recognize a complication and arrange an effective referral.

Although rigorous trials are not available at this time, the committee views the overall association of skilled care with reduced mortality at childbirth, coupled with the need for a skilled birth attendant who can apply the clinical strategies identified in this report when they are needed as sufficient grounds for recommending that a skilled attendant assist at every birth. Providing every delivery with an attendant who has certification in the essential skills, and also the necessary supplies and equipment, access to essential obstetric and neonatal care for complications, an effective referral system, a regular caseload, and appropriate accountability and oversight have been found to be effective in the countries with lower maternal and neonatal mortality. Training a cadre of midwives to provide life-saving care for women during childbirth and developing a strong network of essential care for referral of complicated deliveries is a challenge that must eventually be addressed by all countries.

In most settings, traditional birth attendants (TBAs) are guided by traditional, often untested practices, rather than medical experience. They generally do not carry a regular caseload and do not therefore have the opportunity to build the experience of a nurse or midwife. Many TBAs have received training on safer birth practices, including clean delivery and avoidance of harmful practices. However, they have not been effective in reducing mortality during childbirth. Managing normal deliveries, recognizing complications, and managing and referring patients with complications requires more knowledge, training, and oversight, as well as the ongoing experience that is gained from a regular caseload. Since TBAs are trusted and respected in their community, they can provide comfort for the mother and family during labor and delivery and introduce and facilitate the work of a midwife in the community, but they should not be seen as a substitute for a skilled birth attendant.

In some settings, auxiliary nurse/midwives, community midwives, village midwives, and health visitors have received some training in childbirth skills. These workers may have more education, training, and supervision than TBAs, and (unlike some midwives) live in and know the community, and be less expensive in both their training and continuing compensation. Despite the attractiveness of an apparently less expensive option, the ability of attendants without the skills and experience of a skilled birth attendant to reduce maternal, neonatal, and fetal mortality must be established in trials in similar settings before being adopted for a wider population.[3]

Management of Childbirth

The first stage of labor

In order to prevent maternal mortality and morbidity associated with prolonged labor, the progress of labor should be monitored. Simple and effective monitoring of labor was first used in Zimbabwe in the 1970s (Philpott and Castle, 1972a; Philpott and Castle, 1972b). This involved

[3]This issue is also discussed in Appendix E, Dissenting Note by Dr. Abhay Bang.

BOX 2-1 Monitoring Labor with the Partograph

The partograph is intended for use by health workers trained in childbirth who can observe and conduct normal labor and delivery, perform vaginal examinations, and assess and accurately plot cervical dilation on a graph against time. (WHO Partograph: Figures 2-7a and 2-7b; see following pages).

During first-stage labor, before the cervix has dilated to 3 centimeters, progress may be slow and irregular. This latent phase normally lasts 8 hours or fewer. In active, second-stage labor, cervical dilatation normally progresses at the rate of at least 1 centimeter per hour, indicated as the alert line. Slower rates would be recorded to the right of the alert line, signaling that the woman should be referred to a central facility. There, medical personnel must decide, based on their determination of maternal and fetal condition and the effectiveness of contractions, whether labor should be augmented with oxytocin or delivery should proceed by cesarean section.

The WHO multicenter trial found that using the partograph along with an agreed labor-management protocol produced several significant benefits. Labors lasting more than 18 hours were reduced from 8.3 percent to 4.5 percent in nulliparous women, and from 6.4 percent to 3.4 percent in all women. The proportion of labors requiring augmentation with oxytocin declined from 20.7 percent to 9.1 percent, and the rates of forceps deliveries and postpartum sepsis in both nulliparous and multiparous women reduced to a significant extent. Intrapartum late fetal deaths declined as well from 0.5 percent to 0.3 percent (World Health Organization, 1994b).

graphically tracking cervical dilation over time. A refined version of the initial device, known as the partograph, is now widely used to reduce maternal and fetal morbidity due to prolonged or obstructed labor. The central feature of the partograph is a graphical representation of the progress of labor—cervical dilatation, descent of presenting part, and duration and frequency of contractions—and its relationship to maternal and fetal condition (see Box 2-1). The pattern of cervical dilatation in normal labor among different ethnic groups is so similar that a partograph is useful throughout the world (Lennox and Kwast, 1995).

In the early 1990s, a partograph produced and promoted by WHO was tested in a multicenter trial in Southeast Asia involving 35,484 women (World Health Organization, 1994b). Based on the encouraging results of this trial, WHO recommends widespread use of the partograph. The partograph was revised in 2002 (Figures 2-7a and 2-7b). When used at a health center or maternity center, the device provides an early warning that labor is likely to be prolonged, and the woman should be transferred to a hospital. In the hospital, it can provide a warning that extra vigilance or an

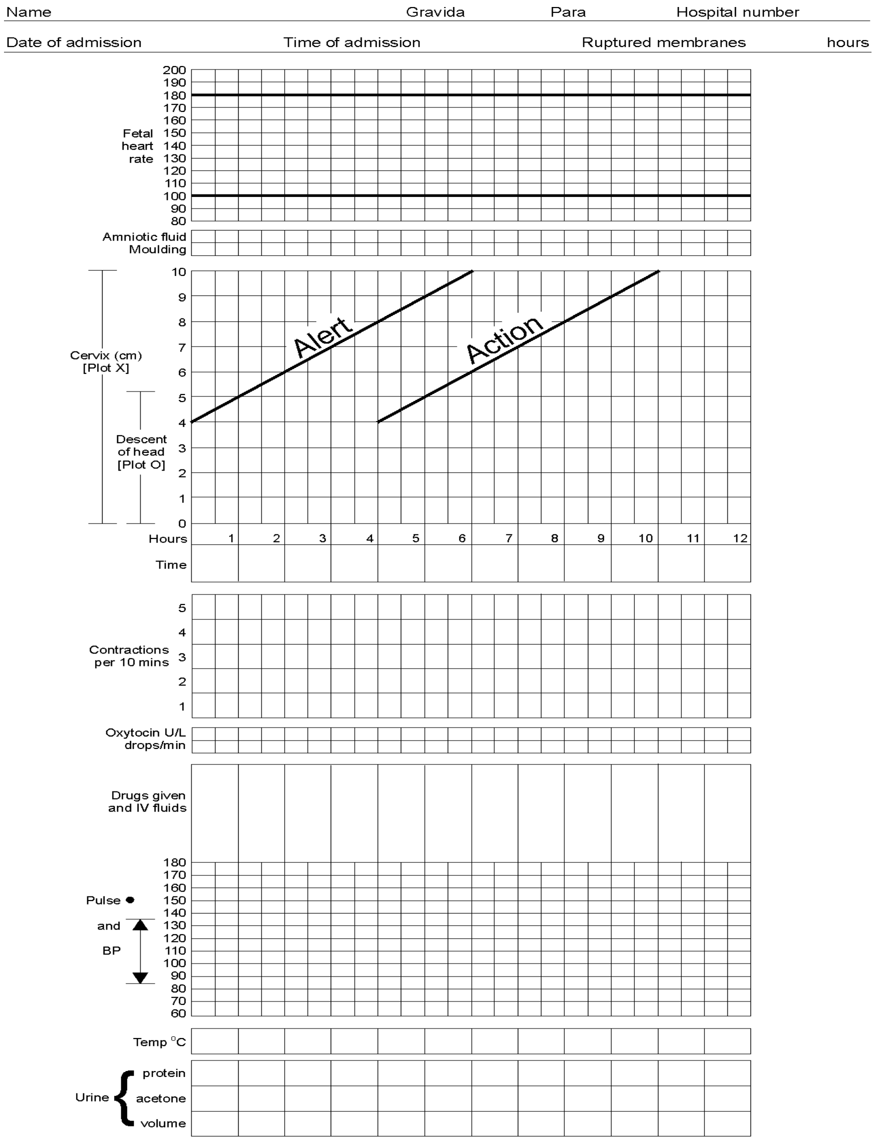


FIGURE 2-7a The WHO Partograph.
SOURCE: World Health Organization, 2002b.

USING THE PARTOGRAPH

Patient information: Fill out name, gravida, para, hospital number, date and time of admission, and time of ruptured membranes or time elapsed since rupture of membranes (if rupture occurred before charting on the partograph began).

Fetal heart rate: Record every half hour.

Amniotic fluid: Record the colour of amniotic fluid at every vaginal examination: I: membranes intact; R: membranes ruptured; C: membranes ruptured, clear fluid; M: meconium-stained fluid; B: blood-stained fluid.

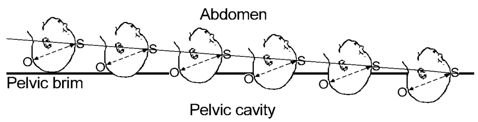
Moulding: 1: sutures apposed; 2: sutures overlapped but reducible; 3: sutures overlapped and not reducible.

Cervical dilatation: Assessed at every vaginal examination and marked with a cross (**X**). Begin plotting on the partograph at 4 cm.

Alert line: A line starts at 4 cm of cervical dilatation to the point of expected full dilatation at the rate of 1 cm per hour.

Action line: Parallel and four hours to the right of the alert line.

Descent assessed by abdominal palpation: Refers to the part of the head (divided into five parts) palpable above the symphysis pubis; recorded as a circle (***O***) at every abdominal examination. At 0/5, the sinciput (S) is at the level of the symphysis pubis.



5/5	4/5	3/5	2/5	1/5	0/5
Completely above	Sinciput high, Occiput easily felt	Sinciput easily felt, Occiput felt	Sinciput felt, Occiput just felt	Sinciput felt, Occiput not felt	None of head palpable

Hours: Refers to the time elapsed since onset of active phase of labour (observed or extrapolated).

Time: Record actual time.

Contractions: Chart every half hour; count the number of contractions in a 10-minute time period, and their duration in seconds.

- Less than 20 seconds:
- Between 20 and 40 seconds:
- More than 40 seconds:

Oxytocin: Record the amount of oxytocin per volume IV fluids in drops per minute every 30 minutes when used.

Drugs given: Record any additional drugs given.

Pulse: Record every 30 minutes and mark with a dot (•).

Blood pressure: Record every four hours and mark with arrows.

Temperature: Record every two hours.

Protein, acetone and volume: Record when urine is passed.

FIGURE 2-7b Directions for use of the WHO Partograph.
SOURCE: World Health Organization, 2002b.

emergency procedure, such as cesarean section, is needed. Use of the partograph has been reviewed by the Cochrane Database of Systematic Reviews (Buchmann et al., 2002). It has been found to assist labor management by clearly indicating departures in the progress of labor and anticipating interventions before complications occur. Interventions that may prevent mortality or serious morbidity for mother or fetus include labor augmentation, cesarean section, or transfer to a more sophisticated facility. The Cochrane review does caution against assuming that all women will progress through labor at the same rate. This assumption could have adverse effects such as increased rates of artificial rupture of the membranes, oxytocin augmentation, and use of analgesia. Despite its effectiveness, however, the partograph has not been universally adopted. A recent survey of 420 physicians and midwives in Enugu, Nigeria, revealed that although about 90 percent of respondents had heard of the partograph, only about 25 percent used it (Umezulike et al., 1999). Introduction of the partograph needs to be accompanied by training in its use with appropriate supervision and follow-up.

The second stage of labor

A recent review of clinical trials concludes that an inadequate number of methodologically stringent comparisons of labor positions have been conducted to allow recommending one position over another; thus women should be encouraged to give birth in the position they find most comfortable (Gupta and Nikodem, 2000). Sustained, early bearing down may slightly decrease the duration of the second stage of labor, but can result in maternal exhaustion and compromised maternal-fetal gas exchange (Mayberry et al., 1999/2000). Several brief periods of breath holding and bearing down during each contraction, which tend to occur spontaneously, appear to be safer for the fetus than Valsalva-type extended pushing with sustained breath holding (Sleep et al., 1989; Mayberry et al., 1999/2000).

Episiotomy is used in many deliveries for first-time mothers despite the fact that there is little evidence to support the frequent use of this technique (Sleep et al., 1989). In fact, episiotomies have been shown in some cases to cause an increase in the rate of perineal trauma (Moller Bek and Laurberg, 1992).

Active management of third-stage labor

Delivery of the placenta and membranes is a particularly hazardous part of childbirth for mothers, because of the risk of postpartum hemorrhage (PPH). Active management involves three steps to augment uterine contractions and prevent PPH due to uterine atony: (1) give a uterotonic drug within one minute of birth; (2) clamp and cut the umbilical cord soon after birth; and (3) deliver the placenta by controlled cord traction and counter pressure on the uterus through the abdomen (McCormick et al., 2002).

Three large RCTs have compared postpartum hemorrhage and other outcomes in deliveries with active management of the third stage of labor and those with physiologic management. These trials—undertaken in Bristol (Prendiville et al., 1988), Hinchingbrooke (Rogers et al., 1998), and Abu Dhabi (Khan et al., 1997)—have been reviewed by the Cochrane Library (Prendiville et al., 2001) and McCormick et al. (2002). The components of active management in the three trials included a prophylactic oxytocic drug during or after delivery of the anterior shoulder, immediate clamping of the umbilical cord, and delivery of the placenta by controlled cord traction or maternal effort. Mothers in the physiologic management group received no oxytocic drug in two trials and only after the delivery of the placenta in the third; no cord clamping until the placenta was delivered, pulsation ceased, or the baby was delivered; and delivered the placenta without assistance. In these RCTs, there was a significantly higher rate of postpartum hemorrhage in the physiologic management group than in the active management group (17.9 vs. 5.9 percent, 16.5 vs. 6.8 percent, and 11 vs. 5.8 percent). Active management thus reduced the need for blood transfusion, the occurrence of a prolonged third stage, and the need for additional uterotonic drugs. There was no difference between the two groups in blood pressure or need for manual removal of retained placenta. The maternal position (upright or supine) did not influence PPH in either group, and neonatal outcomes were not affected by the management of delivery. Giving a uterotonic drug immediately after birth rather than after the placenta is delivered was shown in the Abu Dhabi trial to provide the greatest reduction in PPH. When the placenta was delivered by maternal effort, use of oxytocin reduced the risk of PPH, shortened the time for the third stage of labor, raised hemoglobin levels at 48 hours postpartum, and did not increase the risk of retained placenta.

Currently, oxytocin or syntometrine (oxytocin and ergometrine) are the prophylactic drugs of choice to prevent postpartum hemorrhage (Rogers et al., 1998). The Cochrane Library (McDonald et al., 2000) and McCormick et al (2002) have reviewed several RCTs comparing oxytocin and syntometrine (oxytocin and ergometrine) for their effectiveness in the active management of third-stage labor. While one study showed syntometrine to produce a small but significant reduction in PPH compared with oxytocin (McDonald et al., 2000), the latter was the preferred drug because ergometrine can raise blood pressure and is, therefore, contraindicated for women with hypertensive disease of pregnancy, and it frequently causes nausea and vomiting (El-Refaey et al., 2000). Both drugs require refrigeration and protection from light to maintain their potency, and must be injected, which reduces their practicality in low-resource settings. Increasing evidence indicates that oral or rectal misoprostol, an inexpensive, stable drug, shows promise for reducing postpartum hemorrhage (Ng et al., 2001; Goldberg et al., 2001; Hofmeyr et al., 1998; Surbek et al., 1999; Walley et al., 2000; Bamigboye et al., 1998; O'Brien et al., 1998). Misoprostol[4] is particularly suitable in developing-country settings where oxytocin and ergometrine are unavailable.

An essential package of interventions for care during labor and delivery

In conclusion, an essential package of interventions for care during labor and delivery should include the following:

- Monitoring the progress of labor using a partograph
- Using aseptic practices
- Supporting the birthing position of the mother's choice
- Avoiding medical episiotomy unless specifically indicated
- Preventing postpartum hemorrhage through active management of the third stage of labor

Complications of labor and delivery and provision of essential obstetric care

Even when women receive the highest-quality antenatal care and have skilled providers at the delivery, complications can arise and cause maternal, neonatal, or fetal death. The major causes of maternal mortality described earlier in the chapter (hemorrhage, sepsis, unsafe abortion, hypertensive disease of pregnancy, and obstructed labor) can be addressed by essential obstetric care (EOC) in developing county settings (United Nations Children's Fund, World Health Organization, United Nations Population Fund, 1997). See Table 2-3.

Basic EOC involves six signal services: antibiotic, oxytocic, and anticonvulsant drugs; manual removal of the placenta; removal of retained products of conception (by manual vacuum aspiration with a large syringe); and performance of assisted vaginal delivery (manual assistance, vacuum extraction, or forceps delivery). Other functions are also important, but for

[4]In some Central and Latin American countries, misoprostol is prohibited because it can be used illegally to cause abortion. It is important that a mechanism be established to allow the promising use of misoprostol for reducing postpartum hemorrhage.

TABLE 2-3 Essential Obstetric Care Services to Address Major Causes of Maternal Mortality

EOC services
Basic
1. Administer parenteral[a] antibiotics
2. Administer parenteral oxytocic drugs
3. Administer parenteral anticonvulsants for pre-eclampsia and eclampsia
4. Perform manual removal of placenta
5. Perform removal of retained products (e.g., manual vacuum aspiraton)
6. Perform assisted vaginal delivery
Comprehensive
All basic EOC services
7. Perform surgery (cesarean section)
8. Perform blood transfusion

[a]Parenteral administration of drugs is administration by injection or intravenous infusion (“drip”).
SOURCE: United Nations Children’s Fund, World Health Organization, United Nations Population Fund, 1997.

the purposes of monitoring, the six functions are considered sufficient for most EOC activities.

These six services can prevent a large portion of obstetric deaths and can be carried out by a skilled attendant in a clinic or community health center prepared with medication and intravenous fluid—if the skilled attendant is trained and focused on the frequent direct causes of obstetric deaths. For some cases of postpartum hemorrhage these services would be sufficient. Such a clinic can function as a referral site for patients with these complications who have delivered at home or it can serve as a delivery site. Massive hemorrhage or true obstructed labor will require a hospital facility with blood transfusion, anesthesia, and the capacity for major surgery (cesarean delivery or hysterectomy.) Even then, basic EOC can save women’s lives by stabilizing them before referral and a journey that may take many hours (United Nations Children’s Fund, World Health Organization, United Nations Population Fund, 1997).

Comprehensive EOC involves the six basic services and two additional ones: the ability to perform surgery, including administering anesthesia, and provision of blood transfusion.

In developing countries, women with complicated labors face many barriers to receiving timely and appropriate medical care. These obstacles can be summarized as the following four delays (Lawn et al., 2001), which have been adapted from the original three delays described by Thaddeus and Maine (1994) and Maine (1997):

- Delay in recognizing complications
- Delay in deciding to seek care
- Delay in reaching a health facility because of a lack of transportation or resources
- Delay in receiving appropriate care at the facility

Significant reductions in maternal—as well as neonatal and fetal—mortality can be achieved if complications are anticipated and addressed promptly. For example, a major reduction in maternal mortality achieved over a 15-20 year period in a rural area of the Gambia has been attributed to a combination of increased availability of emergency obstetric care, improved transport, and increased communication (Walraven et al., 2000). These and other interventions to strengthen health care delivery, which are critical to the success of any strategy to improve birth outcomes in developing countries, are discussed in Chapter 5. The following section describes specific interventions to address major complications of labor and delivery.

Management of postpartum hemorrhage requires vigilance to prevent and detect this frequently fatal condition, as well as rapid response to address it when it arises. While the use of blood transfusions may be limited to hospital deliveries, other interventions can be performed at peripheral health centers. These include manual removal of the placenta; bimanual uterine compression; repair of cervical, vaginal, or perineal lacerations; administration of parenteral oxytocics; and uterine massage.

The medications used to control postpartum hemorrhage in the United States include oxytocin (pitocin), methylergonovine (Methergine), 15-methyl PGF (Hemabate), and Dinoprostone (Prostin E2). Unfortunately, most of these require parenteral administration and/or refrigeration,[5] conditions that make them unsuitable for use in many rural areas of developing countries. Misoprostol, discussed above as a possible means of preventing postpartum hemorrhage as part of active management of third-stage labor, also appears promising as a means of controlling hemorrhage, particularly in low-resource settings. Unlike other oxytocic agents, misoprostol does not require refrigeration, an important advantage (O'Brien et al., 1998).

Management of hypertensive disease in pregnancy aims to prevent the occurrence or recurrence of convulsions, which can be life threatening. Magnesium sulfate has been used extensively in the United States for the management and prevention of eclamptic seizures. Several studies, including

[5]In some rural areas, refrigeration is present but not available to obstetric programs.

BOX 2-2 Comparing Anticonvulsant Treatments for Eclampsia

In 1995, the results of an international multicenter randomized trial enrolling nearly 1700 women offered the most compelling evidence to date in favor of magnesium sulfate over diazempam or phenytoin for the treatment of eclampsia (Eclampsia Trial Collaborative Group, 1995). The risk of recurrent convulsions was 52 percent lower for women allocated magnesium sulfate than among those treated with diazepam, and 67 percent lower than among women who were given phenytoin. Although no significant difference in maternal mortality was found among the treatment groups, fewer women allocated magnesium sulfate were ventilated, treated for pneumonia, or admitted to intensive care facilities than women who received phenytoin.

Similarly, no significant differences were found between the groups for major outcomes of perinatal morbidity and mortality. However, infants of women receiving magnesium sulfate were less likely to be incubated at the place of delivery, or to be admitted to a special care nursery, than babies of mothers who had been allocated phenytoin. Other studies have also suggested that the use of magnesium sulfate may reduce the risk of cerebral palsy and possibly mental retardation for very low birth weight infants (Nelson and Grether, 1995; Schendel et al., 1996).

A 1996 quantitative overview of nine randomized, controlled trials of magnesium sulfate for the treatment of preeclampsia and eclampsia—that is, to prevent recurrence of seizures in eclampsia and for seizure prophylaxis in pre-eclampsia—also found the drug to be superior to phenytoin and diazepam (Chien et al., 1996). A 1999 analysis of five trials (involving more than 1200 women) comparing the ability of magnesium sulfate and diazepam to control eclamptic seizures and prevent further seizures concluded the drug was "substantially more effective than diazepam for the treatment of eclampsia" (Duley and Henderson-Smart, 2000).

A more recent study, the Magpie Trial, showed that in comparison with placebo, magnesium sulfate halved the risk of eclampsia among 10,000 women worldwide. Magnesium sulfate also reduced the risk of maternal death by half, but this result did not reach statistical significance (Magpie Trial Collaborative Group, 2002; Greene, 2003; Belfort et al., 2003).

a large collaborative trial, have shown the drug to be superior to phenytoin and diazepam for seizure prevention (See Box 2-2). Results of the collaborative trial suggest that magnesium sulfate confers additional advantages for both mother and neonate (Eclampsia Trial Collaborative Group, 1995). While magnesium sulfate has been viewed as a promising drug for low-resource settings because it is inexpensive and relatively easy to produce, its delivery by intravenous drip or intramuscular injection restricts its use.

A recent review of randomized trials concluded that there is not enough evidence to establish the benefits and hazards of anticonvulsants for women with pre-eclampsia (Duley et al., 2000). A trial involving 14,000 women is currently under way in the United Kingdom to further evaluate the benefits and risks of treating pre-eclampsia with magnesium sulfate (Duley and Neilson, 1999). The Magpie Trial, a recent international study involving 10,000 women, found that magnesium sulfate halved the risk of eclampsia (Magpie Trial Collaborative Group, 2002). A review of the use of magnesium sulfate for pre-eclampsia concludes that, "There is now international consensus that magnesium is the treatment of choice for preeclampsia and eclampsia, but the mechanism underlying its salutary effect remains debatable" (Greene, 2003).

Management of obstructed labor involves timely interventions, including vacuum extraction, forceps, and cesarean section. These procedures, traditionally the domain of physicians, have been performed successfully by trained medical assistants and nurses in Mozambique (Vaz et al., 1999) and Zaire (Duale, 1992), allowing such services to be maintained in rural areas. Mortality and complication rates for cesarean sections performed by these workers were reported to be comparable to those performed by physicians. This is a topic for further studies.

Prevention and management of maternal infection. Infection during labor and in the postpartum period can be reduced through aseptic delivery practices and careful attention to risk factors for infection, including excessive vaginal examinations, premature rupture of membranes, and prolonged labor. Induction of labor in cases of uncomplicated prelabor rupture of membranes has been shown to reduce maternal and neonatal infection (Tan and Hannah, 2000). The early detection of infection and the timely use of antibiotics also reduce maternal morbidity and mortality (AbouZahr et al., 1998; Kwast, 1991b).

Prevention of abortion-related morbidity and mortality. Of the five major causes of maternal morbidity and mortality discussed in this chapter, complications of abortion are the most amenable to reduction through prevention—that is, through improved access to and use of contraception (Maine et al., 1994; AbouZahr and Ahman, 1998). Better contraception would not only decrease the number of unwanted pregnancies, but also reduce neonatal and fetal mortality and morbidity associated with closely spaced births, multiparity, and maternal age. Unfortunately, many barriers restrict women's access to family planning information and services. Even where family planning resources are readily available, unwanted pregnancies occur as a result of failure to use contraception and contraceptive failure (AbouZahr and Ahman, 1998; Henshaw and Kost, 1996).

Abortion tends to be vastly safer in countries where it is legal than where it is prohibited. Legalization of abortion does not appear to increase abortion rates, but does reduce morbidity and mortality (Serbanescu et al., 1995). Yet even where the procedure is legal, safe abortion may still be unavailable to many women because of expense, distance, or social barriers (AbouZahr and Ahman, 1998).

Overused or Inappropriate Interventions

Interventions such as cesarean sections, episiotomies, and use of oxytocics in the early stages of labor tend to be overused in some developing country settings, while they are not always available when needed in other settings (Buekens, 2001). More than 15 percent of deliveries involve a cesarean section in a majority of Latin American countries (Belizan et al., 1999) and in some regions of Asia (Buekens, 2001; Cai et al., 1998). Cesarean sections are less common in Africa, although they are used in more than 5 percent of deliveries in many urban areas of East and Southern Africa and in Ghana. In the poorest rural areas of Africa, the problem is a lack of access to cesarean sections, which are done in less than 1 percent of deliveries.

Episiotomies have become increasingly common, but a Cochrane review has found this increased use to be without scientific justification (Carrolli and Belizan, 2000). More selective use of episiotomy causes less posterior perineal trauma, reduced need for suturing, and fewer healing complications, but there is an increased risk of anterior perineal trauma. Several studies have shown episiotomy rates in African hospitals as high as 46 percent of all deliveries and 87 percent of primiparae deliveries. Similar high rates have been reported in some Latin American countries (Buekens, 2001).

As discussed earlier in this chapter, the routine use of oxytocics during third stage labor has been found beneficial (Prendiville et al., 2001). Use of oxytocin during the first and second stages of labor is, however, controversial, especially in developing countries where it is may be administered intramuscularly or with less control of the speed of infusion, which may hyperstimulate or cause uterine contracture. Use of oxytocin during labor has been associated, in studies in West Africa and Nepal, with increased risk of fetal distress and neonatal morbidity (Dujardin et al.,1995; Ellis et al., 2000).

Inappropriate interventions include pubic shaving, enema, and vacuum and forceps extraction. In settings where the level of hygiene is less strong, vaginal examination is not appropriate, while in other settings these should not be more frequent than necessary because of the risk of infection. Reducing both overuse and inappropriate use of interventions during labor and delivery is best addressed by basing clinical practice on a strong evidence base. This requires continuing evaluation of practices through randomized controlled trials and comprehensive education of birth attendants through influential health leaders, provision of educational materials, and audit and feedback (Buekens, 2001).

RECOMMENDATIONS

A formidable barrier to improving birth outcomes in many developing countries is the social status of women. Achievement of gender equity, and with it increased resources for primary health care, is a certain but long-term means to improving women's reproductive health. More immediate reductions in maternal mortality can be accomplished by addressing its most frequent causes: hemorrhage, hypertensive disease of pregnancy, obstructed labor, sepsis, and unsafe abortion. Significant reductions in maternal—as well as fetal and neonatal—mortality depend on broad access to essential life-saving services during labor and delivery and immediately thereafter. This requires (1) a skilled birth attendant, and (2) access to good-quality essential obstetric care in the event of complications.

> **Recommendation 1. Every delivery, including those that take place in the home, should be assisted by a skilled birth attendant (a midwife, physician, or nurse) who has been trained to proficiency in basic techniques for a clean and safe delivery, and recognition and management of prolonged labor, infection, and hemorrhage. Where necessary, the birth attendant should also be prepared to stabilize and swiftly refer the mother to a facility providing essential obstetric care.**[6] (See Chapter 3 for the neonatal component to this recommendation.)

> **Recommendation 2. Essential obstetric care should be accessible to address complications of childbirth that cannot be managed by a skilled birth attendant. This requires a network of good-quality essential care facilities that provide basic essential obstetric care: administration of antibiotic, oxytocic, and anticonvulsant drugs; manual removal of the placenta; removal of retained products of conception; and assisted vaginal delivery. Comprehensive essential obstetric care facilities have the capacity to perform these basic services and also surgery and blood transfusion. Access for the majority of a population to the appropriate level of care also requires strong referral systems that include communication with, and transportation to, referral facilities.** (See Chapters 3 and 5 for additional components to this recommendation.)

These two interventions, which represent the highest priority for reducing maternal mortality, should be extended where possible by a program of postpartum maternal care addressing major causes of maternal mortality and morbidity during the first month after childbirth.

[6]This issue is also discussed in Appendix E, Dissenting Note by Dr. Abhay Bang.

Recommendation 3. Postpartum care is critical during the first hours after birth and important throughout the first month. For the mother, such care should emphasize the prevention, timely recognition, and treatment of infection; postpartum hemorrhage; and complications of hypertensive disease of pregnancy. (See Chapter 3 for a neonatal component to this recommendation.)

While many of the benefits of antenatal care accrue to the fetus and neonate, certain preconceptional and antenatal interventions can significantly reduce maternal mortality and morbidity.

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- **Greater access for women and men of reproductive age to family planning services that provide effective contraception along with counseling on the risks for adverse birth outcomes.**
- **Early detection and timely management of hypertensive disease of pregnancy.**
- **Intermittent preventive and early treatment of malaria, especially for primiparae.**

(See Chapters 3, 6, 7, and 8 for other components of this recommendation.)

RESEARCH NEEDS

The challenge for research in the 21st century is to identify interventions that can reduce maternal, neonatal, and fetal mortality in the developing world and thus make childbirth a safe event. This will require particular attention to the obstetric and neonatal problems of populations with high mortality. Promising interventions must be tested with trials that are both rigorous and practical. Successful interventions must be monitored and adjusted for optimal effectiveness. A wide range of basic and applied research will need to be encouraged and funded through partnerships of ministries of health, international organizations and development agencies, nongovernmental organizations, and philanthropic foundations.

Each country will determine its research agenda according to local priorities and the resources that can be made available. Setting priorities for health-related research involves consideration of several factors: the magnitude of a health problem in the local population, the likelihood of identifying a successful intervention, the interests and capabilities of researchers, and the public perception of the importance of the health problem. It is important to consider all factors in each setting and to balance them for the best interests of the population in question (Brown, 1977).

The following areas of research have been identified by the committee as key to the continued improvement of maternal and overall birth outcomes. Research priorities that target other topics appear in the corresponding chapters.

- Studies are needed to determine the burden of disease caused by maternal and neonatal bacterial infections in different settings. Research should include the identification of etiologic agents and their antibiotic susceptibility. Strategies for prevention and treatment should be informed by community-based data, including laboratory evaluations. Simple methods to identify mothers and neonates with presumed bacterial infection (such as algorithms based on patient history and physical findings) are also needed.
- For areas of the world with limited laboratory capacity, there is a need to develop simple, cost-effective diagnostic tests that can be used in a field setting. Diagnostic capabilities at health centers and referral hospitals must also be strengthened.
- Large, multicenter trials are needed to examine the cost-effectiveness of food and micronutrient supplementation in relation to maternal and neonatal health and fetal survival, particularly in areas where undernutrition is common. Local studies can determine the most effective means of supplementation to improve the nutritional status of the population, and thus of women who become pregnant.
- Studies are needed to determine whether the level of antibiotic resistance in rural communities is significantly lower than in urban hospitals.
- Studies are needed to evaluate the targeted use of antibiotics for those women at risk for infection during delivery who cannot be transferred to a hospital or who refuse hospital care.
- Strategies to prevent malaria during pregnancy are needed, including ways to reduce exposure (e.g., insecticide-impregnated bednets). Antimalarial drug resistance is widespread. Research on the safety and efficacy of new drugs and drug combinations should target pregnant women.
- Trials are needed to compare the effectiveness of intermittent prophylactic antimalarials with early treatment of malaria for women having their first or second baby. These strategies need to be tested in populations where malaria is endemic and women have some acquired immunity and in those where malaria is not endemic and there is less acquired immunity.
- Trials are needed to identify more effective approaches to accomplishing behavior changes that reduce risks for adverse birth outcomes. The behavioral changes sought include stopping smoking, avoiding pregnancy over the age of 35 years, and recognizing the need for skilled care in pregnancy.

CONCLUSION

The wide gap between MMRs in developed countries and developing countries, where the vast majority of maternal deaths occur, suggests that much can be done to improve maternal survival. The two central, interdependent elements of any strategy to improve maternal health are the provision of skilled assistance for every delivery and access to essential obstetric care for complicated cases. Efforts to improve maternal outcomes could be greatly strengthened through programs of antenatal and postpartum care focused on the prevention and recognition of complications of pregnancy and childbirth. Substantial reduction of maternal mortality and morbidity will require long-term investment in community education and family planning and, ultimately, the empowerment of women.

Many measures that can be taken to improve maternal health—from specific medical interventions, to research, to the strengthening of women's socioeconomic status—are likely to benefit the fetus and neonate as well. The interventions recommended in this chapter can work in conjunction with interventions that address neonatal and fetal mortality.

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Summary of Findings: Reducing Neonatal Mortality and Morbidity in Developing Countries

- An estimated 4 million neonates (aged up to 28 days) die each year. These deaths account for about 40 percent of under-5 mortality and two-thirds of infant (aged up to 12 months) mortality. Ninety-eight percent of neonatal deaths occur in developing countries.
- The true burden of neonatal mortality in developing countries is unknown because many deaths occur in the home and are not reported. Limited epidemiological research indicates the main causes of neonatal deaths are infections, birth asphyxia, birth injuries, complications of preterm birth, and birth defects.
- Because complications of childbirth too frequently cause neonatal death, skilled assistance is recommended for all deliveries along with access to the appropriate level of neonatal care when needed.
- Preconceptional and antenatal care provide an opportunity to reduce risk factors for neonatal mortality and morbidity. These include detection and treatment of maternal infections; immunization of women of reproductive age against tetanus; and counseling on risks to a healthy pregnancy and birth preparedness, emphasizing the importance of a clean and safe delivery assisted by a skilled birth attendant.
- Clean and safe newborn care should prevent and manage neonatal infections and other illnesses that can otherwise become life threatening. Caregivers must be able to recognize signs of illness, and when they appear, promptly seek appropriate medical assistance.

3

Reducing Neonatal Mortality and Morbidity

The greatest risk of childhood death occurs during the neonatal period, which extends from birth through the first month of life. About 60 percent of all deaths to children under age 5 and nearly two-thirds of infant deaths (birth to 12 months) occur during the neonatal period (Rutstein, 2000). About two-thirds of all neonatal deaths occur during the first week of life. Current estimates place the annual neonatal death toll at 4 million (Save the Children, 2001).

Approximately 98 percent of neonatal deaths occur in the developing world (World Health Organization, 1996b). The highest annual neonatal rates are in South Asia, where an estimated 51 deaths occur for every 1,000 live births. Each year in South Asia alone, 2 million children die within a month of their birth. By comparison, the rates per 1,000 live births are 42 in Africa, 25 in Latin America, and fewer than 10 in Europe and North America (World Health Organization, 1996b). The burden of neonatal morbidity in developing countries is unknown; however, a recent study of neonatal morbidity in rural India revealed that nearly half of the 763 infants observed developed high-risk morbidities (those with a case fatality greater than 10 percent), and nearly three-quarters suffered low-risk morbidities, some in addition to high-risk conditions (Bang et al., 2001).

CAUSES OF NEONATAL MORBIDITY AND MORTALITY

Most neonatal deaths occur at home, following unsupervised deliveries; thus little accurate information is available as to their causes (Stoll,

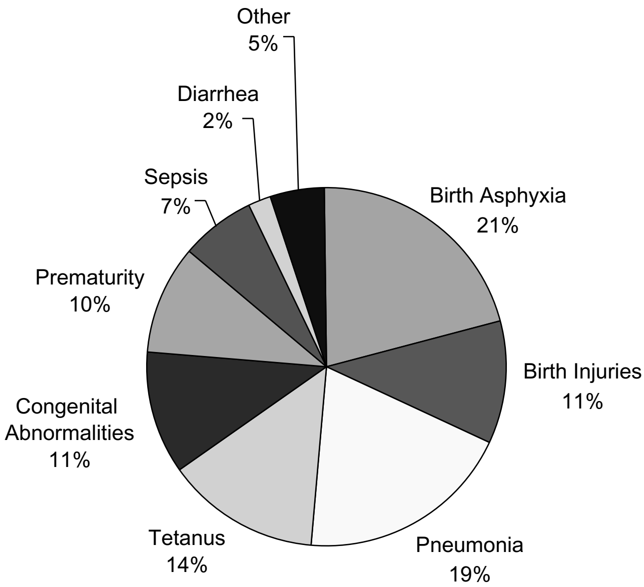

FIGURE 3-1 Global estimates of the direct causes of neonatal mortality.
SOURCE: WHO Mother-Baby Package, 1994.

1997). Limited epidemiological research indicates that the principal direct causes of neonatal death are infectious diseases, birth asphyxia, birth injuries, and the sequelae of preterm birth and birth defects (Figure 3-1). During the early neonatal period (0-7 days), the major causes of death are asphyxia, infection, complications of prematurity, and birth defects; infections cause most late neonatal deaths (8-28 days) (Lawn et al., 2001).

This chapter addresses neonatal infections, birth asphyxia, birth injury, hypothermia, and hyperbilirubinemia. Strategies to reduce mortality and morbidity associated with low birth weight are discussed in Chapter 6; those associated with birth defects, in Chapter 7; and those associated with perinatal transmission of HIV, in Chapter 8.

Infectious Diseases

Infections are the major cause of mortality and morbidity in infants under 3 months of age in developing countries (Stoll, 1997). As noted in Chapter 1, more than 20 percent of children born in developing countries acquire an infection during the neonatal period, leading to an estimated 30 to 40 percent of all neonatal deaths (Stoll, 1997; Stoll, 2000). Most of these deaths are caused by acute respiratory infections, bacterial sepsis and/or

TABLE 3-1 Estimated Global Burden of Disease Due to Major Neonatal Infections

Infection	Estimated No. of Cases	Estimated Case Fatality Rate*	Estimated No. of Deaths
Sepsis	750,000	40%	300,000
Meningitis	126,000	40%	50,400
Tetanus**	355,000	70%	248,000
Acute respiratory infections	2,650,000	30%	800,000
Diarrhea	25,000,000	0.6%	150,000
HIV	550,000	na	na
Total	29,431,000	—	1,548,400

na = Data unavailable: Most HIV-related deaths occur after the neonatal period.
* Fatality rates may be much higher in developing countries.
** Updated data from World Health Organization, 1999a.

SOURCE: Stoll, 2000 (data from 1995).

meningitis, neonatal tetanus, and diarrhea (Table 3-1). Maternal infections, including sexually transmitted diseases (STDs) such as HIV (the topic of Chapter 8) and syphilis, can be transmitted to the fetus or newborn in utero, through contact during labor and delivery, and in some cases, through breastfeeding.

Sepsis

In many countries, bacterial sepsis accounts for a substantial burden of disease and has a 40% case fatality rate (Stoll, 2000). Early-onset neonatal sepsis (48-72 hours) usually results from organisms acquired from the maternal genital tract during birth and often is associated with maternal complications; late-onset neonatal sepsis (7-28 days) is more likely to be caused by organisms acquired from the environment (Korbage de Araujo et al., 1999; Martius et al., 1999; Moreno et al., 1994; Kuruvilla et al., 1998; Schuchat et al., 2000; Stoll et al., 2002a,b).

Estimates of the incidence of neonatal sepsis are based largely on cases that reach the hospital, which undoubtedly underestimates the incidence in the community. In pooled data from hospital-based case series, the incidence was 6 cases per 1000 live births (Stoll, 2000); other studies suggest that rates may be even higher (Kuruvilla et al., 1998; Asindi et al., 1999). Among patients enrolled in the WHO Young Infants Study—a study of infants under 3 months of age with serious infections conducted at four sites (Ethiopia, the Gambia, Papua New Guinea, and the Philippines)—30 percent of infants with a positive blood culture died (WHO Young

Infants Study Group, 1999a). In 47 hospital-based studies, case fatality rates were as high as 69 percent (Stoll, 2000). Left untreated, bloodstream infections can spread to the meninges, resulting in meningitis. Estimates of neonatal meningitis incidence range from 0.3 to 2.8 per 1,000 live births (average 1/1000 live births), and reported case fatality rates range from 13 to 59 percent (Stoll, 2000).

Omphalitis (umbilical infection) continues to be a problem in developing countries (Cushing, 1985). Births in the home, nonsterile cutting of the cord, and unhygienic cord care after birth all increase the risk of omphalitis. Because localized umbilical infection is not prevented and may be inadequately treated in developing-country settings, it may be associated with the subsequent development of necrotizing fasciitis and/or neonatal sepsis (Faridi et al., 1993; Weber et al., 2001). Moreover, omphalitis in patients with neonatal tetanus (discussed below) is associated with an increased risk of bacterial sepsis (Egri-Okwaji, 1998).

Because the majority of developing-country studies that present data on the bacterial etiology of neonatal sepsis and meningitis are hospital-based, they may not reflect what is happening at the community level. While group B streptococcus (GBS) remains an important cause of early neonatal sepsis in industrialized countries (Schuchat, 1998), it appears to be a much less important pathogen in developing countries (WHO Young Infants Study Group, 1999a; Stoll, 2000). The most frequent organisms reported from case series in developing countries are gram-negative organisms (especially *Escherichia coli* and Klebsiella) and *Staphylococcus aureus* (Stoll, 2000; Mulholland, 1998). The organisms responsible for neonatal sepsis and meningitis are similar, change over time, and vary by geographic region. Therefore, prospective microbiological surveillance is key for prevention and appropriate treatment of these diseases.

The emergence of antibiotic-resistant pathogens is a particularly alarming problem in developing countries. Hospital-based studies of the bacterial etiology of neonatal sepsis and reports of nosocomial outbreaks from a variety of countries demonstrate that the problem of antibiotic resistance is of global concern (Banerjee et al., 1993; Reish et al., 1993; Haddad et al., 1993; Bhutta, 1996; Ako-Nai et al., 1999; Musoke, 1997; Musoke and Revathi, 2000). The widespread availability of antibiotics and their indiscriminate and inappropriate use contribute to this problem, along with poor infection-control practices in hospitals.

Surveillance capacity and the transfer of surveillance information must be developed to determine both the global and local impact of resistant microorganisms and to identify interventions that can address this threat (Williams, 2001). Strategies are needed to reduce the risk of infection, as well as to encourage the judicious prescription and appropriate use of antibiotics in the community and in hospital (Levy, 2001; Boyce, 2001;

Perchère, 2001; Bell, 2001; de Man et al., 2000). Some epidemiologists caution, however, that the prudent use of antibiotics is unlikely to reverse resistance trends and that the true clinical impact of antibiotic resistance has not yet been measured (Phillips, 2001).

Acute respiratory infections

Pneumonia and other acute respiratory infections (ARIs) account for up to a quarter (Pan American Health Organization, 1999) or perhaps more of all mortality in children under 5, but it is difficult to determine the incidence of neonatal ARI in developing countries because many sick neonates are not referred for medical care. The risk of death due to ARI is highest in young neonates and decreases with age (Garenne et al., 1992).

Most ARI deaths are due to pneumonia, which annually kills more than 3 million children under the age of 5 in developing countries (Garenne et al., 1992). Like sepsis, neonatal pneumonia may have an early onset if acquired from the maternal genital tract or a late onset due to infection from the hospital or home environment. Bacterial pneumonia is the most common; streptococcus pneumoniae is the most frequent cause. Low birth weight is associated with higher mortality (Misra et al., 1991). The risk of pneumonia increases in infants who are of low birth weight and/or malnourished, and in those who are not breastfed (Victora et al., 1999).

In preterm neonates of low birth weight, respiratory distress syndrome, due to surfactant deficiency, is a major risk for early death (Mlay and Manji, 2000). Information on the prevalence of this disorder in developing countries is especially difficult to obtain because most infants of very low birth weight (those weighing less than 1500 grams, who are at greatest risk) die soon after birth. In these cases, causes of death other than prematurity are poorly recognized (Bhutta et al., 1999).

Tuberculosis

A leading infectious disease, tuberculosis (TB) kills more than 2 million people worldwide each year, including 250,000 children, despite the availability of cost-effective prevention and treatment (United Nations Children's Fund, 2000). The vast majority of these deaths occur in developing countries; approximately 70 percent of all TB cases occur in Asia (United Nations Children's Fund, 2000). TB is a particular risk in areas where HIV is prevalent, as approximately 40 percent of people whose immune systems have been weakened by HIV develop TB (United Nations Children's Fund, 2000; Thillagavathie, 2000). The reportedly higher TB prevalence in men than in women appears to be an artifact of gender differences in notification rates (Thorson and Diwan, 2001).

In pregnant women, TB has been shown to increase the risk of fetal loss, preterm delivery, and low birth weight (Starke, 1997; Jana et al., 1994). Although rare, transplacental congenital infection may occur (Connelly Smith, 2002; Starke, 1997); infection with HIV increases a woman's risk for placental or genital TB. The most common route of mother-to-child transmission is postnatal from an untreated infected mother to her newborn. Infected newborns are at high risk for severe disseminated TB and death (Starke, 1997; Adhikari et al., 1997).

Diarrheal disease

Several community-based studies suggest that diarrhea is responsible for approximately 3 percent of all neonatal deaths (Stoll, 2000). Diarrheal episodes tend to occur with greatest frequency among children aged 6 months to 2 years; in many developing countries, initial episodes frequently occur in the first 6 months of life (Bern et al., 1992; Snyder and Merson, 1982; Jacobson, 1999). Some factors common to developing countries—home delivery; relative segregation of newborn infants for a period of time after birth; and the high prevalence of early, exclusive breastfeeding—protect against neonatal diarrhea. Among hospitalized newborns in developing countries, nosocomial diarrhea is an important problem (Aye et al., 1991; Yankauer, 1991; Tessema, 1994).

Rotavirus

Rotavirus is an important cause of diarrhea among infants and children worldwide, occurring most commonly in those aged 3 months to 2 years. However, several studies from developing countries report rotavirus infections in newborns (Haffejee, 1995; Parashar et al., 1998b; Cicirello et al., 1994; Espinoza et al., 1997; Gomwalk et al., 1990).

Tetanus

Worldwide, about a quarter-million infants die from tetanus each year (Table 3-1). Risk factors for neonatal tetanus occur in the antenatal, perinatal, and neonatal periods: failure to immunize the mother against tetanus; unhygienic delivery and cutting of the umbilical cord at birth; and unsterile handling of the cord in the early days of life. Cultural practices prevalent in specific areas, such as the application of ghee (Pakistan and India) and other unclean substances to the cord after birth increase risk (Traverso et al., 1991). Diagnosis of neonatal tetanus is relatively straightforward: the newborn can suck at birth and for the first few days of life, then loses this ability between 3 and 10 days of age, then develops spasms, stiffness, convulsions, and death. For decades, community surveys have determined the burden of disease and mortality rates for tetanus (Galazka and Stroh, 1986). Routine national surveillance, however, may still underestimate the true occurrence of the disease (Singh et al., 1997). In some of the least-developed countries, neonatal tetanus remains a major cause of neonatal death, particularly among infants delivered at home and without skilled assistance (Gasse, 1995; Gupta and Keyl, 1998; Gurkan et al., 1999; Davies-Adetugbo et al., 1998).

Between 1990 and 2000, deaths caused by neonatal tetanus declined by half through a combination of maternal immunization and clean delivery practices (United Nations Children's Fund, 2002). Substantial reductions in neonatal mortality due to tetanus occurred in China, Indonesia, Bangladesh, India, and Pakistan. Nevertheless, approximately 250,000 neonates died of tetanus during 1997; the majority of these deaths occurred in Africa and Southeast Asia, with nearly 20 percent in India (World Health Organization, 1999a).

Sexually transmitted diseases

More than 333 million cases of the four major curable STDs—syphilis, gonorrhea, chlamydia, and trichomoniasis—were estimated to occur in 1995, the vast majority in developing countries (Gerbase et al., 1998). Collectively, STDs rank among the leading causes of morbidity worldwide, a burden borne disproportionately by women of reproductive age. STDs among pregnant women often receive delayed treatment or none at all, largely because they are asymptomatic or unrecognized (Sturm et al., 1998). Most STDs are readily transmitted from mother to child during pregnancy and/or childbirth (Moodley and Sturm, 2000). The extent of neonatal infections with these agents in developing countries is difficult to estimate. Adverse pregnancy outcomes associated with STDs range from miscarriage and preterm birth (see Chapter 7) to congenital infections to maternal, fetal, and neonatal mortality (Carroli et al., 2001a; Moodley and Sturm, 2000). Neonatal HIV is discussed in detail in Chapter 8.

Among women worldwide, there are approximately 7 million new cases of syphilis each year (Gerbase et al., 1998). Rates of congenital syphilis parallel those of syphilis in women of reproductive age. Many developing-country studies have found seroprevalence rates of syphilis among pregnant women of 5 to 15 percent, or up to two orders of magnitude higher than typical rates in developed countries (Carroli et al., 2001a); in South Africa, rates of infection in pregnant women have been reported to range from 6 to 19 percent (Rotchford et al., 2000). Untreated syphilis during pregnancy increases the risk of late fetal death, low birth weight, preterm birth, and severe neonatal disease (Lumbiganon et al., 2002). Data from a demonstration project in Zambia determined that syphilis was the most significant cause of adverse pregnancy outcome among women attending antenatal clinics (Hira et al., 1990); a more recent prospective study of congenital syphilis in a Papua New Guinea hospital found that the infection was responsible for 6 percent of admissions and 22 percent of all neonatal deaths (Frank and Duke, 2000).

Syphilis is transmitted from an infected mother to the fetus largely via transplacental infection, and rarely via contact with an infectious genital lesion during delivery. Active infection with syphilis in pregnant women is estimated to result in fetal or infant death or disability for 50 to 80 percent of affected pregnancies (Gloyd et al., 2001). The majority of infants born to mothers with untreated syphilis are asymptomatic at birth, but if left untreated may develop clinical manifestations of disease months to years after birth (Dorfman and Glaser, 1990; Sanchez et al., 1991). Symptoms of early congenital syphilis include intrauterine growth restriction, anemia, thrombocytopenia, jaundice, and hepatosplenomegaly (Stoll et al., 1993). The most devastating complications of untreated or late congenital syphilis are neurological manifestations that include mental retardation, hydrocephalus, cranial nerve palsies, and seizures (Stoll, 1994). With adequate treatment of infected mothers, syphilis is a preventable cause of neonatal morbidity and mortality.

Neonates delivered vaginally to mothers with untreated gonorrhea are at great risk of developing gonococcal conjunctivitis, which, if left untreated, can lead to blindness. Rarely, neonates develop disseminated gonococcal infection (Desenclos et al., 1992; Rawstron et al., 1993). Similarly, chlamydia infections occur in approximately two-thirds of infants born by vaginal delivery to infected mothers (Moodley and Sturm, 2000). Chlamydia can cause conjunctivitis and/or pneumonia, which may not be evident until the infant is several weeks old.

Neonatal infection with herpes simplex usually occurs during delivery, via an infected birth canal or an ascending infection following the rupture of membranes to women with primary genital herpes at the time of delivery (Prober et al., 1988; Brown et al., 1996; Brown et al., 1987). The infection can spread to the central nervous system and beyond, and has both a high mortality rate and a high likelihood of neurodevelopmental sequelae among survivors (Tookey and Peckham, 1996; Brkic and Jovanovic, 1998; Jacobs, 1998; Whitley et al., 1991).

Maternal urinary tract infections

Infections of the urinary tract, particularly asymptomatic bacteriuria, occur in an estimated 4 to 7 percent of all women (Carroli et al., 2001a; Dempsey et al., 1992;). Unless the infection is treated with antibiotics, an estimated 20 to 40 percent of pregnant women with asymptomatic bacteriuria will develop pyelonephronitis (Smaill, 2003); of those who do, 20 to 50 percent will experience preterm deliveries (Carroli et al., 2001a). Antibiotic treatment is associated with reductions in preterm delivery and low birth weight (Smaill, 2003).

Malaria

Malaria in pregnancy has serious health consequences for both mother and newborn. Because it causes significant maternal morbidity, its prevention and treatment are discussed in Chapter 2. The primary malaria-associated risk for neonates is reduced birth weight, which is discussed in Chapter 6. In highly endemic settings, malaria has been estimated to account for 13 percent of low birth weight (LBW) due to intrauterine growth restriction (IUGR) (Steketee et al., 1996).

Noninfectious Conditions

Perinatal asphyxia

Of the estimated 4 to 7 million neonates born each year worldwide that require some form of resuscitation immediately after birth, approximately 1 million die and another million suffer serious sequelae (Saugstad et al., 1998). Epidemiological data provide only rough estimates of the global burden of perinatal asphyxia, in part because of the imprecision of diagnosis. Numerous definitions of perinatal asphyxia, all of which correspond to the failure to initiate and sustain normal breathing, have been used in studies from developing countries. These include apnea or gasping with a slow heart rate (<80) at birth, absent or poor respiratory effort at 1 minute, gasping at 1 minute, low Apgar scores (variously defined), and the need for assisted ventilation for more than 1 minute (Paul et al., 1997; Chandra et al., 1997; Daga et al., 1990; Saugstad et al., 1998; Kinoti, 1993). In addition, data on perinatal asphyxia are largely hospital-based and therefore may either underestimate or overestimate the true magnitude of the problem, as seen in many studies (Paul et al., 1997; Chandra et al., 1997; Daga et al., 1990; Kinoti, 1993; Chaturvedi and Shah, 1991; Boo and Lye, 1991; Nathoo et al., 1990; Ellis et al., 2000).

The incidence of perinatal asphyxia is thought to be higher in developing than developed countries because of the higher prevalence of risk factors for the disorder, as well as the lack of appropriate interventions (Deorari et al., 2000). Mortality is greater among preterm than term infants, and decreases with increasing birth weight. However, asphyxia also has an important effect on mortality among normal-weight term infants, who otherwise have a good chance for survival (Paul et al., 1997). The contribution of perinatal asphyxia to long-term neurodevelopmental disability in developing countries is unclear (Ellis et al., 1999).

Conditions that increase the risk of asphyxia include antepartum hemorrhage, prolonged labor and/or prolonged rupture of membranes, drugs given to the mother that may depress respiration (e.g., magnesium sulfate, narcotics), cord accidents, vaginal breech deliveries, multiple gestation, pregnancy-induced hypertension, congenital anomalies, and IUGR with placental dysfunction (Chandra et al., 1997; Daga et al., 1990; Chaturvedi and Shah, 1991; Boo and Lye, 1991; Nathoo et al., 1990). In most resource-poor countries, where the vast majority of births take place at home, asphyxia is difficult to anticipate. The passage of meconium in the amniotic fluid and an abnormal fetal heart rate (bradycardia or persistent tachycardia) are the only simple ways to predict asphyxia prior to delivery in most developing countries; only about half of all cases can be detected this way (Chaturvedi and Shah, 1991).

Birth injury

Birth injury is a nonspecific term that includes potentially preventable and unavoidable injuries—mechanical or hypoxic-ischemic—suffered by the neonate during labor and delivery. Specific injuries include intracranial hemorrhage; blunt trauma to the liver, spleen, or other internal organs; injury to the spinal cord or peripheral nerves (the most devastating is cord transection; the most common is brachial plexus injury); and fractures to the clavicles or extremities.

Although WHO has estimated that birth injuries are responsible for 11 percent of neonatal deaths worldwide (World Health Organization, 1996c), the incidence of specific injuries in most developing countries is unknown. Birth injuries can result in transient neonatal problems, long-term morbidity, and death. Predisposing factors include macrosomia, cephalopelvic disproportion, dystocia, prolonged or obstructed labor, breech presentation, and prematurity. Although injury may occur despite skilled care at delivery, some injuries result from inadequate medical knowledge or suboptimal care during labor and delivery and are therefore potentially preventable. A specific diagnosis is preferable to the use of the nonspecific term "birth injury," especially when considering prevention strategies.

Hypothermia

Hypothermia, defined as a body temperature below 36.5°C, is frequent in newborns, especially those of low birth weight. Several studies have shown that without adequate care, many newborns will experience severe hypothermia, reaching core temperatures lower than 32°C (Ellis et al., 1996). Neonatal hypothermia has been reported to increase the risk of infection, coagulation abnormalities, acidosis, complications of preterm birth, and death (Dragovich et al., 1997; Dagan and Gorodischer, 1984; Manzar, 1999).

Dragovitch et al. (1997) evaluated the knowledge and practices of health professionals on thermal control of newborns in seven countries: Brazil, India, Indonesia, Kazakhstan, Mozambique, Nepal, and Zimbabwe. They found that thermal control practices were frequently lacking in the following areas: ensuring a warm environment at the time of delivery, initiation of breastfeeding and contact with the mother, bathing, checking the baby's temperature, thermal protection of low-birth-weight neonates, and care during transport. The study also demonstrated that health professionals involved in newborn care underestimate the impact of hypothermia on neonatal morbidity and mortality. A recent survey of health professionals involved in newborn care in an Indian hospital revealed similarly weak knowledge of hypothermia diagnosis and care; for example, fewer than one-fifth of the respondents knew the correct method of measuring the body temperature of a newborn (Choudhary et al., 2000).

Neonatal jaundice/hyperbilirubinemia

Since most births occur at home, the magnitude of this problem is unknown. Although a relatively rare cause of death in neonates, untreated extreme bilirubinemia can cause devastating neurologic injury, long-term disability or death. With adequate vigilance, detection, and treatment such infrequent but severe damage can be prevented. The major risk of untreated hyperbilirubinemia is bilirubin encephalopathy or kernicterus (Dennery et al., 2001; Alpay et al., 2000). In the first week of life, visible jaundice occurs in approximately 15 percent of newborns (Cashore, 1994). However, many more with elevated bilirubin below 7 to 8 mg/dL do not develop jaundice and the bilirubin elevation remains undetected. However, mild elevation, though common, need not cause harm to the baby. Causes of hyperbilirubinemia include prematurity, blood group incompatibility, and peripartum infection. Most often, elevated levels of bilirubin in the baby's blood come about from breakdown of hemoglobin in old or hemolyzed red blood cells (Dennery et al., 2001). There are many causes of indirect hyperbilirubinemia, including increased production of bilirubin, impaired conjugation, and increased enterohepatic circulation. The reason for racial differences in hyperbilirubinemia has some genetic basis but is not completely understood (Setia et al., 2002; Dennery et al., 2001; Akaba et al., 1998). The risk of Rh hemolytic disease has been markedly reduced in industrialized countries by the use of Rh immune globulin (Rhogam)

(Queenan, 2002). However, Rh disease remains a problem in developing countries, where most women deliver at home, blood type is unknown, and Rhogam is not available.

Kernicterus or bilirubin encephalopathy results from deposition of unconjugated bilirubin in the basal ganglia. Kernicterus is rare in healthy term infants in the absence of hemolysis if the serum bilirubin level is under 25 mg/dL (Gourley, 1997; Hansen and Bratlid, 1986). The duration of exposure required for toxicity is unclear. Preterm infants are at greater risk for kernicterus, but the exact level at which toxicity occurs is unknown. The early signs of bilirubin encephalopathy are nonspecific (lethargy, poor feeding), but the infant may become critically ill with bulging fontanel, opisthotonus, shrill cry, spasms, and seizures. Late sequelae of kernicterus include extrapyramidal abnormalities, choreoathetosis, involuntary muscle spasms, and sensorineural deafness.

INTERVENTIONS

Reducing neonatal mortality and morbidity often involves established interventions or strategies along with the means to make them effective in each setting. For many conditions, improved education and behavioral change among women, families, and health care providers would have a major impact on birth outcomes. For direct impact, emphasis must be given to the delivery of care: getting appropriate services to those who need them and doing so in a timely manner. Interventions to reduce neonatal mortality and morbidity are discussed below, with emphasis on antenatal care, care during labor and delivery, and care during the early days and weeks of life.

Antenatal Care

Medical factors that may contribute to neonatal morbidity and mortality include several components that can be directly addressed by antenatal care: poor maternal health and nutrition, maternal infections, and lack of immunization against tetanus (Villar et al., 2001; Carroli et al., 2001a, 2001b; Bergsjo and Villar, 1997). Equally important, as described in the previous chapter, antenatal care can teach mothers to recognize signs during pregnancy, labor, and delivery and encourage them to plan clean and safe deliveries—preferably with trained assistance (Bloom et al., 1999). Appropriate antenatal care also includes explaining the benefits of breastfeeding, childhood immunization, and personal and domestic hygiene, and teaching parents to recognize danger signs that can occur in newborns.

As noted in the introduction to this report, maternal education has a significant and far-reaching impact on antenatal care (Bicego and Boerma, 1993; Victora et al., 1992; Terra de Souza et al., 2000; van Ginneken et al., 1996; Rao et al., 1996). Better formal and health education of girls leads them in later years to seek preventive services, increase food intake during pregnancy, reduce tobacco and alcohol use, understand the implications of danger signs during labor and delivery, and seek referral care for obstetric and/or newborn complications (World Bank, 1993; Ahmed et al., 2001).

The discussion in this chapter focuses on those antenatal interventions that are directed at preventing and treating maternal conditions that directly affect the neonate. Antenatal care directed at maternal morbidity and mortality is discussed in Chapter 2, at low birth weight in Chapter 6, at birth defects in Chapter 7, and at mother to infant transmission of HIV in Chapter 8. Findings from these chapters are assembled in a list of essential antenatal care interventions in the executive summary and the concluding chapter (9).

Diagnosis and treatment of maternal infections

Timely diagnosis and treatment of maternal infections and other health problems during pregnancy can lead to significant improvement in fetal and neonatal outcomes, as well as prevention of maternal mortality and morbidity. These are discussed in Chapter 2. Conditions of particular concern to the neonate include the following:

Sexually transmitted diseases. Treatment of STDs is cost-effective (Mayaud et al., 1995), but clinical diagnosis is difficult because the symptoms are not specific, laboratory support is often unavailable (Bosu, 1999), and simple, inexpensive, sensitive tests exist only for syphilis (Moodley and Sturm, 2000). For these reasons, WHO has recommended a syndromic approach to diagnosing and treating STDs in low-resource settings (World Health Organization, 1994). However, the efficacy of syndromic treatment, especially among pregnant women, is unclear (Mayaud et al., 1995, 1998; Sturm et al., 1998). Several studies have documented that STDs facilitate HIV transmission (Fleming and Wasserheit 1999). A randomized, controlled trial in the Mwanza region of Tanzania concluded that STD treatment significantly reduced the incidence of HIV infection (Grosskurth et al., 1995) and was highly cost-effective (Gilson et al., 1997). A community-based, randomized trial of STD control in the Rakai district of Uganda (where the HIV infection rate is higher) demonstrated that reduction of STDs improved pregnancy outcome (reduced the rate of low birth weight, infant ophthalmia, and early neonatal mortality), but did not reduce transmission of HIV to mother, fetus, or neonate (Gray et al., 2001). All women were treated for syphilis if their serological test was positive. Other STDs were treated presumptively in randomized fashion using antibiotics effective against a wide range of pathogens. Further research is needed to determine the optimal strategy to reduce the neonatal impact of STDs in developing countries. Two possibilities are presumptive therapy for all pregnant women and development of cost-effective diagnostic tests for use in field settings to facilitate prompt maternal therapy.

Serologic screening of pregnant women for syphilis has been shown cost-effective even in areas where disease prevalence is low (Carroli et al., 2001a; Gloyd et al., 2001; Frank and Duke, 2000; Schmid, 1996). WHO recommends universal antenatal screening for syphilis; in areas of high prevalence of the disease, screening should be performed at the first antenatal visit and repeated early in the third trimester (Lumbiganon et al., 2002). Treatment in the last trimester of pregnancy may not ensure that the fetus/newborn is uninfected at birth. If adequate maternal treatment cannot be documented, the infant should be treated for syphilis.

Rapid, inexpensive serological tests for syphilis increase the likelihood a woman will receive adequate treatment by allowing her to be screened and treated in the same clinic visit (Rotchford et al., 2000; Wilkinson and Sach, 1998). Routine screening is less effective as it involves follow-up of both the mother and her sexual partner(s). A "second-best" strategy in areas of low syphilis prevalence is the screening of high-risk groups, then examination of women with symptoms and those whose partners report symptoms (Carroli et al., 2001a).

Routine screening for chlamydia during pregnancy has not proven cost-effective (Carroli et al., 2001a). WHO recommends that maternal screening and antibiotic treatment be considered in populations where chlamydia prevalence in pregnant women exceeds 10 percent and where some infants with chlamydial pneumonia are hospitalized at high cost. Sexual partners must also be treated to prevent reinfection during pregnancy (World Health Organization, 1996a).

In areas where HIV testing and counseling are readily available, WHO recommends that those services be offered to pregnant women, especially those at high risk for HIV infection (World Health Organization, 1996a). Chapter 8 examines the role of antenatal care in prevention of mother-to-infant transmission of HIV.

Urinary tract infection. Evidence from several randomized controlled trials indicates that antibiotic treatment of urinary tract infection and/or asymptomatic bacteriuria reduces the risk of low birth weight, but the mode of prevention is unclear. Screening for and treatment of asymtomatic bacteriuria during pregancy are recommended in order to prevent maternal pyelonephritis, as well as reduce risk to the neonate (Smaill, 2003).

Tuberculosis. Policies for screening pregnant women for TB, a leading cause of death in some parts of the world, may be adapted to local epidemiology and TB control programs (Ahmed et al., 1999). Some experts believe that only women with specific risk factors for tuberculosis infection or disease should receive a tuberculin skin test as part of antenatal care. Women coinfected with tuberculosis and HIV are at particularly high risk (Pillay et al., 2001). Women with positive skin tests require a chest radiograph to rule out active pulmonary disease and are referred for therapy if the radiograph is abnormal. Treatment of tuberculosis during pregnancy is essential (Pillay et al., 2001); the specific drugs provided depend on safety and efficacy in pregnancy (Starke, 1997), as well as local patterns of drug sensitivity (Davidson, 1995).

Malaria prevention and treatment in pregnant women is discussed in Chapter 2.

Rubella infection during pregnancy (especially the first trimester) can result in miscarriage, late fetal death, or congenital rubella syndrome. Congenital rubella syndrome and possibilities for prevention are discussed in Chapter 7. Immunization of school children and preconceptional women is recommended in countries as long as immunization reaches more than 80 percent of the population.

Maternal immunization

Fetuses, neonates, and young infants can be protected from a variety of infections through passively acquired transplacental and breast milk antibodies. For example, antenatal immunization against rubella provides low-cost, effective protection from congenital rubella syndrome. Because most IgG antibody is transported across the placenta in the last 4–6 weeks of pregnancy, maternal immunization to protect the infant is most promising for term babies. For preterm infants there is insufficient passage of maternal antibodies. However, boosting breast milk antibodies by immunizing mothers can protect both term and preterm infants.

Tetanus. Immunization of pregnant women with tetanus toxoid, which has dramatically reduced cases of neonatal tetanus, is an important, low-cost antenatal intervention (Gupta and Keyl, 1998; Jeena et al., 1997; Bergsjo and Villar, 1997. Moreover, maternal tetanus immunization has been associated not only with lower neonatal mortality but also with lower early childhood mortality (Luther, 1998). In a study in Bolivia, traditional birth attendants employed single-use, prefilled injection devices to immunize more than 2,000 pregnant women against tetanus during routine antenatal visits. Because tetanus toxoid is relatively heat-stable, the prefilled devices could be stored for up to one month without refrigeration (Quiroga et al., 1998). A study in Bangladesh showed that tetanus toxoid immunization rates were positively associated with proximity to outreach clinics and the presence of a health worker in community and home visits. The effects were greatest in poorer households (Jamil et al., 1999).

Pneumonia. Maternal vaccines have been developed to protect neonates and infants against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and Group B streptococcal infections (Child Health Research Project Special Report, 1999; Glezen and Alpers, 1999; Mulholland et al., 1996; Mulholland, 1998; Monto and Lehman, 1998). Studies in Bangladesh and Papua New Guinea showed that maternal immunization with pneumococcal polysaccharide vaccines produced an increase in type-specific serum IgG antibody level in both mother and newborn (Shahid et al., 1995; Lehmann et al., 2002). Combination vaccines would be especially useful for populations with limited access to health services (Monto and Lehman, 1998).

***H. influenzae* type B.** In developed countries, invasive disease resulting from *H. influenzae* type B (HiB) has been almost eliminated by the use of HiB conjugate vaccines (Bisgard et al., 1998). In many countries, however, HiB remains an important cause of life-threatening infections in infancy, particularly pneumonia and meningitis. Maternal immunization with HiB polysaccharide-tetanus protein conjugate vaccine has been shown to increase both maternal and neonatal antibody concentrations: at 2 months of age, 60 percent of the infants of vaccinated mothers had protective levels of antibody (Mulholland et al., 1996).

Before routine maternal immunization with these vaccines can be recommended, further studies are needed to determine each vaccine's short- and long-term safety for the fetus and newborn, and its efficacy in preventing neonatal disease. Moreover, the delivery of vaccines to those who need them in poor countries is a massive task that will necessitate novel public-private partnerships (Smith, 2000).

Prevention and treatment of anemia

In developing countries, anemia has several possible causes, including iron or other micronutrient deficiencies, malaria, and hookworm (van den Broek and Letsky, 2000). Antenatal iron supplementation and prevention and treatment of the salient infections are discussed in Chapters 2 and 6.

Recognition and reversal of breech presentation

Late in pregnancy, abdominal examination can reveal a fetus in breech presentation, a significant risk factor for obstructed labor. To reduce the attendant risk to the fetus and newborn of intrapartum or postpartum asphyxia or birth injuries, external cephalic version may be attempted after 37 weeks' gestation (Villar and Bergsjo, 1997).

Essential antenatal care

Evidence from several randomized trials indicates that similar maternal and neonatal outcomes could be obtained from antenatal care in as few as five visits (on average) by focusing on interventions known to be effective in reducing morbidity and mortality (Villar et al., 2001; Carroli et al., 2001b): counseling on birth preparedness and emergency readiness; provision of folic acid; tetanus immunization; prophylaxis and intermittent preventive treatment for malaria and hookworm as needed; and early detection and timely management of certain diseases or complications (severe anemia at the end of pregnancy, hypertension and proteinuria, asymptomatic bacteriuria and urinary tract infection, syphilis, HIV, and other sexually transmitted diseases prevalent in the local population, and concurrent conditions such as hepatitis, malaria, and tuberculosis); and fetal malpresentation after the 37th week. A multicenter randomized, controlled trial conducted in more than 50 clinics in Argentina, Cuba, Saudi Arabia, and Thailand concluded that women assigned to the new model of essential antenatal care that called for an average of five visits per pregnancy had similar rates of low birth weight, postpartum anemia, urinary tract infection, and several secondary outcomes to those of women enrolled in a standard antenatal care program with an average of eight visits (Villar et al., 2001). This finding is further supported by a systematic review of seven randomized controlled trials that assessed the effectiveness of different antenatal care models in reducing adverse outcomes for mother and infant (Carroli et al., 2001b).

Care During Labor, Delivery, and the Very Early Neonatal Period

Complications of pregnancy and childbirth, a leading cause of death and disability among women of reproductive age (see Chapter 2), can also cause neonatal illness and death. Every pregnancy is at risk for complications, most of which can be managed successfully if recognized and addressed in a timely manner. However, the fact that the majority of births in developing countries occur outside hospitals and other health care facilities presents special challenges.

One such challenge is the use of poor aseptic techniques during labor and delivery, which lead to maternal and neonatal infections. The birth attendant can play a critical role in preventing infections of the mother and newborn by observing the need for clean hands, clean perineum, clean delivery surface, clean instruments, clean cord care, and use of an appropriate clean delivery kit.

The goal is for every delivery to be assisted by a skilled birth attendant such as a midwife, physician, or nurse (as described in Chapter 2). As well as providing a clean and safe delivery, a trained birth attendant recognizes complications such as preterm birth, preterm or prolonged rupture of membranes, and prolonged or obstructed labor and can promptly refer the patient to a health facility with essential obstetric and neonatal care. Skilled interventions are key for saving neonatal and maternal lives during labor, delivery, and the very early neonatal period.

Prevention and treatment of neonatal infections

Neonatal sepsis and pneumonia. Preterm or prolonged rupture of the membranes, maternal fever during labor, and chorioamnionitis are risk factors for early-onset neonatal sepsis and pneumonia. Because the risk of infection increases with the number of vaginal examinations performed during labor, the number of examinations should be minimized (Seaward et al., 1997). Induction of labor in pregnancies at term with prelabor rupture of membranes or chorioamnionitis can prevent infection of both mother and newborn (Tan and Hannah, 2001). In industrialized countries, intrapartum antibiotics are used to reduce both maternal and neonatal sepsis (Gibbs et al., 1988; Benitz et al., 1999): broad-spectrum antibiotics for women suspected to have chorioamnionitis to reduce maternal and neonatal infection (Gibbs et al., 1988); antibiotics for mothers with preterm rupture of membranes to reduce neonatal illness (Mercer et al., 1998); and intrapartum penicillin to prevent mother to neonate transmission of group B streptococcal infection (Schuchat, 1998). Some of these interventions may be adaptable to community-level use in developing countries.

When a mother develops a puerperal infection, the newborn requires special attention and should be treated for presumed sepsis. Ideally, infants at risk for sepsis who are born at home should be referred to the nearest health facility for observation and antibiotic treatment. Where this is not possible, ways to deliver care to the mother and newborn in the home need to be developed and evaluated (see Box 3-1 below).

Cord infections. Use of a sterile blade to cut the cord and a clean tie are essential. Clean cord care in the postnatal period includes washing hands before and after care and keeping the cord dry and exposed to air or loosely covered with clean cloths. The application of antimicrobial or antiseptic agents to the cord after birth reduces bacterial colonization of the cord and is a routine practice in many industrialized countries. In developing countries, where bacterial contamination of the cord is a higher risk, local antimicrobial agents might reduce infection. A small study in Papua New Guinea documented a decrease in neonatal sepsis following a simple cord care intervention: cutting the cord with a new razor blade and applying acriflavine spirit (Garner et al., 1994). Further studies are warranted.

Neonatal tetanus. Neonatal tetanus can be prevented by immunizing women before or during pregnancy and by ensuring a clean delivery, clean cutting of the umbilical cord, and proper care of the cord in the days following birth (Gupta and Keyl, 1998; Parashar et al., 1998a). Although tetanus toxoid is a highly effective immunogen (Gupta and Keyl, 1998; Koenig et al., 1998; McCarroll et al., 1962), cases of neonatal tetanus have been reported in infants born to fully immunized mothers (Hlady et al., 1992; Talukdar et al., 1994; de Moraes-Pinto et al., 1995; Davies-Adetigbo et al., 1998). These outcomes highlight the need for quality control of tetanus vaccine production and promotion of hygienic cord care practices. The protective efficacy of topical antimicrobials has been demonstrated by several case-control studies (Traverso et al., 1991; Bennett et al., 1997; Parashar et al., 1998a). The use of topical antimicrobials as a complement to maternal immunization warrants further study as part of the global effort to eliminate this disease.

Sexually transmitted diseases. Additional intrapartum or immediate postpartum interventions for infants born to mothers with confirmed or suspected STDs can prevent neonatal morbidity. WHO recommends that until syphilis screening and treatment in pregnancy have been fully and effectively implemented, all infants born to seroreactive mothers be treated for syphilis infection (World Health Organization, 2001). Prevention of mother-to-child transmission of HIV is discussed in Chapter 8.

Gonococcal ophthalmia neonatorum is prevented by antimicrobial eye prophylaxis immediately after birth. The cheapest and most widely available agent is silver nitrate (1 percent) eye drops; however, old, more concentrated solutions have been implicated in causing chemical conjunctivitis (Moodley and Sturm, 2000; World Health Organization, 1991). Topical erythromycin and tetracycline are more expensive but safer drugs for prevention of gonococcal ophthalmia (Laga et al., 1988); given increasing tetracycline resistance, erythromycin is the preferred choice (Moodley and Sturm, 2000).

In areas where genital herpes is the predominant cause of genital ulcer disease, WHO recommends cesarean delivery when herpetic lesions are present in the genital tract at the time of membrane rupture or during labor, if the patient presents within 4-6 hours of labor's onset, and if the risk for morbidity and mortality due to surgery or anesthesia are low. If genital herpes is a relatively minor cause of genital ulcer disease—that is, where chancroid and syphilis predominate—cesarean section is contraindicated since the predictive value of genital ulcers for HSV is low, and surgery-related morbidity may be high (Anonymous, 2000; Roberts et al., 1995).

Care of noninfectious conditions

Resuscitation. Skilled birth attendants should be proficient in neonatal resuscitation and ready to perform it at every birth, since asphyxia is usually unpredictable. The basic resuscitation procedure involves having appropriate equipment available (tube/mask or bag/mask); being prepared for and anticipating potential problems; using a warm, clean, flat surface; drying, stimulating, and assessing the newborn; clearing the airway, and ventilating a newborn who fails to initiate respiration. Complex interventions, such as endotracheal intubation, chest compression, and medications, are rarely needed. Use of a simple bag and mask to ventilate the newborn is the established practice in industrialized countries, and has been successfully adapted to low resource settings (Palme-Kilander, 1992; Deorari et al., 2000; Alisjahbana et al., 1999). Preliminary studies indicate that a simple mouth-to-mask (tube and mask) device is as effective as a bag and mask in the resuscitation of asphyxiated newborns (Milner et al., 1990; Massawe et al., 1996). Furthermore, a recent multinational trial demonstrated that neonates can be resuscitated with room air as efficiently as with oxygen (Saugstad et al., 1998). This is particularly important for home deliveries where supplemental oxygen is not available (Saugstad et al., 1998; Saugstad, 1998). The nearly 1 million births annually that are complicated by asphyxia could be improved through management of labor and childbirth that reduces the risk of asphyxia, and prompt resuscitation of newborns who fail to breathe at delivery.

Thermal control. Optimal thermal control of newborn infants in developing countries can be promoted by ensuring a warm environment for delivery in the home or hospital, drying the infant soon after birth, providing clean, dry clothing and blankets for mother and newborn, and keeping all newborns—including preterm infants—with the mother soon after birth. Maintaining skin-to-skin contact between mother and newborn efficiently stabilizes temperature in term infants and permits the early establishment of breastfeeding. Continuing skin-to-skin contact (Kangaroo care), proposed in 1978 by Rey and Martinez (Simkiss, 1999) is even more important for low-birth-weight and preterm infants. In the Kangaroo care method, a well low-birth-weight infant, wearing only a diaper, is placed between the mother's breasts to provide uninterrupted adult body heat by means of skin-to-skin contact. Several studies have shown this method to be safe and effective for maintaining body temperature (Bergman and Jurisoo, 1994; Ludington-Hoe et al., 1999; Alisjahbana et al., 1998; Bosque et al., 1995).

Neonatal jaundice/hyperbilirubinemia. In developing countries, neonates with marked jaundice must be promptly referred for treatment to prevent the unconjugated bilirubin from reaching a level that is toxic to the brain. The treatment generally involves phototherapy but may involve exchange transfusion (Joseph and Kramer, 1998).

Corticosteroids have been found to reduce respiratory distress syndrome, reduce intraventricular hemorrhage, and improve the survival of preterm infants when administered to women in preterm labor in randomized, controlled trials and case-controlled studies (National Institutes of Health, 1994; Crowley, 1995). The benefits extend across a wide range of gestational ages (24–34 weeks) and are not affected by race or sex. In some developing countries, administration of corticosteroids to women in preterm labor has been recommended as a low-cost, low-technology intervention likely to reduce neonatal morbidity and mortality (Bhutta et al., 1999), especially among larger, more mature preterm infants, who are likely to survive if they do not develop respiratory distress syndrome.

Breastfeeding. Evidence indicates that frequent breastfeeding during the first hours of life can prevent hypoglycemia (Biancuzzo, 1999;Yamauchi and Yamanouchi, 1990). WHO recommends that infants be put to breast within an hour of birth (World Health Organization, 1994). Closeness between mother and infant during breastfeeding may also reduce the risk of hypothermia (Bosque et al., 1995).

Breastfeeding is particularly important where safe, affordable alternatives to breast milk are not available, hygiene is poor, and water is unsafe (Horton et al., 1996; Gupta and Khanna, 1999). The risk of transmitting HIV through breastfeeding is discussed in Chapter 8. Breast milk contains many anti-infective factors, including secretory immunoglobulin A antibodies, lysozyme, lactoferrin, zinc, and receptor analogs for certain epithelial structures that microorganisms need for attachment to host tissue and subsequent infection (Hanson et al., 1994, Hanson et al., 1982). The early initiation of breastfeeding is important because colostrum has higher levels of many anti-infective factors compared with mature milk, and because early feeding helps establish an adequate milk supply. Many studies have documented a reduction in infectious diseases, including sepsis, diarrhea, and pneumonia (Narayanan et al., 1984; Ashraf et al., 1991; Brown et al., 1989; Glezen, 1991), and in infection-related mortality (Betrán et al., 2001; Habicht et al., 1986; Srivastava et al., 1994; Victora et al., 1989, 1987; Daga and Daga, 1989; Sachdev et al., 1991) among infants who are breastfed.

WHO recommends that infants be breastfed exclusively for 6 months (Haider et al., 2000; World Health Organization, 1995). There appears to be no advantage to introducing complementary foods to infants before 4 months of age, and in many places, doing so introduces substantial risk that the infant will develop diarrhea (Cohen et al., 1994). While most women in developing countries breastfeed, many do not do so exclusively throughout this period (Betrán et al., 2001; World Health Organization Collaborative Study Team, 2000). Peer counseling of breastfeeding mothers has been found effective in encouraging exclusive and extended breastfeeding (Haider et al., 2000; Leite et al., 1998; Morrow et al., 1999; Sikorski and Renfrew, 2001). Breastfeeding (defined as exclusive breastfeeding in babies up to 4 months of age) has increased in 21 developing countries, aided by campaigns to publicize the benefits of the practice, prohibition of advertising and/or distribution of breast milk substitutes, and hospital-based breastfeeding assistance programs (United Nations Children's Fund, 1999).

Vitamin A supplementation. Providing supplemental vitamin A to very young infants or vitamin A supplements to women during pregnancy has been associated with reductions in postneonatal morbidity and mortality is developed countries (Humphrey et al., 1996; Christian et al., 2001), but not fetal or early neonatal mortality (Katz et al., 2000). Infants are born with very limited stores of vitamin A (less than a 2-week supply) and breastfed infants of well-nourished mothers typically increase their vitamin A stores more than tenfold by their sixth month. However, concentrations of vitamin A in the breast milk of women in developing countries are about half those of well-nourished mothers (Humphrey and Rice, 2000). Studies demonstrate that vitamin A supplements to lactating mothers are efficacious in improving the vitamin A status of their infants (Rice et al., 1999; Stoltzfus et al., 1993), but studies have not evaluated the impact of this intervention on infant mortality.

Neonatal Care

Recognition and treatment of disease

Because untreated illness—especially infection—in newborns can rapidly become life threatening, early identification and treatment of the sick newborn is essential. Efforts are needed to raise family and community awareness regarding danger signs in the neonate and the importance of obtaining care from trained personnel, the availability of services, and the potential impact of medical assistance on neonatal mortality (Ahmed et al., 2001).

An integrated approach to the management of the sick child (IMCI), including young infants, has been developed by WHO and UNICEF (World Health Organization, 1999b; Tulloch, 1999). This approach involves prompt recognition of disease, appropriate therapy using standardized case management, referral of serious cases to health care facilities, and prevention through improved nutrition (including breastfeeding of the neonate) and immunization. Because signs of serious bacterial infection in the newborn are not easily distinguished, newborns with suspected severe infections should be treated. Field studies of IMCI guidelines for neonates have found them to have good sensitivity and moderate specificity. The latter results in overreferral of patients for hospitalization. Continuing development of the guidelines will need to balance the health outcomes for neonates and the ability to handle the additional referrals (Kalter et al., 1997; Gove et al., 1999).

Effective prevention and treatment of neonatal infections requires knowledge of infectious agents in a community and of their antimicrobial susceptibility. Hospital data, while more commonly available, may not represent the infectious disease burden in the community (Darmstadt et al., 2000). Treatment decisions are based largely on patient history and clinical examination; more accurate prediction of serious infections is needed (WHO Young Infants Study Group, 1999b; Sehgal et al., 1997).

Home-based neonatal care

Studies have evaluated the ability of trained village health workers to identify sick newborns in their homes and to treat them appropriately and in a timely manner. Referral to a hospital is recommended for neonates who are seriously ill; however, initiating antibiotic treatment before the transfer can be lifesaving. Moreover, there will be situations in which referral to a hospital is impossible or unacceptable to the family.

A recent field trial, described in Box 3-1, implemented a program of comprehensive home-based neonatal care in a remote area of rural India (Bang el al., 1999). Care was provided by village health workers with 5 to 10 years of education and overseen by physicians. The success of this intervention in reducing fetal and neonatal mortality rates in a community with limited resources is promising for other low resource settings. Before home-based care is recommended for broad scale implementation, scientifically rigorous trials should test its effectiveness in other settings, along with the cost of initiating and overseeing these programs.

In studies by Bang et al. (1993) and by Datta et al. (1987), caregivers (traditional birth attendants, paramedics, and village health workers) were trained to diagnose neonatal pneumonia using simple clinical signs and symptoms. The caregivers in these studies used a specific case management strategy to manage neonatal pneumonia through the use of antibiotics and continued breastfeeding. Both studies demonstrated a reduction in pneumonia-associated mortality in the community intervention groups.

Neonatal immunization

Maternal and neonatal immunization is an increasingly promising strategy given the threat of antibiotic resistance. In developing countries, however, issues of vaccine cost, availability, delivery, and efficacy in the field are major barriers to the use of vaccines established as safe and effective.

A variety of neonatal immunization strategies have already proven successful. For example, the bacillus Calmette-Guérin (BCG) vaccine—a live attenuated strain of *Mycobacterium bovis*—is widely used in developing countries where TB is a common and potentially lethal disease. A meta-analysis of BCG studies involving newborns and infants concluded that the

BOX 3-1 Home-Based Neonatal Care in Rural India

High neonatal mortality results from prematurity, birth asphyxia or injury, and infections. Many such deaths could be avoided if neonatal care were available in poor rural communities. A package of comprehensive, home-based neonatal care, including management of sepsis (septicemia, meningitis, and pneumonia), was field-tested in an underdeveloped district of rural India (the Gadchiroli district of Maharashtra State). This intervention reduced perinatal and infant mortality (about 80 per 1000 births in 1994) by nearly 50 percent, at a fraction of the cost of neonatal care in urban areas of India.

Local government health services in the Gadchiroli district provide a male and a female paramedic worker for every 3000 people and a primary care center with two medical doctors for every 20,000 people. Secondary hospitals are located within 30 km of the most remote villages, but do not provide specialized neonatal care. Reproductive health care is sought from private medical practitioners, herbalists, and magic healers.

For this demonstration project, the 39 intervention villages (selected where there were women with 5 to 10 years of education who could be trained to be village health workers) and 47 control villages had similar sociodemographic constitutions and baseline neonatal mortality rates. Resident women in the intervention villages were trained as village health workers.. Each year their training addressed the capabilities needed for interventions to be introduced in the following year. A physician visited each village to verify recorded data and provide supplemental instruction for the health workers, but did not provide care other than referral to the government hospitals available to all patients.

The study involved a baseline phase (April 1993 to March 1995) and an intervention phase (April 1995 to March 1998). In the first intervention year, the village health workers collected data, observed labor and neonates at birth, made regular home visits during the month after birth, weighed the child, and managed minor

vaccine was effective for up to 10 years after infant vaccination, and that it reduced the risk of infection, on average, by more than 50 percent (Colditz et al., 1995). Likewise, hepatitis B vaccination of newborns has been shown to be effective in preventing neonatal infections and their sequelae (Delage et al., 1993). Studies from both industrialized and developing countries have shown that hepatitis B vaccine administered in the immediate newborn period can significantly reduce the rate of neonatal infection and the development of a chronic hepatitis B surface antigen (HBsAg) carrier state (Andre and Zuckerman, 1994). In 1992, WHO recommended that all countries add hepatitis B vaccine to their routine childhood immunization programs (World Health Organization, 2002).

Other promising vaccines require additional research. After successful vaccination of young children against *Streptococcus pneumoniae* (Obaro et illnesses and pneumonia. A survey conducted after the first year of this program found that more than 97 percent of parents reported they would seek care from trained female village health workers in the future if their neonate was sick. Given this response, the health workers began the project's second year by providing home-based management of neonatal illnesses, and, in the following months, neonatal sepsis. In the third year, mothers and grandmothers were educated about the care of pregnant women and their neonates. The complete package was fully functional in the third year of the intervention.

With the neonatal care package entirely in place, neonatal, infant, and perinatal mortality rates dropped by half or more. During the third year of the intervention, an estimated 51 deaths (32 neonatal and 19 fetal) were averted in the villages that received the intervention, based on comparisons with mortality rates in control villages. As 913 neonates received care that year, one death was averted for every 18 neonates who received care. This was accomplished at a cost of US$5.3 per neonate receiving care, a fraction of the cost of neonatal care available in urban Indian hospitals.

The high acceptance of home-based neonatal care in Gadchiroli district was attributed to several factors: the large unmet need for neonatal care; the close involvement of traditional birth attendants; the provision of home care; the successful management of neonatal illness, particularly sepsis; the confidence of parents in the care provided; the emphasis on health education for mothers; the motivated, well-trained, and well-supervised village workers; and the provision of care free of charge. The trained, literate, female village health workers were key to the project's success. Because they lived in the community, they were not only available and willing to make home visits during labor, delivery, and in the first month postpartum, but were widely accepted in this role.

SOURCE: Bang et al., 1999.

al., 1997; Shinefield et al., 2002), studies in South Africa will evaluate the safety and immunogenicity of protein conjugate pneumococcal vaccines for neonates (Obaro, 2000; Klugman, 2001).

Rotavirus vaccines are being developed to prevent severe diarrheal disease, an important cause of infant and child mortality in developing countries (Glass et al., 1997; Jacobson, 1999; Parashar et al., 1998b). Since children in developing countries experience most severe episodes of rotavirus diarrhea in the first year of life (Cicirello et al., 1994; Kilgore et al., 1996), rotavirus vaccination should be delivered early, possibly at birth (Espinoza et al., 1997; Jacobson, 1999; Cicirello et al., 1994). Further studies are needed on the efficacy and safety of rotavirus vaccines for neonates in developing countries (Cicirello, 1994; Glass et al., 1997; Parashar et al., 1998b).

Care of low-birth-weight infants

One in five infants born in developing countries weighs less than 2,500 grams—the standard for low birth weight (United Nations Children's Fund, 1999). While survival of the very low-birth-weight infant (< 1,500 grams) is generally tied to intensive-care technology, there are affordable opportunities to improve the management of infants with birth weights between 1,500 and 2,500 grams (see also Chapter 6). The appropriate interventions are similar to those for neonates of normal weight. They include skilled care at delivery and immediate evaluation of the infant at birth; basic neonatal resuscitation when needed; attention to thermal control (drying the infant at birth, Kangaroo care); prevention of hypoglycemia through early breastfeeding; prevention of infection through good domestic hygiene including hand washing; exclusive feeding of breast milk[1] (with a cup and spoon if needed); supplementation with vitamins and minerals; growth monitoring; early detection and treatment of illness, particularly presumed bacterial sepsis, pneumonia, or meningitis; frequent home visits by trained health workers to identify signs and symptoms of illness and initiate care or refer to a hospital as needed; and monitoring of breastfeeding, neonatal growth, and overall well-being (Stoll and Measham, 2001). Home-based neonatal care described in Box 3-1 produced a 64 percent reduction in case fatality for low birth weight among neonates in rural India (Bang et al., 1999).

RECOMMENDATIONS

Good quality care for the neonate is critical to reducing infant mortality in developing countries, two-thirds of which occurs during the first 28 days of life. The priorities for reducing neonatal mortality and morbidity parallel those given in Chapter 2 for reducing maternal mortality and morbidity:

- Lifesaving services for labor and delivery
  — skilled attendant for every birth
  — referral to a health facility with basic or comprehensive essential care as needed for deliveries with complications
- Key postpartum service
- Key antenatal services

Recommendation 1. Every delivery, including those that take place in the home, should be assisted by a skilled birth attendant (a midwife, physician, or nurse) who has been trained to proficiency in basic tech-

[1]Perinatal transmission of HIV/AIDS is discussed in Chapter 8.

niques for a clean and safe delivery, recognition and management of prolonged labor and infection; and recognition and resuscitation of neonates who fail to initiate respiration at birth. Where necessary, the birth attendant should also be prepared to stabilize and swiftly refer the neonate to a facility providing essential obstetric and neonatal care.[2] (See Chapter 2 for the maternal component of this recommendation.)

Recommendation 2. Essential neonatal care should be accessible to address all complications of childbirth that cannot be managed by a skilled birth attendant. This requires a network of good quality essential care facilities. Services for essential neonatal care should emphasize the diagnosis and treatment of infection. Access for the majority of a population to the appropriate level of care also requires strong referral systems that include communication with, and transportation to, referral facilities. (See Chapters 2 and 5 for other components of this recommendation.)

Recommendation 3. Postpartum care is critical during the first hours after birth and important throughout the first month. For the neonate, such care should emphasize: the prevention, timely recognition, and treatment of infection, thermal control, and promotion and support of early and exclusive breastfeeding. (See Chapter 2 for the maternal component of this recommendation and Chapter 8 for discussion of breastfeeding in populations with a high prevalence of HIV.)

The following antenatal interventions target the major causes of neonatal mortality and morbidity that are covered in this chapter.

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- **Immunization against tetanus for all women of reproductive age.**
- **Early detection and timely treatment of syphilis and other STDs, asymptomatic bacteriuria/urinary tract infection, and tuberculosis.**

(See Chapters 2, 6, 7, and 8 for other components of this recommendation.)

RESEARCH NEEDS

In addition to research priorities identified in Chapter 2 as important to improving all birth outcomes, the committee identified the following topics as priorities for reducing neonatal mortality and morbidity:

[2]This issue is also discussed in Appendix E, Dissenting Note by Dr. Abhay Bang.

• Several vaccines are being developed or are under evaluation for prevention of mother-to-child transmission of infection (e.g., group B streptococcus, cytomegalovirus, *Haemophilus influenzae, Streptococcus pneumoniae*). Further studies are warranted; such studies must first address safety of the mother, fetus, and young infant, and evaluate protection against the target disease, as well as other causes of mortality. The subsequent response of the infant to active immunization with routine childhood vaccines must also be monitored to ensure that maternal immunization does not hamper the infant's ability to respond to vaccines.

• Studies are needed to determine the optimal strategy to reduce the neonatal impact of STDs in pregnancy in developing countries. This might involve presumptive therapy for all pregnant women or the development of cost-effective diagnostic tests that can be used in field settings to facilitate prompt maternal therapy.

• With the exception of HIV, there is a paucity of data from developing countries on the burden of intrauterine, intrapartum, and/or postnatal infections of importance to newborns. These infections include tuberculosis, syphilis, cytomegalovirus, herpes virus, toxoplasmosis, hepatitis C, and malaria. Targeted studies of newborns are warranted in selected areas with known high rates of infection among adults.

• Hospital-based surveillance systems are needed to determine the rates of hospital-acquired infections for infants born in hospital, as well as for those born at home and referred to hospital for care. In addition to birthweight-specific rates of infection, surveillance should include the spectrum of pathogens isolated, antibiotic treatment, antibiotic susceptibility, and case fatality rates. This is particularly relevant in an era when the promotion of institutional births to reduce maternal mortality may result in more newborns in hospital.

• A simple package of measures to control neonatal infection should be evaluated in low-income hospital settings. The package would include hand washing (available soap, water, and clean disposable towel vs. an agent such as chlorhexidene vs. quick-drying spirit to clean hands without the need for soap, water, or towel); neonatal skin care, including umbilical cord care; clean bassinets or isolettes, and clean clothes and blankets; reduction in nursery crowding; strict guidelines for the use of intravenous fluids and intravenous antibiotics (since reducing the number of infants who require intravenous lines would reduce the rates of bloodstream infection); and exclusive breastfeeding (either directly from the breast or with a clean cup and spoon when an infant cannot suck). See also Chapter 8 re women infected with HIV.

• Research should be conducted to determine the incidence and prevalence of neonatal asphyxia in different geographic regions and settings; whether basic neonatal resuscitation can be implemented safely at the village/home level and if so, how to monitor its effectiveness; and what short- and long-term impacts training of health workers in basic neonatal resuscitation would have on birth outcomes.

- A management package for home-based neonatal and postpartum maternal care should be evaluated in several geographic areas in both rural and urban settings. Research should address issues such as beliefs and practices regarding labor, childbirth, and care of the neonate; selection, training, supervision, and evaluation of health workers to provide home-based care; impact of home care on neonatal and maternal mortality; and cost-benefit analyses.
- Studies are needed to evaluate the efficacy of simple, inexpensive, culturally acceptable regimens for care of the umbilical cord immediately following delivery and in the days until the cord separates. Potential interventions include topical antibiotic versus antiseptic agents, and cord ties versus plastic clamps. Evaluations should include rates of omphalitis, neonatal sepsis, neonatal tetanus, and death. Researchers should also examine whether topical antibiotic treatment of the umbilical cord complements maternal tetanus toxoid immunization and further reduces the risk of neonatal tetanus in countries where that disease is prevalent.
- Hospital-based and community studies with accurate laboratory evaluations are needed to determine the etiologic agents responsible for serious infections in neonates (i.e., both early-onset and late-onset sepsis and meningitis). Surveillance of antibiotic use patterns in different settings (urban vs. rural; community health centers vs. hospitals) is needed to ensure appropriate use of those drugs.
- Research should be encouraged to develop cost-effective health care technology for neonates in low-resource settings that is inexpensive; easy to use; and, if possible, manufactured locally. Existing examples of such tools include mask-and-tube devices for neonatal resuscitation and Kangaroo care to prevent hypothermia.

CONCLUSION

Growing recognition of the magnitude of neonatal mortality and morbidity in developing countries highlights the need for health care interventions that specifically target the newborn. The basic improvements in care that could significantly improve neonatal survival include:

- Antenatal care that includes immunization against tetanus, intermittent preventive treatment of malaria, and early detection and timely treatment of malaria, tuberculosis, syphilis, and asymptomatic bacteriuria or urinary tract infection.
- Clean and safe delivery by a skilled attendant who can perform basic

resuscitation, prevent hypothermia, support early and frequent breastfeeding, recognize serious complications, and provide prompt effective referral to a facility providing essential obstetric and neonatal care.

- Routine neonatal care at home by the mother and family members who have received instruction in clean and safe neonatal care practices. In the event of serious illness, especially systemic infection, prompt evaluation and therapy can save lives. If referral is not possible or acceptable, home-based management of the condition becomes important.

While the interventions recommended in this chapter target the neonate, most either complement or build upon previous recommendations to improve maternal outcomes. Together these services provide the foundation for a comprehensive program of care that can significantly improve maternal and neonatal health and also fetal survival.

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Summary of Findings: Reducing Fetal Deaths in Developing Countries

- Approximately 4 million fetal deaths occur each year, 98 percent of them in developing countries. These are rough estimates, as fetal deaths are infrequently acknowledged or recorded in developing countries.

- Because intrapartum fetal deaths are more easily prevented, as fetal mortality rates decline, an increasingly higher proportion of fetal mortality occurs in the antepartum period.

- Known risk factors for fetal deaths include demographic and social correlates such as advanced maternal age; chronic maternal conditions such as anemia and sickle cell disease; maternal infections such as syphilis, HIV, and malaria; inadequate maternal nutrition; and maternal complications (both antepartum and intrapartum). Many of these factors could be addressed in antenatal care, as well as through comprehensive family planning and health education measures described in previous chapters.

- Surveillance and analysis of fetal mortality will enable developing countries to adapt and implement interventions to reduce fetal deaths as part of an overall effort to improve birth outcomes.

4

Reducing Fetal Mortality

The major causes of embryonic and fetal death vary over the course of gestation. Fetal deaths that occur late in gestation (after 28 weeks) and involve a potentially viable fetus are amenable to prevention. This chapter therefore focuses on factors that strongly influence late fetal survival, such as maternal health and the management of labor and delivery, and reviews promising interventions to reduce late fetal deaths in developing countries. Many of the interventions described in the previous chapter are also effective in reducing fetal mortality.

An estimated 4 million late fetal deaths[1] occur each year, 98 percent of them in developing countries (Save the Children, 2001; World Health Organization, 1996). Despite the magnitude of this public health problem, it has attracted little attention, and information on these deaths is limited. Late fetal deaths are not included in estimations of the global burden of disease, and are not therefore recognized by decisionmakers for their important role in that burden. A substantial proportion of fetal deaths do not have an identified cause. Fetal autopsy, discussed at the end of this chapter, is sometimes useful for this purpose, but is not available in most developing country settings.

Reported fetal mortality rates vary widely, but generally parallel neonatal and maternal mortality. Table 4-1 summarizes fetal death rates reported from several studies in developing countries. Data on fetal death in

[1]For this statistic, late fetal deaths are those that occur after 22 (not 28) weeks of gestation.

TABLE 4-1 Fetal Deaths from Developing Country Studies

Study Population	Fetal Death Rate	% Antepartum Deaths	% Perinatal Deaths	% Births in Hospitals	Number of Fetal Deaths in Study (H or P)	*Reference*
Latin America/Caribbean						
Pelotas, Brazil (1982)	16.5		49.0	99	122 (P)	Barros et al., 1987
Curaçao (1984–1985)	17.8	58.6	52.0	99	116 (P)	Wildschut et al., 1989
Jamaica (1986)	24.3	77.8	57.6	84	255 (P)	Ashley et al., 1994a
Asia						
Quezon City, Philippines (1980–1982) (<1000g)	10.3		51.9	24	42 (Ref H)	Baja-Panlilio et al., 1986
Jiangsu, China (1980–1981)	13.1	58.0	53.5		1140 (H)	Li et al., 1982
Vila, Fiji (1992) (≥500g)	15.9	43.0	46.0	80	23 (Ref H)	Maouris, 1997
Colombo, Sri Lanka (1993)	17.7	86.1	65.0		223 (H)	Lucas and Ediriweera, 1996
Nepal (1989–1990)	26.4	31.2	55.2		395 (H+C)	Geetha et al., 1995
Matlab, Bangladesh (1986)	38.3		49.3	5	2,213 (P)	Fauveau et al., 1990

Africa						
Libya (1984)	11.5	62.5	43.5		189 (H)	Kishan et al., 1988
Gweru, Zimbabwe (1984–1986)	14.9	53.9	48.5		340 (H/MC)	De Muylder, 1989
Dar es Salaam, Tanzania (1981)	25.2	59.6	65.5		171 (H)	Kazimoto, 1982
Farafenni Area, Gambia (1982–1983)	34.9		46.9	4	23 (P)	Greenwood, et al., 1987
Kaduna, Nigeria (1990)	42.8	76.2	63.9		48 (H)*	Künzel et al., 1996
Bulowayo, Zimbabwe (1990)	42.9	44.8	55.1		466 (H)	Aiken, 1992
Maputo, Mozambique (1982–1991)	44.3	83.0	57.3	15	5,958 (H)	Bugalho et al., 1989
Lomé, Togo (1990)	67.0	43.4	86.2		73 (H)*	Künzel et al., 1996
Bamako, Mali (1990)	97.7	30.8	84.9		146 (H)*	Künzel et al., 1996

P refers to population data, H to hospital data, Ref H to referral hospital data, C to community data, and MC to maternity center data.
* Estimated from data in the table.

SOURCE: Dr. Affette McCaw-Binns, UWI (Mona).

developing countries may overestimate fetal mortality in hospitals with many referrals or underestimate it if they serve a higher income segment of the population, because such studies are usually based on hospital data only (Saksena and Srivastava, 1980; Gadow et al., 1991; Conde-Agudelo et al., 2000).

Many of the studies in Table 4-1 include estimates of fetal death as a component of perinatal mortality, which includes fetal deaths occurring between 22 or 28 weeks' gestation (depending on the source) and birth, as well as neonatal deaths that occur during the first week of life. For infants who die shortly after birth, distinguishing between late fetal and early neonatal deaths can be difficult. These diagnoses depend on the skill and experience of clinical staff, who may differ in their application of the broad definitions of fetal and neonatal death (Golding, 1991). In order to recognize the true magnitude of both neonatal and fetal mortality, each outcome and its attendant risk factors need to be measured as accurately as possible. This report addresses fetal mortality separately from neonatal mortality so that the distinctions between them can be clarified and causes of mortality addressed according to their priority. Surveillance of fetal mortality, along with other pregnancy and birth outcomes, is discussed in Chapter 5.

FACTORS CONTRIBUTING TO LATE FETAL DEATHS

In settings where most women give birth without skilled assistance, fetal mortality is high, and the proportion of fetal deaths that occur during labor and delivery is high (Conde-Agudelo et al., 2000). These are intrapartum fetal deaths (IPFDs) or so-called fresh stillbirths. Such deaths can often be prevented by skilled management of labor and delivery as described in Chapters 2 and 3. However, skilled care is generally not available for home deliveries. As health care services are improved and fetal deaths during labor and delivery are reduced, antepartum fetal deaths (APFDs), which occur before the onset of labor, account for an increasing proportion of late fetal deaths (Kiely et al., 1985); thus in developed countries, only about 10 to 15 percent of late fetal deaths occur in the intrapartum period (Ogunyemi et al., 1998, Kiely et al., 1985). Since intrapartum fetal deaths predominate in most developing countries, their causes and prevention receive particular emphasis in this chapter. Low-cost measures to significantly reduce risk factors for APFDs are also discussed.

Intrapartum Fetal Deaths

Intrapartum fetal deaths (IPFDs) generally result from maternal conditions or obstetric complications, and frequently involve suboptimal management of labor and delivery (Sheiner et al., 2000; Kiely et al., 1985;

Stewart et al., 1998; Escoffery et al., 1994). Early recognition and treatment of risk factors can prevent certain fetal deaths. However, the majority of fetal deaths occur in pregnancies considered to be low risk.

Diabetes mellitus

The offspring of women with diabetes tend to be large for gestational age, and therefore at increased risk for intrapartum injury and asphyxia (Gunton et al., 2000; Garner, 1995). Even with improved glycemic control, the fetus is large in 8 to 43 percent of such pregnancies. Smoking among mothers with diabetes increases the risk for fetal mortality (Gunton et al., 2000). Complications for women with diabetes include maternal infections (more common than among healthy women), pre-eclampsia, and diabetic nephropathy (which carries a high risk of hypertension as well), all of which increase the risk of adverse outcomes. Avoiding adverse fetal outcomes requires early dietary advice, an insulin regimen, and consistent monitoring of glucose and maintenance of an optimal level (Garner 1995).

Infections

The risk for IPFD is much higher for pregnancies among women infected with syphilis than in uninfected women (Schulz et al., 1987).

Obstetric complications

Intrapartum hemorrhage. Premature separation of the placenta (abruptio placentae) causes hemorrhage. The separation varies in size from small to complete and the risk of fetal death increases with the degree of placental separation (Ananth et al., 1999).

Hypertensive disease (which includes chronic hypertension, pre-eclampsia, and eclampsia) may be exacerbated by pregnancy or arise for the first time during pregnancy. Hypertensive disease was found to be a major risk factor in analyses of about 15,000 late fetal deaths in Latin America (Conde-Agudelo et al., 2000), almost 600 late fetal deaths in Jamaica (Greenwood et al., 1994), and 93 late fetal deaths in Ghana (Wiredu and Tettey, 1998). In a study in Mozambique, the fetal death rate for 1,275 women with hypertensive disease of pregnancy was 5.7 percent compared with 2.3 percent for the more than 43,000 women without hypertensive disease (Merz et al., 1992). In a study in Shanghai, China, 8,852 of 158,790 pregnancies involved hypertensive disease; 44 percent were classified as moderate or severe, and the adverse outcomes included 48 antepartum fetal deaths and 12 late fetal deaths (Huang, 2001).

Prolonged or obstructed labor. This is one of the most common preventable causes of fetal mortality. It may involve prolonged first or second stage of labor, cephalopelvic disproportion, uterine rupture, or malpresentation. In Zimbabwe, major causes of perinatal mortality were found to include prolonged first- and/or second-stage labor, uterine rupture, and a retained second twin (Aiken, 1992). Although improvements in antenatal, intrapartum, and neonatal care have the potential to reduce perinatal mortality, further study into specific preventive measures is necessary.

Fetal malpresentation, such as breech or transverse lie, has also been associated with increased risk for fetal death in studies in both developing (Conde-Agudelo et al., 2000; Kapoor et al., 1994; Aiken, 1992; Kusiako et al., 2000) and developed (Sheiner et al., 2000) countries.

Multiple pregnancy. Studies of more than 7,000 births in southern Brazil and more than 9,500 births in Jamaica have reported a two- to four-fold higher risk of fetal mortality in multiple pregnancies compared with singleton pregnancies (Barros et al., 1987; McCaw-Binns, 2000).

Cord complications including prolapse, cord around the neck, knots, or other entanglement also contribute to intrapartum fetal death (Sheiner et al., 2000).

Asphyxia

Asphyxia is an important cause of fetal death. Asphyxia can be broadly defined as progressive hypoxaemia and hypercapnia with a significant metabolic acidaemia (Low, 1997; Bax and Nelson, 1993). In the early 1990s, the Jamaican Perinatal Mortality Survey found intrapartum asphyxia to be the cause of 23 percent of fetal deaths in which the fetus weighed at least 2,500 g (Escoffery et al., 1994). The rate of asphyxia is higher in Ghana (56 percent) (Wiredu and Tettey, 1998). Growth-restricted fetuses appear to have a lower tolerance for intrapartum asphyxia (Tuthill et al., 1999).

Birth injury

Birth injury includes preventable and unavoidable mechanical or hypoxic-ischemic injuries suffered by the neonate during labor and delivery. These may include trauma to the head (most significant is intracranial hemorrhage); trauma to internal organs (such as the liver or spleen); injury to the spinal cord or peripheral nerves (most common is brachial plexus injury and most devastating is cord transection); and fractures (to the clavicles and extremities). The predisposing factors include macrosomia (particulaly for diabetic mothers), cephalopelvic disproportion, dystocia, prolonged or obstructed labor, breech presentation, and prematurity. Although injury may occur despite skilled care at delivery, some injuries are the result of inadequate medical knowledge or suboptimal care during labor and delivery. More specific diagnoses can assist efforts to prevent avoidable birth injuries.

Escoffery and coworkers (1994) found evidence of birth trauma in 22 percent of the IPFDs they examined in Jamaica. In a study in Ghana, birth trauma was found to be responsible for a little more than 5 percent of fetal deaths (Wiredu and Tettey, 1998).

Economic factors

To the extent that low family income limits access to quality health care services, it is a risk factor for IPFD. Family income has been negatively correlated with fetal mortality in India (Saksena and Srivastava, 1980) and Brazil (Barros et al., 1987), with women from the poorest families having a fetal death rate two to four times higher than women from the wealthiest families. A similar relative risk of late fetal death was determined for rural women (who tend to have lower socioeconomic status) compared with urban women in Nepal (Jahn et al., 2000). The risk for late fetal death was significantly higher among wives of unskilled laborers (such as subsistence farmers) in Papua New Guinea (Amoa et al., 1998). In a large study of over 850,000 hospital births in 11 Latin American countries, the late fetal death rate was almost twice as high in free hospitals that serve mainly low-income women as in hospitals requiring payment for services (Gadow et al., 1991). This difference may in part reflect a lower quality of care provided to patients who do not pay for services.

Antepartum Fetal Deaths

The risk factors reported for APFDs include maternal conditions, obstetric complications, and advanced maternal age. Some studies, described below, also indicate that inadequate antenatal care, smoking, high parity, and low socioeconomic status increase the risk for APFD.

Hypertensive disease of pregnancy

Hypertensive disease was found to be a major risk factor for APFD. In Sri Lanka, hypertensive disease was associated with 32 percent of antepartum deaths, the majority of which occurred after 31 weeks of gestation (Lucas and Ediriweera, 1996). Hypertension may result in uteroplacental insufficiency, abruptio placentae, or placental infarction—all risk factors for late fetal death.

Antepartum hemorrhage

This was shown to be one of the most important risk factors for fetal death in studies in Latin America (Conde-Agudelo et al., 2000), Jamaica (Greenwood et al., 1994), and Ghana (Wiredu and Tettey, 1998).

Diabetes mellitus

It is well known that maternal diabetes mellitus increases the risk of intrauterine fetal death (Garner, 1995; Casson, 1997; Hawthorne et al., 1994; Mondestin, 2002; Platt et al., 2002). Although the exact cause of fetal death is unknown, uteroplacental insufficiency, vascular disease, and hypertension associated with diabetes increase risk of death. In addition, congenital malformations in diabetic pregnancies also contribute to increased risk of late fetal death. Several studies have shown that diabetes in pregnancy is associated with hyptertension (Cundy et al., 2002) or with hypertensive disorder of pregnancy (Sibai et al., 2000). Maternal hypertension associated with diabetes may result in fetal compromise earlier in gestation and is particularly worrisome (Lagrew et al., 1993). Early recognition of diabetes mellitus in pregnancy and control of maternal glucose levels can reduce fetal mortality and other complications in affected pregnancies (Langer and Conway, 2000).

Sickle cell disease

This inherited disorder occurs worldwide with the highest incidence in malaria-endemic areas of Africa. Sickle cell disease is associated with an increased risk of fetal mortality, presumably due to placental infarcts (Mahomed, 2003). This risk can be substantially reduced with appropriate antenatal care and management of labor and delivery (Sun et al., 2001; Smith et al., 1996); however, this level of care is not generally available in the countries where sickle cell disease is most prevalent.

Infections

Fetal mortality is associated with a variety of maternal infections including sexually transmitted diseases, bacterial infections of the genitourinary tract, and rubella[2] (Goldenberg et al., 1997; Gibbs, 2002).

Syphilis, like rubella, *Toxoplasma*, and cytomegalovirus, can cause

[2]Rubella is discussed in the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* (Institute of Medicine, 2003).

transplacental infection of the fetus. Although a rapid serological test allows on-site diagnosis so that a highly effective treatment of penicillin can be initiated immediately, there continues to be a high level of infectious maternal syphilis in several countries (Hira et al., 1990). The prevalence of syphilis among women attending antenatal clinics is 4 to 16 percent in several countries of Africa and the Caribbean (Hira et al., 1990; Schulz et al., 1987; Prabhakar et al., 1991; McDermott et al., 1993). Untreated syphilis has been shown in several studies to increase the risk of fetal death (de Aquino, 1998; Osman et al., 2001; Schulz et al., 1987; McDermott et al., 1993). In Malawi, a longitudinal population-based study found a population-attributable risk (PAR) for syphilis of 26 percent among mothers who had experienced a fetal death. For antepartum fetal deaths, the PAR was 38 percent for syphilis (McDermott et al., 1993). Syphilis was the attributed cause of 10 percent of late fetal deaths in a case-control study of 315 consecutive late fetal deaths in Papua New Guinea (Amoa et al., 1998).

Other bacterial infections—symptomatic or asymptomatic—are an important risk for late fetal death (Maleckiene et al., 2000). Various reproductive tract infections have been associated with preterm spontaneous labor (Brocklehurst et al., 2002) and rupture of membranes, which can result in fetal death. Infection of normally sterile sites like amniotic fluid, interior of the placenta, and fetal blood can be life threatening (Maleckiene et al., 2000). Chorioamnionitis or amniotic fluid infection has been identified as an important cause of fetal death in several studies in developing (Naeye et al., 1977; Ross et al., 1982, Moyo et al., 1996; Folgosa et al., 1997; Matthews et al., 2001) and industrialized (Tolockiene et al., 2001) countries.

HIV. A systematic review of maternal HIV infection and perinatal outcomes (Brocklehurst and French, 1998) suggests a weak association in developing country studies when there is an attempt to control for confounding. Studies to date have not provided good data on the disease stage of women or their immune function.

Viral hepatitis. Viral hepatitis is a common cause of liver disease during pregnancy and is a cause of fetal death (Michielsen and Van Damme, 1999).

Obstetric complications

Placental abruption, oligohydramnios, and umbilical cord complications have been identified as important risks for APFD in hospital-based, retrospective studies in developed countries (Sheiner et al., 2000; Oron et al., 2001; de Aquino et al., 1998; Ananth et al., 1999). The risk of late fetal death rises steeply when more than half the placenta becomes separated. Hypertensive disease of pregnancy, tobacco use, and drug use are all risk factors for placental abruption (Ananth et al., 1999).

Multiple pregnancy. In Jamaica, antepartum fetal deaths were found to occur about twice as frequently among twins as among singletons (Ashley et al., 1994b).

Prolonged pregnancy is defined as a pregnancy that lasts 42 weeks or more. Developed country studies have shown that prolonged pregnancy increases the risk of fetal death (Hollis, 2002). This risk is increased for growth restricted fetuses; growth restriction itself is an independent risk factor (Divon et al., 1998). In terms of numbers of fetal deaths, however, many more fetuses die between 37 and 42 weeks than after 42 weeks. In low-resource settings, the date of conception is frequently not known, which limits the ability to understand the role of prolonged pregnancy in these populations.

Congenital malformations[3]

These have been found to account for 6 percent of fetal deaths in Jamaica (Ashley et al., 1994a) and almost 8 percent in Zimbabwe (Aiken, 1992). As fetal mortality due to more preventable causes decreases, the proportion of fetal deaths associated with malformations increases (De Galan-Roosen et al., 1998).

Maternal age and parity

Several studies show an increase in fetal deaths with advanced maternal age (Fretts et al., 1995; Huang, 2000; Andersen et al., 2000; Seoud et al., 2002; Sheiner et al., 2000; Amoa et al., 1998; Khandait et al., 2000). Data from India (Saksena and Srivastava, 1980), Brazil (Barros et al., 1987), and Mexico (Bobadilla-Fernandez, 1986) indicate that fetal death rates are lowest among teen mothers and rise with maternal age. Risk ratios vary from 2 to 4 in the oldest versus the youngest age groups. Other studies have found a U-shaped relationship between maternal age and fetal mortality, with the youngest and oldest mothers faring worst (de Aquino et al., 1998; Andersen et al., 2000; Onadeko et al., 1996; Stanley and Straton, 1981; Murphy et al., 1987; Ahlenius and Thomassen, 1999). Multivariate analyses indicate that the high fetal death rates sometimes observed among teenage mothers may result from social and behavioral influences, rather than a specific biological effect of young maternal age although biological factors can have an influence in very young mothers (Bacci et al., 1993; Hardy et al., 1987; La Guardia et al., 1989). The relationship between maternal parity and fetal mortality is unclear. It is often difficult to separate the effects of

[3]Discussed in the companion report, *Reducing the Impact of Birth Defects*: *Meeting the Challenge in the Developing World* (Institute of Medicine, 2003).

advanced maternal age and multiparity (Oron et al., 2001). By contrast, another study shows an association between primiparity and multiparity greater than three and fetal mortality (Huang et al., 2000), and a few studies from industrialized countries have found no association between parity and risk for fetal death (Ahlenius and Thomassen, 1999).

Obesity

Excessive prepregnancy weight has been consistently shown to increase the risk for late fetal death (Conde-Agudelo, 2000; Huang et al., 2000). This relationship remains after controlling for maternal age and excluding maternal diabetes and hypertensive disease.

Social and economic factors[4]

In both developed and developing countries, low socioeconomic status increases risk of late fetal death. Multivariate analysis of Jamaican data shows social and economic factors to be associated with antepartum fetal deaths. These factors include single motherhood (compared with married or common-law relationships), women assessed by midwives as malnourished, and women living in households that share toilet facilities—an indicator of relatively lower socioeconomic status (Greenwood et al., 1994; Huang, 2000; Stephansson et al., 2001).

Additional factors

The following have been associated with APFD but have yet to be established as significant risk factors for fetal death:

Alcohol consumption. Heavy alcohol consumption during pregnancy has been associated with fetal alcohol syndrome,[5] fetal alcohol effects, and increased fetal and neonatal mortality (Jacobson et al., 1993; Faden et al., 1997; Sulaiman et al., 1988; Warren and Bast, 1988). There are no conclusive data on the minimum amount of alcohol ingestion during pregnancy

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[4]The committee recognizes that female feticide, which generally occurs early in pregnancy, accounts for significant numbers of fetal deaths. In several countries, diagnostic techniques have been used increasingly to determine gender, followed by termination of pregnancy if the fetus is female (Sheth and Malpani, 1997; Imam, 1994; Xu et al., 1997). Preventing such testing is likely to be difficult (Sheth and Malpani, 1997). In some communities, the male to female sex ratio has increased dramatically (Booth et al., 1994). Female infanticide, which can occur shortly after birth, also contributes to deaths recorded as fetal and to the changing ratio of males and females in some populations.

[5]For more information, see appendix B and the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* (Institute of Medicine, 2003).

that produces adverse effects in the developing fetus (Roebuck et al., 1999). If a pregnant woman drinks, on average, more than five drinks per occasion once or twice a week, growth, intellectual and behavioral problems short of full-blown fetal alcohol syndrome can occur in the offspring. Calculating in a manner analogous to environmental and food contaminants, one drink every 10 days or less might be considered safe and if it happens, the woman may be reassured. However, alcohol is a neurotoxicant and pregnancy is a very vulnerable time and the deleterious effects are lifelong for the child. Thus minimal to no consumption of alcohol during pregnancy is the best course to follow (Jacobson and Jacobson, 1994, 1999).

Two studies of large populations have addressed the effect of maternal alcohol consumption on fetal mortality for a range of drinking levels, and found an association between maternal alcohol consumption and fetal mortality (Faden et al., 1997; Kesmodel et al., 2002). The first, a retrospective study involving nearly 10,000 live births and about 3,300 fetal deaths in the United States, found that women who consumed more alcohol also smoked more, and were younger and less educated than those who consumed no alcohol or a lower level. Multivariable logistic regression nevertheless showed a significant association of alcohol consumption and fetal death (Faden et al., 1997). The second study, a prospective study in Denmark of nearly 25,000 pregnancies, analyzed the deaths of 116 fetuses of at least 28 weeks' gestation. In this population, the risk of late fetal death for women who consumed five or more alcoholic drinks (each the equivalent of a bottle of beer or glass of wine) per week was found to be nearly three times higher than for those who consumed less than one drink per week (Kesmodel et al., 2002). This result was adjusted for smoking habits, caffeine intake, age, prepregnancy body weight, marital and occupational status, education, parity, and sex of the fetus. The alcohol-associated risk for fetal death was attributed in large part to uteroplacental dysfunction.

Smoking. Several large studies, all conducted in industrialized countries, have found smoking during pregnancy to be a risk factor for late fetal death (Wisborg et al., 2001; Cnattingius et al., 1988; Meyer and Tonascia, 1977; Meyer et al., 1976; Kleinman et al., 1988; Tuthill et al., 1999; Ahlenius and Thomassen, 1999). The association between smoking and fetal death is most likely explained by placental complications and effects on fetal growth.

A study in Sweden of more than 280,000 births, which controlled for confounders, found that smoking increased the risk of fetal death by 40 percent during the third trimester and doubled the risk for mothers who smoked and were aged 35 years or more (Cnattingius et al., 1988). A study of more than 25,000 deliveries in Denmark concluded that continuing to smoke one or more cigarettes per day beyond 16 weeks' pregnancy increased the risk of late fetal death twofold, after adjustment for numerous factors including maternal age, weight, parity, marital and socioeconomic status, and alcohol and caffeine intake (Wisborg et al., 2001). A case-control study of more than 600 late fetal deaths in Wales found that maternal smoking was associated with an increased risk (odds ratio [OR] of 1.72) of fetal death and, most strongly (OR of 2.07), with placental abruption (Tuthill et al., 1999). A similar association between cigarette smoking and placental abruption was found in a prospective Canadian study of more than 87,000 pregnancies (Ananth et al., 1996).

Illegal drug use. Assessing the health risks associated with a particular drug is complicated by the unhealthy lifestyle of many drug users, who frequently use other drugs, tobacco, and alcohol, as well as by the difficulty of obtaining accurate data on individual exposure (Lutiger et al., 1991; Richardson et al., 1993). A meta-analysis of cocaine use, including two studies reporting fetal death as an outcome, yielded a combined odds ratio of 6 (95 percent [CI] 1.2–31.5) for fetal death among cocaine users compared with nonusers (Lutiger et al., 1991). This risk may be due to the association of cocaine use with fetal growth restriction, preterm delivery, and placental abruption (Handler et al., 1991). Studies of cannabis use in pregnancy have failed to show a relationship between antenatal exposure and fetal death (Richardson et al., 1993; Fergusson et al., 2002).

Anemia, highly prevalent in pregnant women in developing countries (Beard, 2000), can result from the increased demands of pregnancy for iron, folic acid, and other micronutrients. The condition may be exacerbated by inadequate diet, malaria, and helminthic infestation. Randomized control trials on the effect of daily supplements to pregnant women of iron alone or iron (100 milligrams) and folic acid (350 milligrams) have been reviewed (Mahomed, 2000, 2002), but found to provide inadequate information on fetal outcomes. These trials are further limited by their rarely being undertaken in the communities where iron and folate deficiency are common (Mahomed, 2002). Two additional reviews reached similar inconclusive findings about the ability of iron or iron and folic acid supplementation[6] during pregnancy to prevent fetal death (Xiong et al., 2000; Rasmussen, 2001). There is little information available, particularly in populations where these micronutrients are limited (Mahomed, 2000), and more research is needed.

Malaria contributes to antenatal anemia but has not been shown to be a risk factor for fetal mortality (Luxemburger et al., 2001). Regular treatment with antimalarials, while associated with fewer episodes of severe

[6]This conclusion is specific to the use of folic acid supplementation solely to prevent fetal death due to maternal anemia. The ability of folic acid supplementation to prevent neural tube defects, which can result in fetal death, is well established, as discussed in the companion report on birth defects (Institute of Medicine, 2002).

anemia and fever in the mother, and with higher average birth weights, has not been shown to change perinatal mortality, even in studies of women of low parity (Garner and Gülmezoglu, 2000). Placental malaria infection was not associated with increased perinatal mortality in a prospective study in Malawi (McDermott et al., 1996).

Nutritional deficiencies. Poor maternal nutritional status is associated with adverse birth outcomes (Kramer, 1987; Pojda and Kelley, 2000), but the association with fetal mortality is less clear. A meta-analysis of the effect of dietary supplementation during pregnancy showed that it improved fetal growth and may reduce risk of fetal death (Kramer, 2002). This analysis is based on controlled clinical trials that used balanced supplements, defined as those in which protein contributes 25 percent or less of the total energy content. Most trials were able to provide only a modest increase in net energy intake, and only three trials provided data on fetal mortality.

A controlled trial in Gambia (Ceesay et al., 1997) provided a higher energy supplement (about 1,000 kilocalories) to chronically undernourished pregnant women and significantly reduced fetal deaths; the odds ratio was 0.47 (0.23 to 0.99, $P<0.05$). Further controlled trials are needed to confirm the benefits of increased dietary consumption on perinatal outcomes in a range of settings. However, given the importance of maternal nutrition before and during pregnancy for other aspects of pregnancy outcomes, lack of findings with respect to fetal death should not preclude the implementation and evaluation of potentially effective interventions to improve maternal nutritional status in developing countries.

Whether deficiencies of micronutrients other than iron and folic acid (discussed above and in detail in Chapter 6) increase risk of fetal death has yet to be established. Deficiencies in zinc and other micronutrients are associated with a broader range of adverse birth outcomes (Black, 2001). Their potential roles in fetal health warrant further study (Fawzi et al., 1998; Chappell et al., 1999).

INTERVENTIONS

De Muylder (1989), who systematically investigated perinatal deaths in a district of Zimbabwe, found that 76 percent of the fetal deaths he reviewed were potentially preventable. Many late fetal deaths were found to be complicated by conditions that are amenable to treatment: hypertension, diabetes, syphilis, or amniotic fluid infection. Better health care—to diagnose and manage maternal diseases that put the fetus at risk, to diagnose acute conditions such as intrauterine infection or hypertension, and to respond to danger signs in a timely manner—would improve fetal survival.

The interventions discussed below target late fetal mortality (beyond 28 weeks' gestation). They emphasize the prevention of IPFD, as it is generally understood that these deaths, which predominate in settings where fetal mortality rates are highest, are more easily prevented than APFDs (Sheiner et al., 2000; Kiely et al., 1985).

Intrapartum Care

The greatest influence of health care on fetal mortality occurs during labor and delivery. Effective referral systems for managing pregnancy complications through basic and comprehensive essential obstetric care are critical to improving all birth outcomes (see Chapter 5). In order to reduce IPFDs, facilities for basic essential obstetric care should monitor labor; manage major obstetric complications, such as severe pre-eclampsia and eclampsia, obstructed labor, and hemorrhage; and address other complications, such as diabetes mellitus, that are associated with high rates of fetal mortality.

Facilities offering comprehensive essential obstetric services can reduce fetal deaths by providing cesarean delivery and blood transfusion, in addition to the services discussed above under basic essential obstetric care. Women with medical complications (e.g., heart disease, sickle cell anemia, diabetes) or poor obstetric history (e.g., previous preterm delivery, fetal or neonatal death, intrauterine growth restriction, malpresentation, ante- or postpartum hemorrhage, eclampsia, or uterine scars) are at high risk of a recurrence of these complications and should plan skilled assistance for delivery, preferably in a hospital that provides comprehensive essential care for labor and delivery.

Many obstetric and maternal complications that may be best treated earlier in pregnancy can still be managed successfully by a skilled birth attendant (physician, midwife, or nurse). Thus, where resources are limited, the most cost-effective means of reducing late fetal mortality is through skilled attendants who can implement the following key interventions:

Detection and management of fetal distress

Fetal monitoring allows early detection of the compromised fetus and alerts the birth attendant to the need for a prompt delivery. The use of tools such as kick charts may be tested in settings where inadequate hygiene increases the risk of infection associated with vaginal examinations. For the induction of labor, intravaginal misoprostol can serve as an effective, low-cost alternative to intravenous oxytocin infusion (Fletcher et al., 1993), particularly in women with severe pre-eclampsia (Hofmeyr, 1998).

Detection and management of prolonged or obstructed labor

Studies have concluded that IPFDs due to asphyxia or trauma can be reduced with adequate monitoring of labor and prompt management of the problems that arise (Wildschut et al., 1990; Escoffery et al., 1994). Active monitoring of the progress of labor with the partograph (see Chapter 2) has been shown effective in alerting skilled birth attendants to obstructed or prolonged labor, which can then be managed to prevent fetal death (Dujardin et al., 1992; World Health Organization, 1994). However, since the partograph necessitates repeated vaginal examinations, good hygiene is a prerequisite for its use.

Detection and management of malpresentation

Breech presentation is associated with increased risk of fetal mortality. Some of the increased mortality reflects the tendency of fetuses with certain birth defects (e.g., neurologic or muscular) to manifest hypotonia and secondarily present as a breech (Jones, 1997). The use of routine external cephalic version (ECV) can safely lower the number of breech deliveries, with minimal risk of fetal or maternal morbidity (Hofmeyr, 2002). Intrapartum deaths due to malpresentation (breech/transverse lie) may be prevented by cesarean section when ECV fails.

Prevention, detection, and treatment of intrapartum infection

The risk of chorioamnionitis can be reduced by limiting vaginal exams, restricting the introduction of anything into the vagina, and ensuring the proper management of women with preterm and/or prolonged rupture of the membranes and/or prolonged labor (Seaward et al., 1997, 1998). If a woman does develop an intrauterine infection, early detection followed by prompt antibiotic treatment is necessary to prevent the infection from becoming life threatening to the mother and/or fetus. Fever during labor, uterine tenderness, and foul-smelling amniotic fluid all suggest intrauterine infection.

Preconceptional and Antenatal Care

Family planning

Chromosomal abnormalities such as Down syndrome can be reduced by discouraging women from bearing children after they reach 35 years of age and by ensuring that these women and their partners have ready access to permanent methods of family planning (e.g. tubal ligation or vasectomy). These methods should also reduce the number of fetal deaths due to chronic medical disorders associated with advanced maternal age, such as hypertension and diabetes.

Antenatal care

Severe complications often begin earlier in pregnancy and, if recognized, can be addressed by early treatment, which provides the best protection against fetal death (Sheiner et al., 2000; Kiely, 1985). Lack of antenatal care is associated with a marked increase in late fetal deaths (Conde-Agudelo, 2000). Early initiation of antenatal care (before 20 weeks of gestation) provides the best opportunity to identify and address risk factors for fetal mortality. Educational programs are needed to convince all pregnant women to obtain key antenatal services (De Muylder, 1989). The following antenatal services can significantly reduce both antepartum and intrapartum fetal deaths:

Detection and treatment of syphilis. Screening for and treatment of syphilis is a cost- effective means of reducing fetal deaths (Temmerman et al., 2000). Universal screening of pregnant women and immediate treatment (at the same visit) for those infected is the most effective means to achieve this goal (Delport and van den Berg, 1998; Patel et al., 2001). Women at high risk for syphilis should be screened again in the third trimester.

Detection and management of hypertensive disease of pregnancy. There is no proven treatment for preventing or delaying hypertensive disease of pregnancy. Effective management may require early delivery for women with severe hypertension and proteinuria. When possible this should occur after 32 weeks' gestation, when the risk of neonatal mortality is lower. It is more difficult to save the fetus when hypertension is associated with placental abruption.

Management of sickle cell disease. Blood transfusions in patients with sickle cell disease (SCD) can dilute their circulating sickle hemoglobin levels and maintain hemoglobin levels at 60-70 percent of the normal level, which reduces pain crises and severe anemia. Blood transfusion in the countries where SCD is prevalent is expensive, and blood supplies may be limited and contaminated with infectious pathogens. A Cochrane review compares SCD management using regular transfusions with selective blood transfusion (only when hemoglobin fell below 6 g per dL). It found the data inadequate for identifying the ideal approach and suggested that hemoglobin may need to be maintained at a slightly higher level (Mahomed, 2003). A study in Benin suggests that practical, inexpensive approaches in conjunction with selective blood transfusions can significantly lower fetal mortality (Rahimy et al., 2000). Since SCD has serious health consequences for women during pregnancy, counseling provides strategies to reduce the risk of an acute event: ways to improve nutritional status with local foods; supplementation with iron, folate, and vitamins; maintaining hydration through high fluid intake; prophylaxis against *Plasmodium falciparum* malaria; and early detection of bacterial infection (Rahimy et al., 2000).

Detection and Management of Diabetes. Identification and management of women with pre-gestational diabetes improves pregnancy outcome. Screening for gestational diabetes is appropriate for women at high risk due to a previous large for gestational age infant, previous unexplained fetal death, previous congenital malformation, or obesity. Cesarean section, where safely available, may be needed for large for gestational age infants if there is failure of the normal progression of labor.

Recognition of Fetal Deaths

Fetal deaths often go unacknowledged or unrecorded in developing countries, which hinders attempts to adapt interventions and set health care priorities to meet local needs. In Jamaica, for example, researchers found that only 13 percent of late fetal deaths and 25 percent of infant deaths had been registered, compared with 94 percent of live births (McCaw-Binns et al., 1996). In Thailand, a comparison of official records with a community-based survey showed that only 55 percent of infant deaths and none of the late fetal deaths recorded in the survey had been officially registered (Lumbiganon et al., 1990).

Obtaining accurate measures of both fetal and neonatal mortality will require renewed efforts to record all births and accurately assign deaths as fetal or neonatal. Only when the full magnitude and causes of fetal and neonatal mortality are established can policy makers and health professionals identify and implement appropriate health services. Chapter 5 describes strategies for the surveillance of all pregnancy outcomes; the measures described here represent key steps toward establishing surveillance of fetal death.

Autopsy and fetal death audit

A well-performed autopsy may be the sole means of establishing diagnoses in fetal deaths, and is likely to contribute information that differs from clinical findings (Bendon, 2001; Magee, 2001; Tennstedt et al., 2001; Meier et al., 1986; Porter and Keeling, 1987). Congenital anomalies may not be grossly apparent and postmortem findings can contribute to genetic counseling of parents on their fetal loss and future pregnancies (Doyle, 2000; Berger, 1978), and to subsequent monitoring of patient care. In addition, examination of the placenta may help elucidate the cause of death (Naeye, 1992). Autopsies are not widely available in developing country settings.

Classification systems

Unlike most systems for classifying perinatal deaths, the Wigglesworth (1980) system does not rely on autopsy data (Hey et al., 1986). This overcomes a difficult challenge for many developing country settings. A modified form of this method, which permits the classification of fetal deaths, can be used to analyze trends in fetal death and identify critical needs (Keeling et al., 1989). For example, studies using this system in Zimbabwe (De Muylder, 1989) and Jamaica (Ashley et al., 1994a) found asphyxia to be a major cause of fetal death, suggesting the need to improve obstetric monitoring and resuscitative procedures (Golding, 1991).

RECOMMENDATIONS

Recommendations 1, 2, and 4, in the executive summary and chapter 9 have been developed in other chapters. They also address priority interventions for reducing fetal mortality. Surveillance of fetal deaths is even more limited than for neonatal deaths. Until the magnitude of fetal mortality is established, it is likely to remain high.

RESEARCH NEEDS

As a result of the substantial overlap in the causes of fetal and neonatal mortality, several of the research topics in the previous chapter apply here as well. There are two additional priorities for research:

- Strategies are needed to determine how to monitor labor and delivery more effectively so as to ensure early recognition of complications in low resource settings.
- Given the high prevalence of unexplained fetal death in developing countries, autopsy studies in diverse settings could help identify potentially preventable deaths, especially those related to infection.

CONCLUSION

The most significant risk factors for fetal death also profoundly affect maternal and neonatal health. In most developing countries, IPFD accounts for a high proportion of fetal mortality. Skilled management of labor and delivery, including access to emergency obstetric care (see Chapters 2, 3, and 5), could prevent many of these deaths, in addition to those of mothers and neonates. The decrease in intrapartum fetal mortality in developed countries can be attributed to improved obstetric monitoring and management of labor and delivery (Goldenberg et al., 1987). Reducing APFD involves addressing maternal factors such as advanced age, prior fetal loss, infectious disease, hypertension, obesity, and other health problems through focused antenatal programs, comprehensive family planning, and health education, as described in previous chapters.

Continued surveillance and analysis of fetal death, as well as maternal and neonatal mortality and morbidity, will allow communities and countries to adapt interventions to local conditions and set health care priorities. The recommendations and research priorities presented in the next chapter emphasize the need to recognize fetal deaths as part of an overall effort to improve birth outcomes.

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PART III

Improving Health Care Systems

**Summary of Findings:
Improving Birth Outcomes Within
Health Care Systems**

- Successful implementation of the interventions recommended in previous chapters requires an effective health care system. The essential elements in that system for improved birth outcomes include skilled birth attendants at labor and delivery; trained, supervised staff (including village health workers) for other services; and, in the event of complications, access to essential obstetric and neonatal care through an effective referral system.

- An effective referral system includes good communication between the referral hospital or health center and the skilled attendant, transportation to the referral facility, and access to a loan if needed.

- Community trials of appropriate models of reproductive and neonatal health care will be instrumental in building accessible, acceptable, cost-effective health services to improve birth outcomes.

- Each country should develop a strategy, a framework of activities, and the commitment of its leaders to reducing maternal, fetal, and neonatal mortality.

- Surveillance of birth outcomes—especially maternal, fetal, and neonatal mortality—is essential to recognizing the burden of disease associated with pregnancy and childbirth, and to providing the data needed for identifying, prioritizing, and evaluating interventions to provide those services.

- Each country should strengthen its public health capacity for recognizing, implementing, monitoring, and tuning interventions that meet their population needs and have been proven effective in similar populations.

5

Improving Birth Outcomes Within Health Care Systems

The previous chapters have described a broad range of conditions that contribute to adverse birth outcomes. Most of these conditions can be addressed through affordable interventions that have been proven effective in clinical trials, and in some cases, in population-based studies. In order for these interventions to have the maximum impact on birth outcomes in large populations, however, they must be implemented within an effective health care system. As discussed in Chapters 2 and 3, the key requirements for reducing maternal, fetal, and neonatal mortality are skilled birth attendance and, for complicated deliveries, access to the appropriate level of essential obstetric and neonatal care (World Health Organization, 1999; Li et al., 1996). Building strong reproductive health care capacity both requires and contributes to a strong and equitable system for overall health care (Graham, 2002).

This chapter addresses the overall process of developing and strengthening a health care system. Countries meet their specific needs by tailoring that overall process. The chapter first reviews the evidence base for strengthening health care systems, then addresses primary care and referral by reviewing current models of care for labor and delivery, and considers the limitations in access to these health care services. The next section addresses the building of health care capacity, which involves staff development and training, the role of the private sector, financing, and health care reforms. This is followed by a section on management of health care systems, which includes the roles of surveillance and evaluation. The chapter concludes with three recommendations and the research needed to develop health care systems that support sustained and future improvements in birth outcomes.

THE EVIDENCE BASE

Evidence concerning the effectiveness of specific interventions to prevent adverse birth outcomes has been reviewed in earlier chapters. This chapter addresses the implementation of these interventions within primary health care systems, a process that has not been evaluated with the same methodological rigor as the effects of the component services or activities. The clinical and cost-effectiveness of interventions within a health care system would ideally be determined through randomized, controlled trials (RCTs), since they provide the most reliable evidence. However, RCTs have not been used extensively in evaluating community interventions (Smith et al., 2000) because of the cost and complexity of very large trials or because denial of services to a control group when they are widely believed to be beneficial may be considered unethical. Because maternal mortality is a relatively rare event, very large populations need to be studied. Such trials are also complex owing to their multiple components and the involvement of several levels of government (Sorensen et al., 1998)

Clearly the evidence base for improving birth outcomes within the health care systems of diverse countries would be strengthened by conducting RCTs of interventions in the systems in question. It is important for future research to meet the challenges imposed by cost and complexity so that policies and programs can be based on a stronger scientific footing. For now, given the current lack of RCTs to evaluate the effectiveness of health care systems, and the urgent need to improve birth outcomes, the committee has examined less rigorous attempts to integrate interventions into health care systems and programs. This chapter therefore focuses on the feasibility of implementing systems and programs of maternal and infant care in different settings, the problems encountered, and the lessons learned. When published evidence on the overall effectiveness of these systems and programs is available, it has been reviewed. Since this evidence often consists of comparisons before and after interventions in the same geographic setting, participants versus nonparticipants in the same setting, or settings that have implemented a program versus those that have not, caution is advised in drawing inferences about the causal effects of the systems or programs of care.

PRIMARY CARE AND REFERRAL

The 1978 International Conference on Primary Health Care produced the Alma-Ata Declaration, a strategy promoting "health for all" that has been broadly accepted. The main goal of this strategy is to make primary health care—defined as essential health care based on practical, scientifically sound, and socially acceptable methods and technology—accessible to people in every community and affordable to communities and countries at every stage of development. The Alma-Ata Declaration recognizes primary health care as the centerpiece of a country's health system, and an important component of its overall social and economic development (World Health Organization, 1978).

More recently, "close-to-client" health care has been identified as the principal vehicle for addressing the small number of conditions, including maternal, fetal, and neonatal mortality, that account for much of the excess mortality in developing countries (Jha et al., 2002). In this model of primary care, relatively simple hospitals and health centers deliver effective interventions against major causes of death and disability in poor populations. Care in these settings, which can often be provided by nonphysicians (nurses, midwives, community or village health workers, and other paramedical staff) is complemented by a referral system that provides access when needed to higher-level care (World Health Organization, 1994, 1996a). The goal of referral is to assure that patients receive effective care in an appropriate facility at minimal cost (Murray et al., 2001). Box 5-1 lists the essential features of effective referral systems.

Several interventions recommended in this report, such as those for family planning, preconceptional care, and refocused antenatal care (Villar et al., 2001)—all primary care services—can be offered through community facilities linked to district hospitals. Antenatal care can be provided at a community health clinic. Skilled birth attendants can provide clean and safe deliveries and immediate postpartum care in homes or clinics. Postnatal

BOX 5-1 Essential Features of Effective Referral Systems

- An adequately resourced referral center (see Chapter 2 and Table 2-3)
- Communications and feedback systems
- Designated transport
- Protocols for the identification and management of complications in specific settings
- Teamwork between referral levels
- A unified records system
- Mechanisms to ensure that patients do not bypass referral levels (good patient information and structured fee and exemption systems)

SOURCE: Murray et al., 2001.

care for the infant can be provided by a midwife, nurse, or possibly a village health worker (Bang et al., 1999) (see Box 3-2). Trials are needed to test this approach in other settings and determine whether a similar approach can be effective for maternal postnatal care. Local services can easily be tailored to meet community needs and local participation in decisions on the delivery of health services increases the use of services, improves patient satisfaction and knowledge, and strengthens health care capacity.

Since the risks for adverse birth outcomes are so high at the time of labor and delivery and the immediate postpartum period, the quality of care at that time becomes the major focus. Reducing the significant burden of maternal, fetal, and neonatal mortality will require good-quality maternal and neonatal services along with effective referral systems (Jha et al., 2002; Murray et al., 2001; Ross et al., 2001; Kusiako et al., 2000; Fauveau et al., 1990). This can be accomplished in this "close to client" model by providing a skilled birth attendant—a midwife, doctor, or nurse—who can manage normal deliveries, recognize complications early, and promptly refer patients to the level of care needed. For complicated deliveries, referral to a basic or comprehensive essential obstetric care facility is critical. Patients who need care for complicated deliveries require a caregiver with a higher level of skill and a facility with the necessary equipment, drugs, and other materials. An enabling environment for labor and delivery includes specialized equipment, reliable supplies of drugs and other materials, and efficient transportation from the home or health facility to the referral facility (Ross et al., 2001; Graham et al., 2001). To be sustainable over time, it also requires ongoing staff development and training, adequate financing, supportive policies, and strong leadership.

Models of Care for Labor and Delivery

The essence of primary care and referral for labor and delivery is the presence of a skilled attendant backed up by good-quality, readily accessible emergency care. The wide range in services and settings in countries for labor and delivery can be described in terms of four models of care, based on the type of caregiver and the setting in which delivery takes place (Table 5-1) (Koblinsky et al., 1999). Each model is presented below along with examples of country programs. The models do not include one for home birth with a nonprofessional attendant and without referral for complicated cases. While this is the reality for many poor, rural populations, it is inevitably associated with high maternal, fetal, and neonatal mortality and is, therefore, in urgent need of being upgraded.

TABLE 5-1 Models of Health Care During Labor and Delivery

Model of Health Care	Birth Attendant	Location of Delivery	Referral Capacity	Country examples, each with its with Maternal Mortality Ratio (per 100,000)
1	Nonprofessional: often a community member with little or no medical training	Home	Referral and transport needed for complicated cases Many barriers and may involve long distances	Rural China (1994): 115 Fortaleza, Brazil (1984): 120
2	Professional: often a midwife who can recognize complications and provide basic essential care	Home	Referral and transport needed for complicated cases Some barriers may involve long distances	Malaysia (1970s-1980s): 50 Netherlands (1983-1992): 7
3	Professional: often a physician, alternatively, a midwife	Health clinic or hospital with basic essential care	Referral and transport needed for complicated cases	Malaysia (1980s-1990s): 43 Sri Lanka (1996): 30
4	Professional: most often a physician	Hospital with comprehensive essential care	No referral needed	United Kingdom: 9 United States: 12 Mexico City (1988): 114

SOURCE: Adapted from Koblinsky et al., 1999.

Model 1: Home birth with nonprofessional attendant and referral for complicated cases

In countries with high rates of maternal and neonatal mortality, traditional birth attendants (TBAs) and relatives are the most common providers of care for mothers and infants during labor and delivery, especially in rural areas (Schaider et al., 1999; Itina, 1997; Eades et al., 1993). TBAs are typically older women who lack formal education, but are accorded social status in their communities due to their years of assisting women during childbirth (Eades et al., 1993; Itina, 1997; Abioye-Kuteyi EA et al., 2001). To begin to address the need in developing countries for skilled assistance during labor, delivery, and the postpartum period, several field projects have attempted to train TBAs in critical skills (Daga et al., 1997; Kwast, 1996; Miller et al., 1995; O'Rourke, 1995; Pratinidhi et al., 1986; Schaider et al., 1999; Smith et al., 2000). Some TBAs have learned to recognize complications and refer patients to medical facilities (Janowitz et al., 1985; Bailey et al., 2002); however, the training of TBAs has not been associated with reduced maternal and neonatal mortality rates (Jaffre and Prual, 1994; DeBrouwere et al., 1998; Graham, 2002; Smith et al., 2000).

China, in one of the rare successful large-scale scenarios for Model 1 care, achieved dramatic reductions in maternal and infant mortality in the 1960s to 1980s (see Box 5-2). Over this time, most births in rural China were attended by relatives or lay persons with some training (Goldstein, 1998; Hesketh and Zhu, 1997; Young, 1990). However, the Chinese experience stands as an exception to the generally high frequency of deaths during labor, delivery, and the first 24 hours postpartum that occur in Model 1 settings.

Model 2: Home birth with professional attendant and referral for complicated cases

Delivery at home and care of the newborn, usually by a midwife, is available in some developing countries, generally in rural areas (see Appendix C for a detailed definition of "skilled birth attendant"). In countries where skilled birth attendants manage at least half of all deliveries, such as Sri Lanka and South Africa, maternal and neonatal mortality rates are among the lowest in the developing world (see Figures 2-5 and 2-6).

Providing quality Model 2 care involves the training of competent birth attendants and provision of equipment. It also involves transportation and communication capacity for referrals. Provider and community attitudes that can be major barriers to the use of skilled birth attendants and other health care services need to be overcome (Mathur et al., 1979; The Prevention of Maternal Mortality Network, 1992). Whereas TBAs work in vil-

BOX 5-2 Model 1 Care in China

In 1949, the government of the newly founded People's Republic of China launched a massive campaign to provide basic health care to all citizens, and particularly to its underserved rural population (Goldstein, 1998; Hesketh and Zhu, 1997; Young, 1990). As part of this effort, programs were developed to educate traditional birth attendants, midwives, and obstetric nurses in "modern birth methods," and millions of village health workers known as "barefoot doctors" were trained. All of these health care providers were connected through a three-tiered referral system. Rural birth attendants were linked to township health centers and to county maternal and child health institutes or county hospitals; these in turn were linked to specialized municipal, provincial, and national maternal and child health services and research facilities.

Over the next 30 years, the campaign was able to overturn centuries of tradition regarding birthing practices and sharply reduced both maternal and neonatal mortality rates. Maternal mortality fell from approximately 1,500 per 100,000 live births in 1950 to 61 per 100,000 in 1995. A strong family planning program, introduced in the early 1970s (abortion had been legal since 1957), appears to account for nearly two-thirds of the decline in maternal mortality (Koblinsky et al.,1999). Social campaigns such as those for late marriage and women's literacy were also associated with mortality reductions for both women and children.

Since about 1980, however, maternal and neonatal mortality rates in China have shown little improvement, and wide disparities continue in both the availability of care and in mortality rates between rural and urban areas. In the mid-1980s, for example, the maternal mortality rate in Shanghai was 18 per 100,000 births, compared with 108 per 100,000 in the central province of Ningxia (Young, 1990). Moreover, the proportions of beds and of physicians remain heavily weighted toward urban areas. This rural/urban disparity can be traced to the 1978 economic reforms, which caused a virtual collapse of the cooperative insurance scheme inaugurated in the villages at the start of the revolution (Young, 1990). As a result, the demand for and availability of primary health care has declined in rural areas.

Some of China's strategies to improve birth outcomes may be applicable in other countries. The national effort to reduce maternal and infant mortality had strong political guidance. The priorities of health care reform were determined by the need and potential impact, and strategies to achieve reform goals were adaptable to local needs. Access to skilled delivery and obstetric care at the time of complications was guaranteed through a referral network that reached into communities. These efforts were complemented by social campaigns that emphasized prevention and good health care practices.

lages where they are known and respected, professional care providers begin their work as strangers to a village. Partnerships with TBAs can facilitate the transition of a new midwife, who will need to show understanding and respect for local birth traditions that are not harmful (Koblinsky et al., 1999; Sibley et al., 2002).

In some developing countries, birthing homes—places in the community where women can go to give birth with a skilled attendant—have been accepted as an alternative to deliveries at home or in a referral facility. Often built by community members, these homes are likely to attract skilled birth attendants by providing a central location for deliveries (Koblinsky et al., 2000). The homes can also foster partnerships between skilled birth attendants and TBAs or community health workers. In Honduras, the use of birthing homes has increased as they are relatively inexpensive and reduce overcrowding in referral hospitals (Danel and Rivera, 2002).

Model 3: Hospital/clinic birth with basic essential care

Deliveries attended by skilled, experienced birth attendants can be further supported when they take place in hospitals or clinics that provide basic essential obstetric and neonatal care. Model 3 services for the mother should include at least parenteral medications (antibiotics, oxytocic drugs, and anticonvulsants) and manual removal of the placenta and other retained products in basic essential obstetric care services. However, in comprehensive essential obstetric care services, provision for surgical procedures, anesthesia, and blood transfusion in addition to the above should be included (World Health Organization, 1996c). Model 3 services for the newborn include cardiopulmonary resuscitation (bag and mask ventilation, endotracheal intubation, cardiac massage), thermal management (using radiant warmers and incubations), supplemental oxygen, parenteral medications (e.g. antibiotics), nutrition management (use of feeding tubes), and fluid managment (Hesketh et al., 1994). Model 3 facilities are typically staffed by physicians, nurses, and midwives. Determining the availability of Model 3 care is difficult because documentation of coverage by health care facilities does not distinguish between basic (Model 3) and comprehensive (Model 4) care.

Increased access to hospital delivery and literate female populations has been associated with reduced maternal mortality in Sri Lanka (Gunaserera and Wijesinghe, 1996) and reduced neonatal mortality in Shunyi County, China (Yan et al., 1989). Similarly, there was a reduction in maternal and neonatal mortality in Malaysia (see Box 5-3). Where there is a demand for hospital delivery, maternity waiting homes—residences near hospitals where women who live far from the facility can stay near the time of delivery—can increase access for rural women (Koblinsky et al., 1999). Unlike birthing homes, maternal waiting homes are not used for deliveries. However, use of these facilities has been limited by their expense and the need for childcare when the mother is away from home (Fawcus et al., 1996). Their value in reducing maternal mortality has not been clearly established (Chandramohan et al., 1994).

BOX 5-3 Labor and Delivery Care in Malaysia: From Model 1 to Model 3

When Malaysia became independent in 1957, the maternal mortality rate was 320 per 100,000 and the reported neonatal mortality rate was 75.5 per 1,000 births (Pathmanathan and Dhairiam, 1990). Free health services were made available to rural populations. Professional midwives and nurses were trained and assigned to villages, where they were supported by an expanding network of local health units (one for every 50,000 people) linked to regional clinics and, by referral, to district hospitals (Koblinsky et al., 1999).

Between the mid-1970s and mid-1980s, most births still took place at home, but were attended by a professional midwife (Koblinsky et al., 1999). During this period, the maternal mortality rate dropped to 50 per 100,000. Midwives in Malaysia are salaried civil servants who provide maternal health care including home visits in the prenatal and postpartum periods, normal deliveries, risk screening, referrals with transport to a maternity home or hospital, family planning, and child health services (Koblinsky et al., 1999). They can administer certain drugs, including oxytocin, but rely on a nurse to provide antibiotics, sutures, or intravenous fluids. Midwives use checklists to recognize the signs and symptoms of complications and make timely referrals. In the mid-1990s, the formal training course of study for midwives was expanded to a two-and-a-half year program for high school graduates with hands-on learning in hospital and community settings.

As the presence of and demand for professional midwives increased, the role of TBAs in Malaysia gradually moved from birth assistant to provider of family support (Koblinsky et al., 1999). This transition was encouraged by government initiatives to limit their role in labor and delivery, while training, registering, and supervising their provision of traditional massage and postpartum care. By 1996, 95 percent of all home births were assisted by midwives and less than 1 percent by TBAs (National Population and Family Development Board/Ministry of Health, 1998).

Although Malaysia had achieved relatively low levels of maternal and neonatal mortality through home deliveries with a skilled midwife, the coverage of births was uneven. A survey at the end of the 1970s revealed many areas of underserved mothers, inadequate communication between rural maternal and child health services and obstetric and pediatric services, and too many inadequately attended high-risk pregnancies (Pathmanathan and Dhairiam, 1990). Concerned by these findings, the Malaysian government encouraged women to give birth in facilities providing basic essential obstetric care (includes all essential obstetric functions except surgery, anesthesia, and blood transfusion). The transition from home birthing to hospital birthing moved relatively rapidly, and by 1998, more than 90 percent of women with high-risk pregnancies, and 80 percent assigned moderate risk, delivered in a hospital. Deliveries by skilled personnel had risen from 51 percent in 1980 to 95 percent in 1996. By 1996, the maternal mortality rate had declined to 43, the perinatal mortality rate was 11, and neonatal mortality rate was 7 (National Population and Family Development Board/Ministry of Health, 1998).

The goal of moving from home birthing to facility-based birthing was achieved in Malaysia by convincing women and their families that it is safer to deliver with skilled providers in a facility with backup support (Koblinsky et al., 1999). To further promote this goal, services and transport were provided at no cost for families, and significant improvements in the quality of hospital care were accomplished through quality assurance efforts.

The transition from Model 2 to Model 3 care, which includes all obstetric services except surgery, anesthesia, and blood transfusion, is generally smoother than the transition from Model 1 to Model 2. In Malaysia, the transition from Model 1 to Model 3 began by evaluating the medical risks for all pregnant women rather than only those at high risk for complications. As a result, health care providers and families became increasingly concerned with safety measures that improve childbirth outcomes. Even women at low risk began to choose a hospital birth (see Box 5-3). Several countries now provide health education for pregnant women that emphasizes safety concerns during labor, delivery, and the postpartum period as well as during antenatal care (Yan et al., 1989).

Model 4: Hospital/clinic birth with comprehensive essential care

Model 4 care incorporates all of the services provided in Model 3, and also anesthesia, surgery (particularly cesarean section and repair of maternal birth injuries, such as vesico-vaginal tears), blood transfusion, and the ability to care for the sick or at-risk neonate. This most sophisticated model of care is available in some urban areas in developing countries and is the usual level of care in developed countries, where maternal and neonatal mortality rates are low. Use of Model 4 facilities is cost-effective for deliveries with complications requiring that level of care, but not for normal deliveries. Delivery in Model 4 facilities in developing countries does not necessarily guarantee low mortality (Koblinsky et al., 1999). The quality of care can be impaired by overuse of the facility, poor clinical judgment, use of inappropriate procedures, inadequate supplies, and poor attitudes on the part of providers toward patients (Bobadilla et al., 1996; Mbaruku and Bergstrom, 1995; Okonofua et al., 1992; Figueroa et al., 1989).

Which model is appropriate?

Determining the best model of labor and delivery care for a particular country or region, and the most effective and efficient steps to reach it, require future research (Graham et al., 2001). Each model, even Model 4, can be recommended only after establishing its clinical- and cost-effectiveness, feasibility, and family/patient acceptance in specific settings. Furthermore, countries must have the resources to successfully implement the changes needed. Variations on Models 2 and 3 care, as described above, are likely to be the most cost-effective facilities for uncomplicated deliveries in low resource settings. Basic and comprehensive EOC are clearly needed for complicated deliveries.

Recognition of pregnancy complications and their management is central to reducing maternal, fetal, and neonatal deaths, yet success in doing so when most women deliver at home not attended by a professional attendant remains a challenge. Scarce health resources should therefore be managed with the primary goal of achieving skilled delivery at all births (i.e., Model 2 or 3). This can be accomplished by creating partnerships between midwives, with their medical skills, (and village health workers [VHWs] or) TBAs, with their knowledge of and access to individual patients, the community, and local birthing traditions. Where resources permit, identification of a specific target, such as the underserved, for improved quality of care and efficiency of referral can facilitate the transition from Model 2 to Model 3 care. Key needs can be identified and met using population-based surveys (Pathmanathan and Dhairiam, 1990), standard risk analysis (Yan et al., 1989), or death audits (Wilkinson, 1997).

In well-functioning health care systems, normal births are supported but not overmedicalized, limiting costs and reducing the risk of iatrogenic complications, while complicated births receive prompt, appropriate treatment (Jahn and De Brouwere, 2001). In Jamaica and Sri Lanka, developing countries in which physicians attend about 15 percent of deliveries—the approximate percentage of all births that involve potentially life-threatening complications (World Health Organization, 1994)—maternal mortality has been considerably reduced (Graham et al., 2001). In Chile, midwives and physicians typically work together to provide a high level of institution-based maternal and neonatal care (Segovia, 1998). Midwives attend 70 percent of all deliveries in that country; physicians handle the remainder. These take place in Model 3 or 4 facilities which also provide the vast majority of antenatal care. However, any country can develop a mix of models to suit local needs such as urban or rural. In places where women equate safe delivery with delivery in a facility, they may prefer a hospital that provides comprehensive care or a birthing facility affiliated with a referral hospital. Because of the higher cost of Model 4 deliveries, policy makers can decide where to provide quality Model 3 care for normal deliveries with links to referral services for pregnancies with complications that require Model 4 care (Koblinsky et al., 1999).

Self-referral for delivery care far outstrips emergency referrals in many hospitals in developing countries (Murray et al., 2001; Jahn and De Brouwere, 2001). Frequent self-referral for delivery without specific medical reason indicates that many women bypass community-level services, while the small percentage of emergency referrals indicates that many complicated births do not receive adequate care (Jahn and De Brouwere, 2001). Where resources are limited, maximum cost-effectiveness will be obtained when the majority of deliveries performed at higher-level facilities are complicated births. This requires strengthening the referral system, as described in the next section.

Improving Access to Referral Care for Labor and Delivery

Reducing maternal, fetal, and neonatal mortality requires broad access to the essential obstetric and neonatal services described in Chapters 2 and 3. The availability and quality of these services is inadequate in most countries. Also needed are referral structures to address major barriers to provision of referral care. The "four delays" in responding to maternal or neonatal complications were introduced in Chapter 2 (Lawn et al., 2001). These delays—in recognizing the problem; deciding to seek care; getting to a facility that can provide it; and receiving appropriate treatment—confront every medical emergency. Several determinants of the use of referral care may need to be addressed to increase referrals for complicated births, such as the ability of pregnant women and their families to recognize symptoms of complications (The Prevention of Maternal Mortality Network, 1992; Bloom et al., 1999); distance to the referral facility (The Prevention of Maternal Mortality Network, 1992) (see Figure 5-1), the availability and cost of transportation (Eades et al., 1993; Fraser and Meli, 1990; Fawcus et al., 1996; The Prevention of Maternal Mortality Network, 1992) and the cost of care (Bloom et al., 1999; Asowa-Omorodion, 1997).

Many women do not recognize the benefits of receiving higher-level care, are wary of the attitude of providers toward patients, and do not understand the medical causes of complications or the importance of specific treatments (Mathur et al., 1979; The Prevention of Maternal Mortality Network, 1992; Thaddeus and Maine, 1994; National Research Council, 1997). The signs of complications during pregnancy and labor and after delivery are not always recognized by women and their families as causes for concern. Recognizing complications and promptly seeking skilled care can be taught during antenatal care. Geographical and financial accessibility also present major barriers to referral care (Thaddeus and Maine, 1994; Bouillin et al., 1994; Haddad and Fournier, 1995). When deciding whether to seek referral care in an emergency, patients and their families tend to weigh the potential expense and effort involved against the perceived benefit of hospital care (Thaddeus and Maine, 1994; Oosterbaan and da Costa, 1995; Asowa-Omorodion, 1997). These decisions are often influenced by fears of discrimination, loss of privacy, and the lack of emotional and social support in a hospital setting.

Where access to referral care is less a problem than the quality of care available, improving provider skills and the availability of drugs and other medical supplies may increase the number of emergency referrals (Jahn and De Brouwere, 2001). However, in the more common situation, where skilled attendants are likely to remain scarce for the foreseeable future, improving referral mechanisms, communication capability, and transportation, so that those who need emergency care receive it, is an alternative means to reduc-

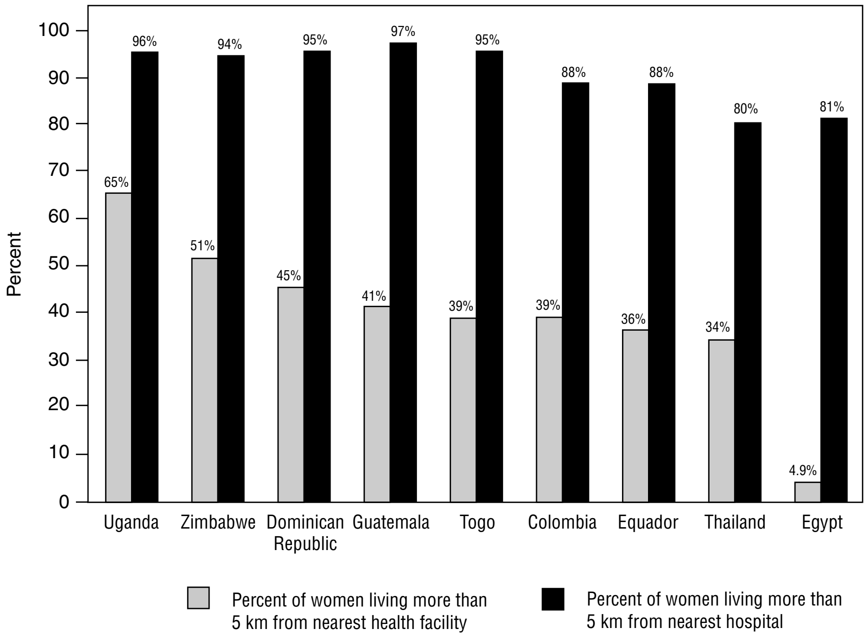

FIGURE 5-1 Percentage of rural women living more than 5 kilometers from a health facility or hospital in selected developing countries, 1990-1996.
SOURCE: World Health Organization, 1998.

ing maternal, fetal, and neonatal mortality (Graham et al., 2001). Community efforts toward this goal can be especially effective. These include coordination of communication with referral facilities, provision of transport, provision of emergency loans to cover transportation and treatment costs, and advocacy by community health staff to ensure that women and their families understand the potentially life-saving benefits of referral for complications (Jahn and De Brouwere, 2001).

In rural areas, providing transport to referral facilities for patients has been found cost-effective (Shehu et al., 1997). Emergency transportation has been organized in Nigeria through local car owners (Olaniran et al., 1997), in Mali with radio calls and ambulances (Maiga et al., 1999), and in Kenya with a hospital emergency vehicle and radio contact with several health centers (Macintyre and Hotchkiss, 1999). Transportation is needed for skilled birth attendants to deliver care to isolated populations. Loans for obstetric emergencies have been financed and managed by communities in Nigeria (Essien et al., 1997; Olaniran et al., 1997; Chiwuzie et al., 1997), and Mali (De Brouwere 1997; Maiga et al., 1999), but whether these loans improve birth outcomes has yet to be established. For example, communities in Ethiopia (Poovan et al., 1990) and Zimbabwe (Chandramohan et al., 1994) have developed maternity waiting homes with easy access to the local hospital for women living in remote areas. Communities in Honduras (Danel and Rivera, 2002) and Guatemala (Bocaletti et al., 2000) have developed birthing centers where women can give birth with a skilled provider. These centers have been able to attract skilled birth attendants to communities and introduce them to local culture and birthing practices.

Guidelines for referral can reflect local epidemiological conditions, health service capacity, and community preferences (Jahn and De Brouwere, 2001). Initially it may be advantageous to focus on emergency referral for life-threatening maternal complications (Jahn and De Brouwere, 2001) such as prolonged or obstructed labor, hypertensive disease of pregnancy, antepartum hemorrhage, and neonatal sepsis. Once established, these procedures provide the foundation for effective referral for other emergency care needs and can lead, through the improved overall functioning of health care systems, to further improvement in birth outcomes (Ronsmans et al., 1997; Campbell, 2001; Jahn and De Brouwere, 2001).

BUILDING CAPACITY FOR REPRODUCTIVE HEALTH CARE

Access to quality reproductive health services is key to improving birth outcomes (Pittrof et al., 2002). In developing countries, this involves building health care capacity in the form of facilities, equipment, supplies, and—most important—personnel. An acute shortage of physicians, midwives, and nurses throughout much of the developing world is exacerbated by their unequal distribution. The vast majority of these professionals and nearly all obstetricians, pediatricians, and other specialists practice in urban areas (Kowalewski and Jahn, 2001). Midwives are more likely to work in rural settings, but their numbers are too small to fill the gap in care; according to a 1990 estimate, developing countries average about one midwife per 30,000-300,000 people (Kwast, 1991). Thus this section first describes several approaches to increasing the numbers of skilled assistants in public health services, the quality of care they provide, and their association with improved birth outcomes. These efforts can be further advanced through collaboration with private care providers, NGOs and other not-for-profit organizations, and professional organizations of health care providers.

An obvious barrier to achieving greater coverage for the most effective health interventions, including those that would reduce maternal and neonatal mortality, is the low level of total health expenditure in developing countries. With the average annual per capita health care expenditure in low-income countries at US$26 in 2002—and only half that amount in the

48 poorest countries—additional funds are clearly necessary to improve birth outcomes and health care worldwide (Jha et al., 2002). The third part of this section, on the financing of reproductive health services in developing countries, identifies potential sources of funding to begin to address this shortfall. The final part of this section discusses health system decentralization and sector-wide approaches to reproductive health. These reforms have been adopted by several countries in an effort to improve access to good quality health care.

Staff Development and Training

Several factors contribute to the lack of general physicians and specialists in most developing countries, including limited resources for health care, the inadequate capacity of medical schools, and the loss of physicians to opportunities abroad. The emigration of physicians can be stemmed by creating a more attractive career path with faster advancements, publicly acknowledging medical and other accomplishments, and providing more competitive salaries. Where the distribution of physicians is the major problem, strong national leadership is needed to establish rural coverage as a priority and provide incentives to physicians to work in rural areas before settling in cities. For example, physicians who agree to serve in rural areas might be forgiven the cost of their training; however, such agreements must be rigorously enforced to be effective (Kowalewski and Jahn, 2001). The need for specialized care in some underserved areas has been filled by general practitioners who have acquired the skills needed for operations such as cesarean delivery.

In order to increase the effectiveness of physicians, nurses and other health assistants can assume certain additional tasks under the supervision of a physician. In countries where it is permitted, nonphysician medical assistants have received further training to enable them to perform emergency surgery and administer anesthesia. In Burkina Faso, Malawi, Mozambique, Tanzania, and Zaire, nonphysician staff are trained to perform surgery and obstetric care in district hospitals or health centers where physicians are not available (Kowalewski and Jahn, 2001; Rosenfield, 1992; Adeloye, 1993; da Luz Vaz and Bergström, 1992; Pereira et al., 1996; Duale, 1992). In addition to increasing the coverage for emergency services, competent nonphysicians incur lower salary and training costs than do doctors, and some evidence suggests that they communicate more effectively with patients (World Bank, 1993). Follow-up costs must also be considered, however, as nonphysicians who provide specialized services may require a high level of supervision (Hopkins et al., 1996; Loutfi et al., 1995).

Skilled birth attendants—whether midwives, physicians, or nurses—

require ongoing training. Programs of instruction for skilled caregivers can be built on evidence-based, nationally approved standards, such as the skill base outlined in Appendix C, Essential Skills Required for Birth Attendants. While midwives need instruction in clean and safe delivery, field reports from Guatemala and Bolivia indicate that many physicians and nurses have not been sufficiently trained in partograph use, breech delivery, newborn resuscitation, and the control of postpartum hemorrhage (Koblinsky et al., 2000). A sound knowledge of procedures for a clean and safe delivery serves as a foundation for training in the treatment of complications. Expertise is gained through hands-on experience and maintained through caseload requirements, on-going training, and evaluation (McDermott et al., 2001; see Appendix C). The performance of skilled birth attendants should be monitored for the purpose of improving health care systems, as well as to ensure individual accountability (Gunathunga and Fernando, 2000).

Regular emergency drills or simulations can help health workers maintain a state of readiness to deal with emergencies. Courses in life-saving skills for midwives have been successful in addressing these needs, and could also be offered to nurses, clinical assistants, and general physicians. Several studies indicate that nonspecialists can be taught to perform life-saving obstetric techniques effectively (da Luz Vaz and Bergstrom, 1992).

Providing universal care during childbirth by training TBAs has not been shown to be effective. After receiving training in clean delivery practices and the recognition of complications, TBAs in the Gambia were initially found to have had a positive effect on maternal health, yet three years later, the maternal mortality ratio remained near 700 per 100,000 births (Greenwood et al., 1990). Training of TBAs—once thought to be an affordable way to reduce mortality during childbirth—is no longer considered an effective investment of limited funding resources.

Patterns of care for women during pregnancy and childbirth in most developing countries, particularly in rural communities, are strongly influenced by cultural and traditional factors. In settings where TBAs are responsible for childbirth, few women receive antenatal care (Nylander and Adekunle, 1990). When obstetric problems arise, sociocultural factors (such as women's social status and the use of traditional healing practices) frequently pose barriers to their seeking medical treatment (The Prevention of Maternal Mortality Network, 1992; Okolocha et al., 1998).

The Role of the Private Sector

Another strategy for increasing access to quality reproductive health care is the creation of alliances between governmental public health agencies and individuals or organizations that provide health services (World

Bank, 1993; United Nations Fund for Population Activities, 1999). Key players in the private sector include physicians and other providers of care for profit, as well as not-for-profit groups such as NGOs, universities and research institutions, charities and welfare organizations, and associations of health care professionals.

Private providers deliver a significant and growing share of health services (Hanson and Berman, 1998). According to a recent survey of 40 developing countries, more than half of all physicians were privately employed, and nearly one-third of all beds were in private institutions or reserved for private patients (Hanson and Berman, 1998). Where women have a choice of public or private health care providers, many seek private care due to its greater accessibility and convenience. Private clinics and practices may be open longer hours, have shorter waiting times, and (in some urban areas) be more accessible than public facilities (Ferrinho et al., 2001; Wyss et al., 1996). In many developing countries, labor and delivery services for significant numbers of births are provided by midwives in private practice (Gani, 1997; Schwartz et al., 1993).

In the rural areas of many African and other nations, NGOs and other private not-for-profit agencies are the main, if not the only, providers of health care. These providers vary widely in their missions and services, but often support government policies and programs (Ferrinho et al., 2001). In some areas, NGOs play a key role in administering family planning services and have significantly increased contraceptive uptake (Phillips et al., 1999). Organizations of health care professionals also contribute to the improvement of reproductive health care in developing countries. For example, the American College of Nurse Midwives has supported programs in South Kalimantan, Indonesia, to train midwives in safe delivery practices and the management of complications (McDermott et al., 2001). Groups such as the International Clinical Epidemiology Network (INCLEN) are well positioned to collaborate on the establishment or expansion of surveillance and evaluation of birth outcomes.

Government alliances with private health care providers—whether for-profit or not-for-profit—best serve the public interest when private providers offer a full range of priority services (e.g. antenatal care, skilled attendance at delivery, and early neonatal and maternal postpartum care), ensure access for all who need care, and are held accountable for the quality of the care they provide (Ferrinho et al., 2001). Few such alliances have been created (DFID Health Systems Resource Center, 2000), and only limited evidence suggests that that they improve health services in general and maternal and neonatal services in particular. In rural areas, there may not be enough providers to create a competitive market, and even if there are, evidence indicates that competition alone does not guarantee efficient services. In such settings, public-private alliances may need to be established through long-term contracts with private health care providers (Palmer 2000).

Financing

Expenditures for reproductive health care in developing countries were projected to reach US$17 billion in 2000 and climb to nearly US$22 billion by 2015 (Borghi, 2001). The mechanisms for financing health care are unclear in many cases, particularly at the national level. Information on health care expenditures in developing countries is often incomplete, of questionable quality, or not internationally comparable. Further, it is often difficult to identify reproductive health expenditures because funds are allocated to broad health care categories such as maternal and child health and family planning (Borghi, 2001).

Governments raise funds to finance health care in a variety of ways. In Sri Lanka, public health care is funded largely through general taxation, with the private sector contributing almost half of the cost of primary care services (Hsaio, 2000). In Egypt a compulsory wage-based social insurance scheme is supplemented with additional government revenues (Borghi, 2001). The Bolivian government disburses funds to municipalities in a decentralized scheme; the municipalities, in turn, control reimbursement of health care providers and capital investment (Borghi, 2001).

Donors that fund reproductive health care in developing countries include international organizations, NGOs, governmental aid agencies, and private foundations. International organizations that fund reproductive health programs include WHO (the lead agency for technical health support), the United Nations Development Fund (through its support for poverty reduction programs), the United Nations Children's Fund, and the United Nations Population Fund. The World Bank, the largest provider of international financial assistance for health care, has worked with governments on programs, financing, and strategies to support reproductive health. Bilateral agencies such as the Swedish International Development Authority and the U.S. Agency for International Development also finance reproductive health care. Projects with direct and indirect effects on maternal health—including family planning, primary health care, nutrition, training, and disease control—represent about 12 percent of bilateral financing. Several private foundations support reproductive health programs; in recent years, the Bill and Melinda Gates Foundation has provided significant funding for maternal and child health. In many developing countries, private voluntary organizations (PVOs) such as CARE and Save the Children support health care programs as part of broader development agendas. These programs are often directed toward low-income, rural populations.

Community-level programs in several developing countries provide funding for reproductive health services through up-front charges for specific services (i.e., prepayment for delivery services in regular installments throughout antenatal care) or loans for referral services (Borghi, 2001; Fox-Rushby and Ford, 1996). Where they are affordable and result in improved care, user fees tend not to reduce the use of health services; however, fees for labor and delivery services do appear to discourage hospital deliveries (Stanton and Clemens, 1989; Hotchkiss, 1998). Where user fees are designed primarily to recover costs, the practice is likely to exacerbate inequities in care and inhibit the use of essential, and in some cases life-saving, services (Russell and Gilson, 1997). Some African communities offer loans for hospital transportation, treatment, and drugs and supplies required for emergency care during pregnancy. Access to these loans, which must be repaid as soon as possible, has increased referrals (Fofana et al., 1997). The effect on birth outcomes has yet to be established.

Health Care Reforms

Sustaining affordable improvements in birth outcomes depends upon improving the functioning of health systems as a whole (Goodburn and Campbell, 2001). Since the 1980s, many developing countries have undertaken health reforms in an effort to improve the accessibility, equity, quality, and efficiency of services. Key reform strategies that have been applied to reproductive health services in developing countries include the decentralization of health care management and sector-wide approaches to coordinate national and donor resources (McDonagh and Goodburn, 2001).

Through decentralization, resources and responsibilities are progressively transferred from the central government to local and provincial governments in order to give local managers greater responsibility and flexibility in meeting health needs. This process is more successful when the transfer of responsibility occurs in parallel with the development of local capacities (Langer et al., 2000; Hardee and Smith, 2000). A major objective of decentralized health systems is to encourage community participation in and responsibility for health services (Ramiro et al., 2001). Decentralization can lead to improvements in maternal and neonatal services. In Senegal, Zambia, and elsewhere, decentralization has improved delivery of general reproductive health services, but not those for more sensitive areas such as abortion, adolescent care, and HIV/AIDS prevention (Wilson, 2000; Population Council, 1998).

Sector-wide approaches focus on all components of health services, including maternal and neonatal health. They allow national health departments to coordinate national and donor resources and include donors as partners in developing a unified, equitable system of quality health services. Traditionally, donors have invested in separate, uncoordinated health activities in different geographical regions, often attracting key staff from government health services and producing services of uneven quality and coverage (Foster et al., 2000a, 2000b; Johanson, 2000; World Health Organization, 1999). The essential services generally include immunization, pre- and post-natal care, oral rehydration, treatment for malaria and lower respiratory tract infections, and family planning. They may include clean and safe delivery, but comprehensive essential obstetric care, which requires a surgeon or other skilled assistant, is rarely covered. Donor agencies can also encourage governments to implement reforms on a realistic timetable, to monitor health and service outcomes, and to continue to identify and incorporate improvements in quality of and access to health services (Cassels and Janovsky, 1998; Johanson, 2000).

Maternal health has been ranked as a high priority for nationally coordinated services (World Bank, 1999; Jha et al., 2001). However, until this strategy is widely implemented, the effects of sector-wide approaches on the quality of maternal and neonatal health services and outcomes are unknown (Johanson, 2000; McDonagh and Goodburn, 2001). Some key activities (such as the training of midwives with the goal of increasing skilled attendance at childbirth) might not be covered by broad funding approaches, and will therefore require focused technical and financial support (Goodburn and Campbell, 2001).

MANAGING HEALTH CARE SYSTEMS

To improve birth outcomes in developing countries, health care leaders must identify the interventions, programs, and strategies likely to have the greatest impact on maternal, fetal, and neonatal mortality. They must then allocate the resources needed to achieve a successful result. An effective process for making such decisions involves the following steps: defining and prioritizing health problems, assessing the performance of current health services, selecting the best intervention, implementing it, and assessing its impact (Lawn et al., 2001). Health care leaders and providers and the community they serve must all participate in this process if it is to be successful.

The definition of key health problems is itself a process, which begins with the collection and analysis of data on health outcomes (in this case, adverse birth outcomes such as maternal, neonatal, or fetal mortality) in the community and comparison with standard populations. Key health problems revealed in this way are further defined in terms of the gaps in services they represent. Both criteria—the magnitude of the problem and the local availability of solutions—are weighed in the setting of priorities among health problems.

To assess the performance of current health services in addressing a priority problem (as defined by an adverse birth outcome), it must be determined whether the most effective services are provided, whether services reach the vast majority of the population, and whether the services are of good quality. Community input, in addition to that of health leaders and health care providers, is critical to obtaining an accurate assessment, and one that reveals opportunities for interventions to reduce adverse birth outcomes.

Selecting the best intervention to address a problem requires a strong evidence base that confirms the importance of the chosen problem in the local population. The promise of each potential intervention is assessed by examining evidence for its clinical-effectiveness, cost-effectiveness, feasibility and sustainability, and acceptability to the local community. In addition to the new interventions being considered, current interventions and the effect of no intervention should be assessed. Involving local leaders early in the assessment process helps ensure that a needed, wanted, and successful intervention is implemented.

The successful implementation of a chosen intervention requires a clear vision of the desired outcome and recognizes the need for community involvement and investment in the project. Plans for implementation must answer many specific questions. How will the intervention be introduced? Who will provide the services, and at what cost? How will the community be involved in making the intervention successful? These and other needs should be anticipated in the planning process. After implementation, health care providers must consider two questions. First, is the chosen intervention the best way to address the problem? Second, is the intervention being effectively carried out? That is, are the services of good quality and are they reaching most of the population? The answers to these questions can be determined through the surveillance of birth outcomes and evaluation of their change as a result of the intervention.

Experience in industrialized countries suggests that interventions must be tailored to local conditions and that continual monitoring and response is key to maximizing cost-effectiveness (Sorensen et al., 1998). Such fine-tuning of interventions and health care programs is achieved by repeating the steps in the decision-making process to solve increasingly well-defined problems. Surveillance of maternal, fetal, and neonatal mortality (and in some cases, proxy indicators for these outcomes) provides the foundation for identifying, prioritizing, and evaluating interventions to improve birth outcomes. Evaluation of services provides the basis for determining cost-effectiveness and establishes benchmarks for continuing improvement.

Surveillance

National programs of birth and death registration provide the information needed to develop and evaluate interventions that reduce maternal, fetal, and neonatal mortality. In many countries the magnitude of maternal—also neonatal and fetal—mortality is only beginning to be recognized after many years without accurate birth and death records. For much of the developing world, this lack of information on birth outcomes has obscured the depth of the need for skilled assistance during labor and delivery (Van Lerberghe and De Brouwere, 2001). Concern about the cost of obtaining data before, during, and after implementation of a new intervention is inevitable for communities with scarce resources. This cost is seen by many as competing with the need to deliver key health care services, yet this is an important investment in selecting and implementing the right interventions and tuning them to be effective. The goal is to collect data that are accurate enough to make the required decisions, but not more accurate than is required. For the implementation to be effective, community and health leaders must reach a consensus on the investment of resources. Such a consensus is facilitated by reliable data on the needs for specific interventions.

Surveillance of births

Birth registration provides a tangible acknowledgement of a child's existence and establishes his or her identity. The United Nations Convention on the Rights of the Child, ratified by virtually every country,[1] requires that "each child shall be registered immediately after birth," yet only about one-quarter of the world's births (and if China were excluded, less than 7 percent) are recorded by civil registration systems (AbouZhar and Wardlaw, 2001). Registration is nearly universal in much of the Americas, Europe, and East Asia; in many such countries, a child cannot receive medical services or enroll in school without being registered. Some countries have taken steps to increase registration by improving training, infrastructure, and technology. For example, in Argentina, Ecuador, Iran, Mozambique, Thailand, and Zimbabwe traveling registrars issue birth certificates. However, in several developing countries—particularly those with the highest neonatal and fetal mortality rates—few births are registered. Reasons for poor birth registration vary, but typically include the following:

- shortages of trained personnel and inadequate technology
- the expectation and acceptance of high mortality during pregnancy and the neonatal period
- logistical difficulties for parents, including travel to registry offices
- parental fear of the registration process

[1]Except the United States of America, although registration there is required.

- financial charges associated with registration
- mismanagement of the registration system.

Surveillance of deaths

The reporting of maternal, fetal, and neonatal deaths is often neglected, even in countries where vital statistics are routinely recorded. For example, even the most widely accepted maternal mortality statistics—the revised WHO/UNICEF/UNFPA estimates based on 1995 levels (World Health Organization, United Nations Children's Fund, United Nations Fund for Population Activities, 2001) which estimate 515,000 deaths per year worldwide—must estimate the total number of maternal deaths, because country data do not include mortality associated with indirect causes or related to abortions or ectopic pregnancies occurring earlier in gestation. Misclassification of maternal death can also occur when certifying offices fail to note that a woman has recently been pregnant (Walker et al., 1990). Accurate measurement of maternal and neonatal mortality is particularly difficult in many settings where the deaths occur in the home and go unrecorded.

Considerable underreporting of fetal and early neonatal deaths is a problem in most developing countries. International comparisons are further complicated by variations among countries in their definitions of live birth versus stillbirth and late fetal versus early neonatal mortality. In some regions, the births and deaths of children who die before a critical "age of acceptance"—which may be as long as 40 days after birth—are unlikely to be reported (Lawn et al., 2001). The births and deaths of low-birth-weight infants are also less likely to be registered than those of larger infants (World Health Organization, 1996b). As a result of all of these factors, estimates of pregnancy- and birth-related mortality in developing countries are almost certainly low.

Surveillance of pregnancy and birth outcomes

Where vital statistics are inaccurate or nonexistent, pregnancy-related data can be collected on a periodic basis in selected geographic areas to produce a "snapshot" of conditions and outcomes for those locations. Sentinel districts, selected as representative of larger areas, can be designated for ongoing surveillance when a universal system cannot be sustained. Surveillance can also monitor intermediate process data such as the use of specific maternal and neonatal services (see below). These measures do not adequately replace a universal system to plan and support health care services over the longer term.

Some regions have developed effective pregnancy-related surveillance systems which, when linked to effective maternal and child health programs, have resulted in improvements in various birth outcomes. In Shunyi County, China, surveillance of late fetal and early neonatal deaths revealed five major causes of mortality: neonatal asphyxia, pregnancy-induced hypertension or eclampsia, breech presentation, neural tube defects, and low birth weight. To address these problems, public education and provider training programs were developed, as well as systems of patient screening and referral. Two years after these interventions were implemented, fetal and neonatal deaths due to eclampsia are reported to have been essentially eliminated, deaths due to asphyxia to have declined by 84 percent, breech home deliveries to have declined by more than 60 percent, and use of prenatal care to have increased significantly (Yan et al., 1989). The identification of neural tube defects as a major cause of mortality in this region prompted a study of periconceptional folic acid supplementation. It determined that supplementation significantly reduced the incidence of neural tube defects, prompting China to initiate a nationwide folic acid supplementation program (Berry et al., 1999).

Since 1988, a prospective surveillance system has monitored birth outcomes in the Gadchiroli district of Maharashtra State, India, a remote, underdeveloped area with a population of nearly 80,000 (Bang et al., 1994; 1999). Village-level workers collect data on pregnancies, live births, late fetal deaths, neonatal, and infant deaths from families and traditional birth attendants and assign a cause of death based on verbal autopsy. A retrospective population-based survey, performed every 6 months, indicates that 98 percent of births and childhood deaths are recorded. The data are compiled, organized into a usable format, and presented periodically to health care program managers, who use the information to identify and implement community-based interventions to reduce neonatal and childhood mortality (Bang et al., 1990, 1994, 1999).

These methods could be adapted to measure maternal, fetal, and neonatal mortality rates in other developing country settings. For example, pregnancies could be registered at 5 months' gestation, and the mother's age and place of residence recorded. A follow-up query would determine whether the mother survived childbirth, whether her infant was born alive or dead, and if born alive, whether the infant survived the neonatal period. If possible, the infant's approximate weight at birth should be recorded; if the infant died, his or her age at death should also be noted. Additional information could include the type of birth attendant, location of delivery, procedures used, and the cause of maternal, fetal, and neonatal deaths.

Under an optimal system of surveillance, every pregnancy would be identified prospectively and every outcome ascertained. To obtain meaningful results, surveillance must be conducted in a standardized manner across broad geographic areas (e.g. nations), although the actual collection of data is probably best accomplished and managed by local authorities. The potential benefits of such surveillance in developing countries must be weighed against the use of scarce resources for medical interventions.

Evaluation

Evaluating the impact of an intervention or health care program may involve measurements of key outcomes such as maternal, neonatal, or fetal mortality, or may be based on process indicators such as the proportion of births attended by a skilled caregiver or taking place in a health care facility. Comparisons based on mortality allow policy makers to track the impact of these services using relatively simple and affordable information systems (Graham, 2002). However, such measures depend on accurate determinations of maternal, fetal, and neonatal mortality, which are not available in most developing country settings. In these cases, process indicators can be used to estimate the large-scale impact of maternal and neonatal services (Ronsmans, 2001). Such process indicators must be shown to be strongly associated with key birth outcomes (Gelband et al., 2001), but causal relationships between process and mortality measures have yet to be established.

Cost of services

Ideally, the budgeting and planning of reproductive health services—and indeed, of health care in general—in a particular setting would reflect the most cost-effective means of meeting significant population needs. However, despite wide recognition of the need for quality, cost-effective maternal and neonatal health care, little comparable "cost per outcome" information exists to aid in identifying priority services. Studies to date have tended to address either the cost or the outcome of interventions (or packages of interventions) to reduce maternal or neonatal mortality in specific countries or regions, but rarely provide information on both cost and outcome (Borghi, 2001). In the absence of detailed data on the cost of implementing effective services, policy makers can use costing instruments to assemble key information on reproductive health care needs and service costs for specific populations. Two such instruments, the Mother-Baby Packaging Costing Spreadsheet and the Cost Estimate Strategy, are described in Box 5-4.

Researchers have examined the cost of packages of maternal health care interventions in terms of cost per death (maternal or neonatal) averted or cost per life-year saved (Gelband et al., 2001). Some of these estimates are cost projections for hypothetical care packages, including delivery with a skilled attendant; others are based on existing conditions in various devel-

BOX 5-4 Instruments for Estimating the Cost of Interventions

The Mother-Baby Packaging Costing Spreadsheet (MB) from WHO is an easy-to-use, Microsoft Excel-based tool for estimating the cost of implementing recommended packages of interventions. It has been applied in Bolivia (Capra et al., 2000). MB can be obtained free of charge. Another such tool, the Cost Estimate Strategy (CES), provides a framework for incorporating commodity cost information into reproductive health care policy and program decisions. It has been used in Kenya and Zambia (Adams and Burn, 2000).

MB and CES allow the costing of similar interventions and are based on similar assumptions about the level of health care facilities used for different activities. However, MB is more comprehensive and includes labor costs as part of the direct costs for each condition, while CES permits detailed analysis of equipment and consumable costs, but does not include labor costs. Thus MB can be used initially to estimate the cost of upgrading services to meet the requirements of the national Safe Motherhood program. Next, CES can be used to estimate the cost of supplies and equipment for these services and identify areas that impede efficient use of resources. Adapting both methods to the country standard can guide revision of national standard treatment guidelines by comparing them with the MB model.

oping country settings and facilities. According to such calculations, the overall cost of averting a maternal or neonatal death through improved maternal health care varies from about US$1,000 to $3,000, depending on the setting (Gelband et al., 2001). Spread across entire populations of developing countries, a comprehensive package of maternal services that could avert 20 to 80 percent of maternal and neonatal deaths would cost an estimated US$1 to $4 per capita (Gelband et al., 2001).

Cost-effectiveness

Since commitments of money, time, and intellectual effort to one health priority inevitably deplete resources for other health priorities, the choice among interventions needs to be based on sound evidence. The purpose of cost-effectiveness analysis is to reconcile competing demands for finite health resources by systematically comparing public health interventions.

Assessment of the relative importance of a disease or the relative impact of a health intervention begins with an understanding of the magnitude of disease burden. Mortality has traditionally served as the basis for such comparisons; however, serious and long-term illness also contributes to the burden of disease. Both mortality and morbidity are incorporated into disability-adjusted years of life (DALY), an indicator that combines losses from premature death (the difference between the actual age at death and life expectancy in a low mortality population) and loss of healthy life resulting from disability, (Murray and Lopez, 1996). Development of this indicator involved many judgments (such as the relative burdens of different conditions and of death at different ages) that continue to be refined as additional data become available. In recent years, comparisons based on the DALY have improved countries' ability to assess health priorities, measure progress in health care delivery, and estimate the impact of conditions that, while they cause relatively few deaths, result in significant disability.

DALYs have been calculated for five major causes of maternal mortality and morbidity (hemorrhage, puerperal infection, eclampsia, obstructed labor, and abortion) and four major causes of neonatal mortality and morbidity (asphyxia, infection, preterm birth, and intrauterine growth retardation); DALYs do not include late fetal deaths. Based on these assessments, pregnancy-related death and disability account for about 18 percent of the total disease burden among women of reproductive age in developing countries (AbouZahr, 1999). Pregnancy-related care and family planning were ranked among the most cost-effective clinical services in the World Bank's report *Investing in Health* (World Bank, 1993). Recent calculations estimate the cost of the mother-baby package at only $3-7 per mother-infant dyad depending on labor costs in the country, making this a cost-effective intervention (Tinker, 1997; Jowett and Ensor, 1999).

While DALY measures can be used to guide resource allocation and priority setting, few studies have evaluated interventions that reduce maternal or neonatal health in terms of cost per DALY averted (Mumford et al., 1998). Based on the outcomes of cost studies such as those described above, however, it is reasonable to expect that for women with uncomplicated pregnancies and deliveries, maternal and neonatal services will be more cost-effective when provided through primary care, rather than at referral facilities. Likewise, since prompt emergency care for complications of labor and delivery can significantly reduce maternal and neonatal mortality, providing access to a hospital and medical staff on an emergency basis is an obvious priority for maternal health services. At the referral level, the evidence-based use of surgical interventions such as cesarean section and episiotomy may substantially reduce costs associated with the overuse of these procedures.

RECOMMENDATIONS

The process of implementing the recommendations presented throughout this report begins with the recognition by health leaders and the general public that every pregnancy and birth is important and is at risk for complications. This risk can be reduced most effectively if every mother is assisted during childbirth by a skilled birth attendant and has timely access, in the event of complications, to a facility where the appropriate level of essential obstetric and neonatal care can be obtained. Where resources for reproductive health care are limited, these goals should be given highest priority. Strong systems of referral will be necessary to overcome the many physical and financial barriers to obtaining good-quality essential obstetric and neonatal care in developing countries.

Establishing health services that reduce maternal, fetal, and neonatal mortality will require national leadership, support, and oversight. The Ministry of Health or another national health agency could coordinate the training of health staff, the organization and management of community health services, the surveillance and analysis of birth outcomes, the evaluation of established interventions, and the implementation of new and revised interventions to target priority outcomes. Support for maternal and neonatal health care policy and services should be sought through community participation, as well as through national, regional, and international collaborations.

Recommendation 5. Each country should develop a strategy to reduce maternal, fetal, and neonatal mortality, a framework of activities by which this can be accomplished, and the commitment of health leaders to accomplish these goals.

A crucial first step in improving health outcomes is the identification of priority outcomes. These must be measured with the precision needed to determine their present status and establish a basis for evaluating progress toward improvement. For health systems and maternal and child health programs, surveillance of maternal, fetal, and neonatal mortality provides the foundation for identifying, selecting, and evaluating interventions to improve birth outcomes. Fetal, early neonatal, and late neonatal, as well as maternal deaths must each be clearly defined to address the distinct causes of mortality for each of these populations. Where vital statistics are inaccurate or nonexistent, pregnancy-related data can be collected on a periodic basis or in sentinel districts or other representative areas and extrapolated to a larger time or geographic scale. Intermediate process data such as the use of specific maternal and neonatal services can also be monitored. However, priority should be given to improving vital statistics, while other data collection should be tailored to match specific conditions and resources.

Recommendation 6. To determine the true burden of disease associated with adverse birth outcomes and measure the effectiveness of interventions to address these problems, basic epidemiological and surveillance data must be collected, analyzed, interpreted, and acted upon. Each country should, as resources permit, incrementally develop complete

national demographic data and ongoing surveillance of maternal, fetal, and neonatal mortality and morbidity.

Once priority outcomes have been identified, interventions to address them must be selected and their impact assessed and improved through continuing surveillance and rigorous, evidence-based evaluation.

Recommendation 7. Each country should strengthen its public health capacity for recognizing and implementing interventions that have proven effective in reducing maternal, neonatal, and fetal mortality in similar populations. This also involves monitoring and tuning interventions for clinical- and cost-effectiveness in the local setting.

RESEARCH NEEDS

Rigorous research is needed to strengthen the evidence base on the effectiveness of interventions to reduce maternal, fetal, and neonatal mortality in the health care systems of developing-country populations. High-priority topics for study include:

- Implement randomized controlled trials to measure, in a range of settings, the clinical- and cost-effectiveness of interventions likely to reduce maternal, fetal, and neonatal mortality.
- Based on country needs (from surveillance) and resources and using rigorous evaluation, determine the optimal model of labor and delivery care for a particular country or a region of the country along with strategies to provide broad access to that level of care.
- Identify appropriate mechanisms for financing reproductive care and measuring the impact of these financing methods on the use and effectiveness of maternal and neonatal services.

CONCLUSION

Health care systems vary widely among developing countries, but every system can be adapted or expanded to provide the fundamental services that reduce maternal, fetal, and neonatal mortality. These include a skilled attendant at every birth; access to essential obstetric and neonatal services for every complicated delivery; and preconceptional, antenatal, and postpartum care that is affordable and effective. Additional maternal and neonatal health services can be added to an effective basic program according to the priorities and resources of countries. Accurate information from population-based surveillance and from clinical and community-based studies is necessary to guide the identification and development of priority services and to improve the effectiveness of new and ongoing interventions.

Historically, governments have achieved significant reductions in maternal and neonatal mortality once they have recognized, through surveillance, the magnitude of the problem and the importance of skilled childbirth assistance in prevention. Policymakers can safeguard the success of such initiatives by monitoring the quality of care provided and ensuring professional accountability. Similar leadership is now needed in developing countries with high maternal and neonatal mortality. Mortality can be lowered most effectively by implementing the evidence-based interventions described in this report, addressing priority needs in underserved populations, and identifying and correcting inefficiencies in the delivery of maternal and neonatal health care services. Adverse birth outcomes cannot be eliminated, even in countries with large health budgets. However, experience in virtually all industrialized countries—and in many developing nations as well—indicates that maternal, fetal, and neonatal deaths can be reduced considerably.

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PART IV

Additional Causes of Neonatal Mortality and Morbidity

Summary of Findings: The Problem of Low Birth Weight

- Although reliable data on the magnitude and global distribution of low birth weight (LBW) are limited, it is estimated that approximately 16 percent of all neonates in developing countries weigh less than 2,500 grams at birth and that more than 20 million such infants are born each year.

- LBW may result from intrauterine growth restriction (IUGR) or preterm delivery. In developing countries, gestational age is frequently not known, which makes it difficult to distinguish between these two conditions. Nonetheless, most LBW in developing countries appears to be disproportionately due to high rates of IUGR, rather than preterm birth. Current interventions are more effective for IUGR than preterm birth.

- The least-developed countries have the highest rates of infant mortality and the highest rates of LBW. Since countries have been more successful in reducing infant mortality than LBW, future efforts should focus on reducing mortality in all neonates and infants regardless of their weight.

- Poor nutritional status is the principal cause of IUGR in developing countries. Although clinical trials have shown that increasing the food intake of pregnant women increases fetal growth, public health programs on larger populations of women have not been more than minimally effective in reducing IUGR. Malaria prophylaxis and intensive smoking cessation programs have been effective in reducing IUGR.

- For preterm birth, the leading causes are genitourinary infection, multiple birth, pregnancy-induced hypertension, and low prepregnancy weight. Additional risk factors include malaria and cigarette smoking. Antibiotic treatments of pregnant women appear to be effective for asymptomatic bacteriuria, are not clearly effective for bacterial vaginosis, and are not effective for trichomoniasis or chlamydia. Antihypertensive treatment has not been efficitive in lowering the risks of IUGR or preterm birth. Malaria prophylaxis, intensive counseling on smoking cessation, and fish oil supplementation are effective. Where resources permit, women with documented cervical incompetence may benefit from a cerclage procedure.

- Two strategies for reducing neonatal and infant mortality among LBW infants that do not depend on expensive care or technology include breastfeeding and/or use of expressed breast milk and Kangaroo mother care.

6

The Problem of Low Birth Weight

Although reliable data on the magnitude and global distribution of low birth weight (LBW, birth weight <2,500 grams) remain limited (de Onis et al., 1998a), World Health Organization estimates that more than 20 million LBW infants are born each year, affecting approximately 16 percent of all newborns in developing countries. LBW is an important risk factor for neonatal and postneonatal mortality. Moreover, LBW neonates who survive infancy are at increased risk for health, growth, and developmental problems, and those who are small for their gestational age may be predisposed to developing chronic adult disorders such as hypertension, type 2 diabetes, and heart disease.

This chapter reviews the prevalence, causes, and consequences of intrauterine growth restriction (IUGR) and preterm birth in developing countries and potential interventions for preventing these two types of LBW. It should be noted that most research on IUGR and preterm birth has been conducted in developed countries and thus may have limited programmatic and policy implications for low-resource nations. This chapter therefore emphasizes the need for studies that reflect the economic, nutritional, and cultural heterogeneity among developing countries, and in particular, those that differentiate between IUGR and preterm birth.

PATTERNS OF OCCURRENCE

In addressing the problem of LBW, it is necessary to distinguish LBW due to restricted fetal growth (IUGR) from that due to preterm birth (delivery <37 completed weeks of gestation) (Kramer, 1987). An infant may be LBW because (s)he is either born small for gestational age (SGA), a proxy for IUGR, or is born early (preterm birth).[1] The distinction depends upon the infant's gestational age, which is not known for many LBW infants born in developing countries. To address this problem, methods have recently been developed for estimating the magnitude of IUGR and preterm delivery where conventional diagnosis is impossible. Where the prevalence of LBW is very high, it is known that most LBW infants are growth-restricted rather than preterm (Villar and Belizan, 1982; de Onis and Habicht, 1996). WHO estimates that each year, 13.7 million infants are born with LBW at term (≥37 weeks), and as many as 30 million infants are born with IUGR (many of these IUGR infants weigh more than 2,500 g and are therefore not LBW). WHO also estimates that 6.8 million infants are born both preterm and LBW; this figure underestimates the total number of preterm births occurring annually, because it excludes the large fraction of mildly preterm infants (34-36 weeks) weighing ≥2,500 g at birth.

Table 6-1 summarizes data on the prevalence of LBW, IUGR, and preterm birth among countries participating in the WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes (World Health Organization, 1995). As seen in the table, the distribution of IUGR varies widely among developing countries. The greatest burden from this problem is borne by specific countries—those with limited resources, large populations, and high fertility rates. As many as 30-50 percent of infants born in South-Central Asia are IUGR, compared with 15-25 percent in Africa and 10-20 percent in Latin America (World Health Organization, 1995). In some developing countries, such as those on the Indian subcontinent, the majority of newborns suffer at least some degree of fetal growth restriction. Preterm birth rates vary less than IUGR rates. All of these rates should be interpreted cautiously, however, given the absence of universal birth registration and poor gestational age data in many developing countries.

In areas where scales are not available to determine birth weight, other newborn anthropometric measurements can provide useful information at the individual and population levels. Studies in various settings have evaluated the use of arm, chest, and calf circumferences as surrogate measures for birth weight, and in particular for identifying LBW infants (Raman et al., 1992; World Health Organization, 1993). Currently, WHO recommends the use of chest circumference; newborns with chest circumferences

[1]SGA is defined by WHO as a birth weight below the tenth percentile for gestational age based on the sex-specific reference by Williams et al. (1982). Some SGA infants are merely constitutionally small rather than truly growth-restricted. Conversely, some IUGR infants who would otherwise be constitutionally large do not meet standard criteria for SGA. Nonetheless, SGA is often used as a convenient proxy for IUGR.

TABLE 6-1 Pregnancy Outcome Among Countries Participating in WHO Collaborative Study

Country	LBW (% of live births)	IUGR (% of live births)	Preterm Birth (% of live births)
Argentina	6.3	9.7	7.2
China	4.2	9.4	7.5
Colombia	16.1	17.8	15.7
Cuba	8.1	14.7	7.2
Gambia	12.1	13.5	13.5
Guatemala	12.5	25.3	15.8
India (Pune)	28.2	54.2	9.7
Indonesia	10.5	19.8	18.5
Ireland	5.6	6.9	6.2
Malawi	11.6	26.1	8.2
Myanmar	17.8	30.4	24.6
Nepal (Rural)	14.3	36.3	15.8
Sri Lanka	18.4	34.0	14.0
Thailand	9.6	17.0	21.3
United Kingdom	6.2	12.3	4.6
US/CDC (Black)	10.6	11.2	16.6
US/CDC (Hispanic)	4.8	5.8	10.2
US/CDC (White)	6.0	6.9	9.3
Vietnam	5.2	18.2	13.6

SOURCE: World Health Organization, 1995.

<29 cm are designated as “highly at risk” and those with circumference ≥29 but <30 cm as “at risk” (World Health Organization, 1993).

CAUSES OF IUGR AND PRETERM BIRTH

The importance of a risk factor for either preterm birth or IUGR is a function of its associated relative risk, as well as the prevalence of exposure to that factor in a specific population setting (Kramer, 1987). As shown in Table 6-2, risk factors for IUGR in developing countries include low maternal prepregnancy weight or body mass index[2] (BMI); low gestational weight gain; short maternal stature; pregnancy-induced hypertension; and, where prevalent, cigarette smoking and (for primiparae) malaria. Important causes of preterm delivery include genitourinary infection, multiple pregnancy, pregnancy-induced hypertension, low prepregnancy BMI, incompetent cervix, history of prior preterm birth, cigarette smoking (where prevalent), and

[2]BMI is a measure of nutritional status and is calculated as (wt in kg)/(ht^2 in m^2).

TABLE 6-2 Determinants of IUGR and Preterm Birth in Developing Country Settings (listed in decreasing order of importance)

IUGR	Preterm Birth
• Low energy intake/gestational weight gain	• Genitourinary infection
• Low pre-pregnancy body mass index	• Multiple birth
• Short stature	• Pregnancy-induced hypertension
• Malaria[a]	• Low pre-pregnancy body mass index
• Cigarette smoking[b]	• Incompetent cervix
• Primiparity	• Prior preterm birth
• Pregnancy-induced hypertension	• Abruptio placentae
• Congenital anomalies	• Strenuous work
• Other genetic factors	• Cigarette smoking[b]

[a]For primiparae in malaria-endemic areas only.
[b]Assuming a prevalence of 10-20 percent.

SOURCE: Kramer and Victora, 2001.

strenous physical labor (Kramer, 1987; Kramer and Victora, 2001). Although pregnancy-induced hypertension and low prepregnancy BMI are highly prevalent in developing countries, the role of genital tract infection (the leading cause of preterm birth in developed countries) remains relatively unexplored in such settings.

Maternal undernutrition (characterized by low energy intake, low gestational weight gain, low prepregnancy BMI, and short stature) accounts for a large proportion of IUGR in developing countries. This is due to the high relative risk for IUGR associated with these factors, as well as their high prevalence. Mean values for these anthropometric factors are summarized in Table 6-3 for countries participating in the WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes (World Health Organization, 1995). Regardless of energy intake or weight gain during pregnancy, women in the lowest quartile of height have an odds ratio (OR) of 1.9 (95 percent confidence interval [CI] 1.8-2.0) of delivering an IUGR infant compared with those in the upper quartile. Similarly elevated risks are seen among those in the lowest quartile of prepregnancy BMI (OR = 1.8 [1.7-2.0]) or of weight gain (OR = 1.8 [1.5-2.2]) (World Health Organization, 1995). Adolescent girls with a low gynecological age (years after menarche) may be at particularly high risk for delivering a growth-restricted infant, possibly as a result of maternal/fetal competition for nutrients (Scholl et al., 1995), and should be considered as a high-risk subgroup in future studies.

Public health professionals have reported that women in developing countries are often reluctant to increase dietary intake during pregnancy,

TABLE 6-3 Maternal Anthropometric Measures (Means) Among Countries Participating in WHO Collaborative Study

Country	Height (cm)	Prepregnancy BMI	Weight gain (kg)
Argentina	157	22.4	10.8
Myanmar	151	19.8	—
China	160	19.5	11.7
Colombia	155	23.3	10.1
Cuba	157	21.8	4.6
Gambia	157	19.7	6.5
Guatemala	148	20.8	7.1
India (Pune)	150	18.3	—
Indonesia	149	20.2	—
Ireland	158	23.7	11.0
Malawi	155	21.0	4.7
Nepal (Rural)	150	19.5	—
Sri Lanka	150	18.8	—
Thailand	153	20.8	8.0
UK	159	22.2	11.6
US/CDC (Black)	162	23.1	13.5
US/CDC (Hispanic)	158	23.7	12.8
US/CDC (White)	163	22.6	14.4
Vietnam	152	19.6	5.6

SOURCE: World Health Organization, 1995.

and may even willfully restrict energy intake, in order to avoid delivery complications associated with a large infant (so-called "eating down"). This phenomenon has been documented in South India (Hutter, 1996), but there are few data to indicate how widespread such beliefs and practices are in developing countries, or the extent to which they can be changed through public health interventions. Clearly, more research is needed to know whether women's reluctance to gain weight is justified and whether public health interventions can be developed that would improve fetal growth without jeopardizing maternal or fetal survival and well-being.

There is no doubt that maternal dietary intake influences fetal growth and that insufficient energy intake reduces fetal size. Perhaps the most dramatic evidence for this comes from the pregnancy experiences of women during the Dutch famine of 1944-1945. When energy rations were reduced from 1700 to 700 kcal/day for women in the third trimester of pregnancy, mean birth weight decreased by more than 300 g; there was no change in the mean length of gestation (Stein et al., 1975; Susser and Stein, 1994).

Few data have been published on the customary dietary intakes of pregnant women in developing countries. Available data—widely recognized as imprecise—suggest daily intakes averaging 1,500 kcal and ranging

TABLE 6-4 Reported Energy Intakes of Pregnant Women in Developing Countries

Source	Country	Energy Intake (kcal/d)
Prentice (wet season)	Gambia	1,350-1,450
Oomen and Malcolm	New Guinea	1,360
Gopalan	India	1,400
Venkatacnalam	India	1,410
Lechtig et al.	Guatemala	1,500
Gebre-Medhin and Gobezie	Ethiopia	1,540
Rajalakshmi	Ethiopia	1,540
Mora et al.	Colombia	1,620
Prentice (dry season)	Gambia	1,600–1,700
Arroyave	Guatemala	1,720
Maletnlema and Bavu	Tanzania	1,850
Demarchi et al.	Iraq	1,880
Bagchi and Bosc	India	1,920
Thanangkul and Amatyakul	Thailand	1,980
Mata et al.	Guatemala	2,060

SOURCES: Institute of Medicine, 1992; Whitehead and Paul, 1982; Prentice, 1980.

from 1,300 to 2,100 kcal/day (Table 6-4), as compared with an average of 2,000 kcal/day in industrialized countries. Whether these lower caloric intakes are inadequate is unclear, however.

Women in developing countries are typically shorter and lighter than women in industrialized countries and likely perform more physical labor. Observational studies in the Gambia report negative effects on fetal growth when limited food intake and strenuous physical activity are combined (Prentice et al., 1983). An observational study from Ethiopia found that women who did not perform strenuous work (housewives with domestic help or women with sedentary jobs) gained more weight during pregnancy and had heavier infants (among those born at term) than women engaging in more physically demanding work (Tafari et al., 1980). Similarly, a Guatemalan study reported that women with three or more children at home and no household help, as well as those employed in manual work outside the home, were at significantly higher risk for delivering an IUGR infant (Launer et al., 1990). Another observational study from Zaire (Manshande et al., 1987) found a positive association between both gestational age and birth weight (among female newborns only) and a longer maternal stay in a maternity rest home; however, this result could also reflect the simple fact that women who delivered later stayed longer in the rest home. Although pregnant women in developing countries are unlikely to greatly reduce their physical activity, additional research is needed to document the work burden of women in developing countries during pregnancy (Institute of Medicine, 1992). Because of the strong potential for both confounding and selection bias in observational studies of physical activity, randomized trials would be very helpful in assessing the causal impact of reductions in physical work on pregnancy outcomes in developing countries.

As noted earlier, cigarette smoking is a strong risk factor for IUGR, and it is also a weaker but nonetheless important determinant of preterm birth (Kramer, 1987; Cnattingius and Haglund, 1997; Kyrklund-Blomberg and Cnattingius, 1998). Maternal smoking is an increasingly significant cause of IUGR in developing countries, rising in parallel with cigarette smoking in many areas. Table 6-5 presents the estimated prevalence of cigarette smoking among women aged 15 years or older in various regions of the world, ranging from about 26 percent of women in Eastern Europe and Central Asia to 1 percent of women in South Asia.

Heavy alcohol consumption is an established risk factor for a set of dysmorphic features known as fetal alcohol syndrome, of which IUGR is one component. Because few women consume alcohol at these levels, however, the overall (population-level) public health impact on IUGR is small (Kramer, 1987). Further study of the effects of lower levels of alcohol intake on fetal growth is needed (Lundsberg et al., 1997).

Malaria is a major cause of anemia and has been associated with reduced birth weight and with an elevated risk of IUGR in primiparous women, who make up 30-50 percent of pregnant women. WHO estimates that 30 million pregnancies occur each year in malaria-endemic regions of the world. In these areas, malaria constitutes a serious threat to maternal and fetal well-being.

Several studies from developed countries suggest that bacterial vaginosis, and perhaps other types of genital tract infection/colonization, may initiate spontaneous preterm labor and rupture of membranes (Hillier

TABLE 6-5 Prevalence of Smoking Among Women 15 Aged Years or Older by Region

Region	Prevalence (%)
East Asia and Pacific	4
Eastern Europe and Central Asia	26
Latin America and Caribbean	21
Middle East and North Africa	5
South Asia	1
Sub-Saharan Africa	10
World	12

SOURCE: World Bank, 1999.

et al., 1995; Chaim et al., 1997). Studies from developing countries have tended to focus on the relationship between genital tract infection and fetal and/or early neonatal death (Naeye et al., 1977; Ross et al., 1982; Moyo et al., 1995; Osman et al., 1995), rather than its role in preterm birth.

The maternal environment plays a far larger role in fetal growth than do genetic factors (Walton and Hammond, 1938; Brooks et al., 1995), especially in developing countries (Kramer, 1987). Congenital anomalies are strongly associated with IUGR (Khoury et al., 1988), however. Moreover, moderately high recurrence risks for IUGR within individual women (Bakketeig et al., 1986; Wolfe et al., 1987; Basso et al., 1999), intergenerational (especially mother-to-daughter) associations (Klebanoff and Yip, 1987; Klebanoff et al., 1989; Magnus et al., 1997; Klebanoff et al., 1997), concordance in twins (Clausson et al., 2000) and nontwin siblings (Johnstone and Inglis, 1974; Beaty et al., 1997), and inbreeding effects (Khoury and Cohen, 1987) all point to an important genetic contribution to fetal growth.

Increased recurrence risks (Hoffman and Bakketeig, 1984; Kristensen et al., 1995; Menard et al., 1996; Mercer et al., 1999; Adams et al., 2000; Bloom et al., 2001) and intergenerational associations (Porter et al., 1997; Hennessy and Alberman, 1998) suggest that genetic factors may also play a role in preterm birth, but that role appears less important than for IUGR (Klebanoff and Yip, 1987; Klebanoff et al., 1997; Clausson et al., 2000).

A short interval (<6 months) between pregnancies is often cited as a determinant of preterm birth or IUGR (Zhu et al., 1999; Shults et al., 1999), but few studies have controlled for the outcome of the previous pregnancy and the tendency of preterm birth or IUGR to repeat in subsequent pregnancies (Erickson and Bjerkedal, 1978; Klebanoff, 1999). Moreover, intervals <6 months are infrequent in developing countries where prolonged and exclusive breastfeeding are prevalent.

CONSEQUENCES OF IUGR AND PRETERM BIRTH

Effects on Mortality

Despite the lack of reliable data on the risks of morbidity and mortality associated with IUGR and preterm delivery in developing country settings, several patterns are clear. The least-developed countries generally have the highest rates of IUGR and of infant mortality. Yet because normal-weight infants are at relatively high risk of infant death (compared with those in most developed countries), the *relative risk*[3] (RR) associated with IUGR

[3]The relative risk indicates the strength of the association between a risk factor (e.g., poor nutrition or cigarette smoking) and a health outcome (e.g., infant mortality, IUGR, or preterm birth). It is calculated by dividing the risk in the group exposed to the risk factor by the risk in the unexposed group.

(and with preterm birth) are considerably lower than in more-developed countries.

Thus, for example, a 1982 study from southern Brazil reported an overall infant mortality rate of 38.1 per 1,000 live births, an IUGR rate of 9.0 percent, and a preterm birth rate of 6.3 percent. Relative risks of infant death were 4.5 for IUGR and 10.2 for preterm birth (Victora et al., 1987; Barros et al., 1992). In Bangladesh, on the other hand, a 1993-1996 study reported an infant mortality rate of 107.3 per 1,000, and IUGR and preterm birth rates of 69.2 and 17.1 percent, respectively (Arifeen, 1997). In the latter setting, the relative risks of infant death associated with IUGR and preterm birth were only 1.2 and 1.6, respectively.

Industrialized countries have succeeded in reducing infant mortality without a large reduction in prevalence of LBW. Population-based data from southern Brazil (Pelotas) suggest a similar picture. Between 1982 and 1993, infant mortality fell by 50 percent (from 39 to 19 per 1,000) despite an increase in the LBW rate from 9.0 to 9.8 percent (Barros et al., 1996). Modest reductions in IUGR in developed countries appear to be attributable primarily to an increase in the size of term infants (Kessel et al., 1984; Arbuckle and Sherman, 1989; Skjaerven et al., 2000; Orskou et al., 2001; Robertson et al., 2002), which parallels increases in maternal height, prepregnancy BMI, and gestational weight gain and a reduction in maternal smoking (Kramer, 2002a,b). With the possible exception of France (Papiernik et al., 1985; Bréart et al., 1995) and Finland (Olsén et al., 1995), developed countries have not reported reductions in preterm birth. In fact, recent data from Canada (Joseph et al., 1998) and the United States (Demissie et al., 2001) show a significant increase. In Canada, part of the increase appears to be an artifactual result of the use of ultrasound (correction of earlier errors of gestational age dating based on the last menstrual period) and increased registration of births weighing <500 g. A true smaller increase in preterm birth appears to be associated with increasing obstetric intervention (induction and cesarean section), multiple gestation (secondary to treatment of infertility), and demographic changes (older maternal age, more unmarried mothers) (Joseph et al., 1998; Kramer et al., 1998; Demissie et al., 2001).

Substantial reductions in neonatal and infant mortality have been achieved despite these trends in preterm birth because of improvements in the care provided to high-risk mothers and newborns, including neonatal intensive care (Richardson et al., 1998; Kalter et al., 1998; Gould et al., 2000). In some developing countries, the pattern has been similar. Brazil, for example, has witnessed continued declines in infant mortality despite a significant increase in preterm births (Silva et al., 1998; Bettiol et al., 2000). Mortality reductions associated with improved home care among both LBW and normal-birth-weight newborns in rural India are an impressive example of what can be done in even the most resource-constrained areas of the world (Bang et al., 1999).

Effects on Morbidity, Growth, and Development

IUGR, particularly when severe, can lead to hypoglycemia, hypocalcemia, and polycythemia in the early neonatal period (Kramer et al., 1990). These metabolic consequences of fetal malnutrition and hypoxia require monitoring for detection and prompt treatment to prevent death and serious neurologic sequelae. Such monitoring and treatment are possible, however, only in health care facilities with the requisite personnel and equipment, and are therefore infeasible for births occurring at home or in rudimentary care settings, which predominate in the developing world.

Most IUGR infants survive the early neonatal period without these complications. Yet data suggest that they remain at increased risk for infection (Villar et al., 1990; Barros et al., 1992; Ashworth, 1998). Moreover, although they show some catch-up growth in the first 6 months of life, the catch-up is incomplete in many affected children; indeed, even in developed countries, IUGR infants remain shorter, on average, throughout childhood and into adulthood relative to their normal-birth-weight peers (Albertsson-Wikland and Karlberg, 1994; Strauss, 2000). The resulting short stature and reduced muscle mass and strength may have adverse consequences for physical work capacity (Martorell et al., 1998), an important economic consideration in many developing countries. Moreover, a recent study reports that Guatemalan women with heights of 146 cm (1 standard deviation below the mean) were at a 2.5-fold higher risk of nonelective cesarean section compared with those with heights of 160 cm (1 standard deviation above the mean) (Merchant et al., 2001). Finally, IUGR in girls increases the risk of IUGR in the girls' own offspring, and several generations may be required to achieve optimal fetal growth (Ramakrishnan et al., 1999). A recent study reports that Filipino infants with low gestational age-adjusted birth weight had later menarche, on average, whereas those with lower birth length (adjusted for both birth weight and gestational age) had earlier menarche (Adair, 2001).

Mild neurocognitive deficits and behavioral problems have also been consistently reported in children and adolescents who were growth-restricted in utero (Goldenberg et al., 1998; Hack, 1998; Strauss, 2000; Larroque et al., 2001; Paz et al., 2001). However, most published studies report data from developed countries; more research is needed to address the long-term neurocognitive effects of IUGR in developing countries.

Various body proportionality indices have been used to relate different dimensions of fetal growth, particularly among growth-restricted infants. The most commonly used of these indices is Rohrer's ponderal index, a measure of birth weight relative to birth length (100 × birth weight in g ÷ birth length^3 in cm^3). Infants with high ponderal indices are relatively heavy for their length (or, equivalently, relatively short for their weight); those with low ponderal indices are thin, with low weight for length. Based on the ponderal index, a number of studies have used the concepts of proportionate (also called "symmetric" or "stunted") and disproportionate ("asymmetric" or "wasted") growth restriction (Rosso and Winick, 1974; Miller and Merritt, 1979; Villar and Belizan, 1982).

The importance of this distinction is unclear, however. Many investigators have inferred that differences in proportionality reflect differences in timing of in utero growth restriction, based on highly diagrammatic velocity curves published by Tanner (1989) suggesting a deceleration in length in the second trimester. In fact, however, studies based on serial ultrasound measurements (Campbell and Newman, 1971) or prostaglandin-induced pregnancy terminations (Birkbeck et al., 1975a,b; Kaul et al., 1986) clearly demonstrate that crown-to-heel length, biparietal diameter, and head circumference increase linearly throughout the second trimester. Moreover, proportionality among IUGR infants is strongly confounded by the severity of the growth restriction; disproportionate IUGR infants tend to be more severely growth-restricted than their proportionate counterparts (Kramer et al., 1989).

The above-noted Scandinavian study found no difference in IQ at age 5 years in infants with asymmetric versus symmetric IUGR (Sommerfelt et al., 2000). Recent data from Brazil indicate no difference in catch-up growth in disproportionate versus proportionate IUGR infants once birth weight for gestational age (severity of IUGR) is adjusted for using multivariate analysis (Horta, 2001). In a small Guatemalan study, proportionate IUGR infants (n = 38) born in 1969-1977 were shorter and lighter and had lower developmental scores than those with disproportionate IUGR (n = 21) despite similar birth weights (Villar et al., 1984). But, a more recent publication based on the same sample studied at age 5 years found no remaining deficits in weight, height, or verbal or memory cognitive function in proportionate IUGR infants (Gorman and Pollitt, 1992). A study of Guatemalan infants born in 1984-1986 revealed an increased risk of severe neonatal morbidity in disproportionate IUGR infants, however, even after controlling for their lower birth weight (Villar et al., 1990).

In recent years, researchers have identified an additional area of concern regarding the adverse consequences of IUGR: the fetal origins of adult disease (Barker, 1992; Leon, 1998). Robust associations have been reported with subsequent hypertension, type 2 diabetes, and coronary heart disease. While most early studies in this area were based in the United Kingdom and other developed countries, the reported associations have also been documented for several developing countries, including India

(Fall et al.,1998; Bavdekar et al., 1999), Zimbabwe (Woelk et al., 1998), South Africa (Levitt et al., 1999), and Brazil (Barros and Victora, 1999); by contrast, no significant association between IUGR and blood pressure was observed in school-aged children from Argentina (Bergel et al., 2000). Whether these associations are causal remains to be established, however, as does their importance in explaining geographic and temporal trends in adult chronic diseases (Joseph and Kramer, 1996; Kramer, 2000).

More research on the relationship between IUGR and adult chronic disease is clearly required, particularly from developing-country settings, where IUGR is especially prevalent. Some studies suggest that the shift from energy scarcity to plenty may be particularly important. In India, for example, the rise in obesity coupled with deficits in fetal growth may be contributing to the current "epidemic" of insulin resistance and type 2 diabetes in that country (Yajnik, 2001). Nonetheless, conventional adult risk factors appear to explain most of the variation in prevalence of coronary heart disease among developing countries (Li et al., 1994).

Extremely preterm infants (those born at <32 weeks of gestation) are unlikely to survive in developing-country settings without access to neonatal intensive care. Even in developed countries, extremely preterm infants who survive are at increased risk of severe morbidity in infancy and childhood, including retinopathy of prematurity (a major cause of blindness) and chronic lung disease (bronchopulmonary dysplasia[4]), which can lead to a requirement for oxygen for many months and long-term reactive airway complications of common viral respiratory infections (McCormick, 1985; Institute of Medicine, 1985; Page et al., 1993). The most serious long-term morbidity associated with extreme preterm birth, however, is neurocognitive, including cerebral palsy, mental retardation, seizure disorders, and less severe neurobehavioral deficits (Robertson et al., 1992; Stewart et al., 1999; Hack et al., 2000).

Mildly preterm infants (gestational age 32-36 weeks) have somewhat elevated risks of respiratory distress syndrome, infection, and both neonatal and postneonatal mortality (Dollfus et al., 1990). Although the magnitude of these risks is lower than in more premature infants, their greater numbers have a substantial impact on both morbidity and mortality at the population level (Kramer et al., 2000). Unfortunately, almost all of the research on the long-term consequences of preterm birth comes from developed countries.

[4]Bronchopulmonary dysplasia, or chronic lung disease of prematurity, can lead to oxygen dependency, recurrent wheezing, and complications of common viral respiratory infections.

INTERVENTIONS TO PREVENT PRETERM BIRTH AND IUGR

Sources of Evidence

The following sections review the available evidence concerning interventions to prevent preterm birth and IUGR in developing country settings. The discussion relies primarily on evidence from randomized controlled trials (RCTs) and systematic reviews of RCTs in the Cochrane Database of Systematic Reviews (CDSR), which provide the most rigorous evidence of the effects of these interventions on reducing preterm birth and IUGR. In the absence of RCTs, other methodologically less-rigorous scientific information is considered, although the potential for confounding in observational studies of clinical and public health interventions suggests the need for caution in interpreting the study results. This is particularly true for nutritional interventions, because of the strong associations among specific macro- and micronutrients and the robust relationship between dietary compliance and beneficial pregnancy outcomes. The non-RCT evidence reviewed here was identified from a computerized search of MEDLINE (with restriction to publications in English or French) based on the following medical subject headings and logic: infant, premature; infant, LBW; birth weight; infant, small-for-gestational age; fetal growth retardation; and labor, premature.

Prepregnancy Energy/Protein Supplementation

Interventions to increase maternal BMI before pregnancy may be impractical in many settings because their target is so broad: all women of childbearing age, rather than those who are currently pregnant. The committee is aware of programs targeting newly married women and adolescent girls as a means of improving nutritional status (including BMI) before the first pregnancy, but could find no documentation of evaluation of the impact of these programs on birth outcomes. The only RCT of preconceptional nutritional supplementation is from Taiwan (Blackwell et al., 1973). In this study, supplementation began after a previous pregnancy and continued through the index (study) pregnancy. The effects of this combined pre- and intrapregnancy supplementation did not appear to be larger than the effects reported for trials in which supplementation was restricted to pregnancy (Kramer, 2002b). An observational study of supplemented women in Guatemala (Villar and Rivera, 1988) showed an enhanced effect on fetal growth associated with high levels of continuing nutritional supplementation through a prior pregnancy, the subsequent interbirth interval, and the index pregnancy, as compared with supplementation during the index pregnancy only. Because each woman decided whether to take the supplement and how much of it to take, however, such an association is prone to confounding by self-selection. More research is needed to identify and evaluate strategies for enhancing maternal nutritional status before pregnancy as a means of improving birth outcomes, especially given the above-noted intergenerational tendency toward suboptimal fetal growth.

Energy/Protein Supplementation During Pregnancy

Controlled clinical trials providing food supplements to pregnant women have yielded only modest effects in enhancing fetal growth and in reducing IUGR (de Onis et al., 1998b; Rush, 2001). A Cochrane systematic review examines 13 of these trials, including studies from Colombia, Indonesia, Taiwan, and the Gambia, as well as studies among undernourished women in several developed countries (Kramer, 2002a). In these trials, the supplements were balanced with respect to their protein and energy content (≤25 percent of the energy content was derived from protein). Overall, balanced energy/protein supplementation appears to have only a modest effect on mean birth weight (weighted mean difference = 25 g [95 percent CI = –4 to +55 g]), but a more substantial effect on reducing IUGR (RR = 0.68 [95 percent CI = 0.57-0.80]). No evidence was found that these effects are larger in undernourished than in well-nourished women. However, the magnitude of the birth weight increase was substantially larger (136 g) in the Gambia (Ceesay et al., 1997), where the supplement provided an additional 900 kcal per day, as compared with a 200 to 250 kcal per day increase in most of the other trials. Supplementation is not associated with an increase in mean gestational age (weight mean difference = –0.1wk [95 percent CI = –0.2 to +0.1wk]) or a significant reduction in preterm birth (RR = 0.83 [95 percent CI = 0.65-1.06]).

Nutritional Advice

Improvements in energy intake could occur through the provision of nutritional advice during prenatal care or as part of broader community-based mass media strategies. The committee could not find examples of these approaches in developing countries, however. The CDSR contains a systematic review of four trials from developed countries in which nutritional advice was given to pregnant women to increase their energy and protein intakes (Kramer, 2002b). Although the results suggest such advice can be successful in increasing dietary intake, no significant effect was seen on mean birth weight or IUGR. One trial (Kafatos et al., 1989) reported a significant reduction in preterm birth (RR = 0.45 [0.22-0.92]) in women randomized to receive nutritional advice, but that result is inconsistent with the total absence of effect on mean gestational age (weighted mean difference = –0.1 [–0.4 to +0.2] wk). The relevance of these findings for developing-country populations is not known.

Micronutrient Supplementation

There is little evidence that supplementation with specific micronutrients improves fetal growth or lowers the risk of IUGR or preterm birth. A systematic review in the CDSR associates magnesium supplementation with reduced risks for both preterm birth (RR = 0.73 [95 percent CI =0.57-0.94]) and IUGR (RR = 0.70 [95 percent CI = 0.53-0.93]), but the quality of the trials included in the review is poor (Makrides and Crowther, 2002). No significant effect on reducing preterm birth or IUGR has been found in a systematic review of trials of supplementation with iron (Mahomed, 2002b) or folate (Mahomed, 2002a), even in combination (Mahomed, 2002c). In the case of zinc, the most recent Cochrane review (Mahomed, 2002d) reports a significant effect of supplementation in reducing preterm birth (RR = 0.74 [95 percent CI = 0.56-0.98]), although not IUGR (RR = 0.90 [95 percent CI = 0.64-1.28]). However, the encouraging result for preterm birth has not been confirmed in two recent trials from Peru (Caulfield et al., 1999) and Bangladesh (Osendarp et al., 2000), which are not included in the Cochrane review. A systematic review of maternal iodine supplementation (in iodine-deficient areas) revealed a significant increase in mean birth weight (147g, 95 percent CI 51-244 g), although no data were reported on preterm birth or IUGR (Mahomed and Gülmezoglu, 2002). In the systematic review by Atallah et al. (2002), no effect of calcium supplementation on reducing preterm birth is evident overall (RR = 0.95 [95 percent CI = 0.82-1.10]), but a strong effect was noted in four small trials in women at high risk for hypertension (RR = 0.42 [0.23-0.78]).

Diets rich in fish oil contain high concentrations of n-3 long-chain polyunsaturated fatty acids. Such diets have been reported to prolong gestation and augment fetal growth, perhaps by inhibiting prostaglandin synthesis and/or through their antioxidant properties (Olsén, 1993). The evidence from observational studies and randomized trials is mixed (Olsén et al., 1991, 1992; Onwude et al., 1995; Reece et al., 1997; Sattar et al., 1998), although six recent multicenter trials suggest a protective benefit, at least in singleton pregnancies (Olsén et al., 2000). No systematic review of the existing trials has yet been published (Makrides et al., 2002).

Further randomized trials are needed before evidence-based recommendations can be made with respect to the role of micronutrient supplements in preventing IUGR or preterm birth. Because many women routinely receive iron and folic acid supplements during pregnancy (to prevent or treat maternal anemia), such trials should evaluate the impact on pregnancy outcomes of multiple micronutrient supplements, instead of continuing with single-nutrient approaches (de Onis et al., 1998b). For example, a multivitamin mineral preparation was shown to improve a number of pregnancy outcomes (including a reduction in preterm birth) among poorly nourished HIV-positive women in Tanzania who were not receiving antiretroviral therapy (Fawzi et al., 1998).

Treatment of Genitourinary Infection

The Cochrane systematic review on treatment of asymptomatic bacteriuria reports a pooled relative risk of 0.64 (95 percent CI = 0.50-0.82) for the risk of a composite outcome of preterm delivery or LBW, based on ten controlled clinical trials of questionable methodological quality (Smaill, 2002). On the other hand, antibiotic treatment has not been shown to reduce the risk of preterm birth in women with either preterm prelabor rupture of membranes (Kenyon and Boulvain, 2002) or preterm labor with intact membranes (King and Flenady, 2002; Kenyon et al., 2001). The treatment of women with bacterial vaginosis is more controversial. Despite strong epidemiological evidence of an association between bacterial vaginosis and preterm birth (as discussed above), randomized trials of systemic antibiotic treatment with erythromycin, amoxicillin, or metronidazol and of topical clindamycin have not shown clear evidence of benefit (Brocklehurst et al., 2002). A recent large trial from the National Institutes of Health (NIH) Maternal-Fetal Medicine Network (Carey et al., 2000) showed no evidence of effectiveness overall and, in contrast to a previous trial (Hauth et al., 1995), not surprisingly a slightly increased risk of preterm birth in women with a prior history of preterm birth.

A recent publication from the same NIH network reported even more discouraging results for metronidazole treatment of women with asymptomatic trichomoniasis; treatment (versus placebo) actually led to an *increased* risk of preterm birth (Klebanoff et al., 2001). A single trial provided no evidence that antibiotic treatment in pregnant women with chlamydia infection reduces the risk of preterm birth (Martin, 1997).

Three studies from sub-Saharan Africa have indicated an association between use of antibiotics during pregnancy and a reduction in either LBW or prolongation of pregnancy. In a recent Kenyan study, a single oral dose of cephalosporin administered to pregnant women with poor obstetric histories was found to be associated with a significant reduction in LBW (probably due largely to preterm birth) and postpartum endometritis (Gichangi et al., 1997). Large losses to follow-up suggest the need for cautious interpretation of these results, however. A small trial in South Africa using metronidazole and ampicillin among women in early preterm labor reported a significant prolongation of pregnancy, but preterm birth rates were not reported, and no reduction was observed in either neonatal death or length of neonatal hospital stay (Norman et al., 1994). Finally, a recently published trial in pregnant women living in the Rakai District of Uganda revealed that those randomized to receive a single presumptive treatment dose of azithromycin, cefixime, and metronidazole had borderline significant reductions in risk of preterm birth (RR = 0.72 [95 percent CI = 0.56-1.05]) and of early neonatal death (RR = 0.83 [95 percent CI = 0.71-0.97]) (Gray et al., 2001).

Smoking Cessation

Intensive smoking cessation interventions (as opposed to the routine advice provided in standard prenatal care) have been found moderately successful in improving fetal growth, with a pooled difference in mean birth weight of about 29 g (95 percent CI = 9-49 g) (Lumley et al., 2002). This review does not specifically report on IUGR. The modest reduction reported for LBW (RR = 0.81 [95 percent CI = 0.69-0.96]) may be due at least in part to a significant effect on preterm birth (RR = 0.84 [95 percent CI = 0.71-0.99]).

Malaria Prophylaxis and Treatment

A systematic review of antimalarial prophylaxis from the CDSR indicates an increase of approximately 100 g (weighted mean difference = 102 g, 95 percent CI = 33-171 g) in mean birth weight and a reduction of approximately 40 percent (RR = 0.59 [95 percent CI = 0.41-0.85]) in the risk of LBW for primiparous women (Garner and Gülmezoglu, 2002). No specific analysis for IUGR is presented in this Cochrane review, although the lack of a significant reduction in the risk of preterm birth among women with a first or second pregnancy (RR = 0.91 [95 percent CI = 0.64-1.29]) (based on two small trials) suggests that the effect of antimalarial prophylaxis is restricted to improving fetal growth, presumably by reducing placental parasitemia.

One small nonrandomized trial showed that a two-dose regimen of sulfadoxine-pyrimethane was associated with a nonsignificantly higher mean birth weight (2,864 versus 2,748 g) and a lower risk of LBW (17 versus 27 percent) compared with weekly chloroquine prophylaxis (Schultz et al., 1994). These results deserve further investigation in larger trials with randomized allocation because of the greater practicability of two single treatments as compared with weekly prophylaxis.

Other Interventions

A recent observational study from Sri Lanka reported a 53 percent reduction in very low birth weight (birth weight <1,500 g) for women who reported having taken mebendazole during the pregnancy as compared with those who did not (de Silva et al., 1999). Because of the potential for confounding differences between women who took the drug and those who did not, however, no causal inference can be drawn with confidence. Yet in light of the beneficial effect of treatment on maternal anemia (Stoltzfus and Dreyfuss, 1998), a randomized trial is likely to be unethical.

Although antenatal care could theoretically have a beneficial impact, evidence for the efficacy of early antenatal care or frequent visits to the clinic in improving intrauterine growth or gestational duration is unconvincing (Kramer, 1987; Alexander and Korenbrot, 1995). The type of antenatal care received may be more important than early initiation or frequent visits, but no definitive conclusions are possible based on the available evidence. In Latin America, for example, 2,235 women at higher-than-average risk for delivering an LBW infant were given psychosocial support and health education through four home visits between weeks 22 and 34 of gestation, but such care did not reduce the incidence of IUGR or preterm delivery (Villar et al., 1992). Indeed, despite the evidence that psychosocial stress may be an important contributor to preterm birth, social support during pregnancy has not been shown to reduce the risk (Hodnett, 2002). A recent cluster-randomized trial in Argentina, Cuba, Saudi Arabia, and Thailand investigated whether a reduced number of antenatal care visits that still included antenatal actions that are evidence-based would affect the birth outcome; no impact was observed on either preterm birth or IUGR (Villar et al., 2001). In fact, a recent systematic review of randomized trials yielded no strong evidence that the content, frequency, or timing of currently recommended antenatal care visits has an effect on reducing the incidence of IUGR or preterm delivery (Carroli et al., 2001).

One particular aspect of antenatal care of beneficial potential is the timely recognition and treatment of cervical incompetence. The diagnosis of cervical incompetence is usually based on some combination of previous second- or early third-trimester pregnancy loss and first- or early second-trimester cervical dilatation, although the criteria used are highly variable (Berry et al., 1995). Where resources permit, placement of a cerclage stitch may be beneficial in reducing the risk of preterm birth (Grant, 1989; Medical Research Council/Royal College of Obstetricians Working Party on Cervical Cerclage, 1993). The safety and efficacy of cerclage remain controversial, however, and a recent systematic review of randomized trials has yet to be published (Drakely et al., 2002).

Although pregnancy-induced hypertension is a major cause of both

IUGR and preterm birth, antihypertensive treatment has not proven efficacious in lowering the risks (Gülmezoglu et al., 1997). Prophylaxis with low-dose aspirin or other antiplatelet agents in women at risk of developing pre-eclampsia is associated with a small and statistically borderline reduction in the risk of preterm birth (RR = 0.92 [95 percent CI = 0.88-0.97]) and IUGR (RR = 0.92 [95 percent CI = 0.84-1.01]) (Knight et al., 2002).

Strategies for reducing neonatal and infant mortality among LBW infants that do not depend on neonatal intensive care or other expensive technologies would be of particular benefit to the least-developed countries. Breastfeeding and/or use of expressed breast milk represent one such "low-tech" strategy, which can reduce infection (and perhaps mortality due to infection) in LBW infants (Narayanan et al., 1980, 1981). For infants born weighing less than 2,500 g in areas where resources for perinatal and neonatal care are scarce, nurseries are overcrowded, and staffing is insufficient, the Kangaroo method of care may be a feasible therapeutic intervention for improving the survival of these neonates (Charpak et al., 1994). Kangaroo mother care is an intervention for LBW babies in which the mother acts as an "incubator" by providing skin-to-skin contact with her newborn in an effort to keep the infant's temperature within a normal range. Further studies of this method are needed, however, to determine its efficacy in reducing mortality (Conde-Agudelo et al., 2002).

RECOMMENDATIONS

Although LBW (particularly IUGR) is very frequent in low- and middle-income countries, these countries tend to have very high infant mortality not only in LBW but also in normal-weight infants. Efforts to reduce infant mortality on a population-wide basis have thus far been more successful than efforts to reduce LBW. Therefore, while not abandoning their attempts to prevent IUGR and preterm birth, developing countries should focus their efforts on preventing infant death in normal-weight, as well as LBW, fetuses and infants, with only limited, if any, reliance on neonatal intensive care units (NICUs) and other expensive medical technologies. Antenatal maternal steroids, infant warming, oxygen, antibiotics, and nasal continuous positive airway pressure are inexpensive and feasible interventions even in resource-poor countries.

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- **Early detection and timely management of asymptomatic urinary tract infection**

- **Intermittent prophylactic and early treatment of malaria, especially for primiparae.**
- **Counseling and other forms of support to stop smoking during pregnancy.**

(See Chapters 2, 3, 7, and 8 for other components of this recommendation.)

RESEARCH NEEDS

Several lines of research will be instrumental for the improvement of existing interventions to prevent IUGR and preterm birth and the creation and implementation of additional options to further address their impact. Priorities for such research include:

- Testing strategies to improve maternal energy intake prior to and during pregnancy; such research should consider how different approaches (supplementation, nutritional advice, etc.) might be applied in different settings.
- Designing and testing interventions to reduce the risk of preterm birth posed by bacterial vaginosis and genital tract infection.
- Measuring the impact of IUGR and preterm birth on child morbidity, growth, and neurocognitive development.
- Determining the long-term consequences of IUGR as a risk factor for chronic adult diseases, and the economic impact of those consequences in developing countries.

CONCLUSION

Although data on the worldwide prevalence of IUGR and preterm delivery are incomplete and of variable quality, it is reasonable to conclude that LBW due to both causes is a major public health problem throughout the developing world. Some high-income countries have succeeded in lowering their rates of IUGR. Preterm birth is more resistant to intervention; currently, proven strategies for preventing preterm birth are limited to the treatment of asymptomatic bacteriuria, smoking cessation, and (perhaps) fish oil supplementation. For certain groups of high-risk women, calcium supplementation, antiplatelet agents, and cervical cerclage (where resources permit) may be of benefit.

Maternal undernutrition is the single most important cause of IUGR in low- and middle-income countries. There is good evidence from systematic reviews of randomized trials that increasing food intake during pregnancy can increase fetal growth and reduce the risk of IUGR. However, no evidence is available that public health *programs* in poor countries have succeeded in increasing food intake and thereby reducing the risk of IUGR. Factors other than nutrition that increase the risk of IUGR, such as pregnancy-induced hypertension, cigarette smoking, and malaria during pregnancy, can be addressed through antenatal care.

As economic conditions improve in developing countries, more and better food tends to be available to pregnant women, resulting in decreased rates of IUGR. To reduce the prevalence of IUGR in low-income settings in the face of continued poverty remains a difficult challenge.

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Summary of Findings: Reducing Mortality and Morbidity from Birth Defects

- In developing countries, more than 4 million children are born each year with birth defects. As infant mortality and morbidity due to infectious diseases, birth asphyxia, and other causes are controlled, the relative contribution of birth defects is expected to increase.

- Birth defects have three major causes: genetic, environmental, and complex genetic or unknown. The prevalence of individual conditions varies in different populations.

- The path to reducing the impact of birth defects may be viewed as a multistage process, beginning with the introduction of practical, low-cost interventions for prevention and early diagnosis and treatment where possible, followed by provision of more elaborate treatment and therapy, then by genetic screening and possible termination of pregnancies with a severe birth defect.

- Basic reproductive care, including family planning and preconceptional, antenatal, and neonatal care, is the foundation for reducing birth defects.

- Specific interventions for reducing the prevalence and impact of birth defects include: folic acid supplementation for all women of reproductive age; universal fortification of salt with iodine; rubella immunization during childhood; and efforts to encourage women to limit their childbearing years to before age 35 and to limit alcohol consumption.

- Even where health care resources are limited, there are affordable strategies for the treatment and rehabilitation of some conditions when they are diagnosed early.

- Countries with comprehensive health care and lower infant mortality rates can further reduce infant mortality by establishing preconceptional, antenatal, and neonatal screening programs for common and severe birth defects.

7

Reducing Mortality and Morbidity from Birth Defects

About 2 to 3 percent of all children are born with a birth defect (Van Allen and Hall, 1996). In 2002, there were about 133 million births reported, 90 percent of them in less developed countries (Population Reference Bureau, 2002). Thus in developing countries, about four or more million children are born with birth defects. Birth defects or congenital anomalies are defined as any structural or functional abnormality determined by factors operating largely before conception or during gestation. Birth defects may be apparent immediately after birth or may manifest themselves later in life. As infant mortality and morbidity due to infectious diseases, birth asphyxia, and other causes are controlled, the burden of disease associated with birth defects becomes more important. Comprehensive, reliable data on birth defects are not available for most developing countries. However, there can be no doubt that birth defects cause enormous harm in circumstances where risk factors for many conditions are elevated and resources for health care are limited.

Prevention of certain birth defects can be addressed in almost all settings. This chapter reviews the causes of some of the birth defects that are more prevalent in developing countries and describes ways to reduce their impact through prevention, early identification and treatment, and in settings with more resources, through screening for genetic diseases. A companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* (Institute of Medicine, 2003) discusses these topics in greater detail and describes the treatment of birth defects beyond the neonatal period.

PATTERNS OF OCCURRENCE

While individually rare, birth defects taken together account for a significant proportion of mortality and morbidity among neonates, infants, and children. Figure 3-1 in Chapter 3 shows that congenital anomalies are responsible for 11 percent of global neonatal mortality. Their contribution to neonatal morbidity is also substantial. The role of birth defects increases as other health problems are addressed and infant mortality rates are reduced.

The birth prevalence of individual conditions varies widely in different populations. In low-income countries, birth defects that cause early death or chronic lifelong disability may have a birth prevalence as high as 45 per 1,000 live births—triple that in wealthy countries (World Health Organization, 1985). Two factors that contribute substantially to the birth prevalence and prevalence of birth defects in different settings are inadequate health care and advanced maternal age (Kuliev and Modell, 1990; World Health Organization, 1997, 1999).

Many countries lack health-related statistics and registries, and about one-third of all births—an estimated 40 million each year—are not registered (Murray and Lopez, 1996; World Health Organization, 1997, 1999). Data are also incomplete on birth defects in developing countries, but some large-scale programs monitor the occurrence of birth defects in specific regions of the world. These include the International Clearinghouse for Birth Defects Monitoring System (ICBDMS), the Latin American Collaborative Study of Congenital Malformations (ECLAMC), the Chinese Birth Defects Monitoring Program (CBDMP), and the European Register of Congenital Abnormalities and Twins (EUROCAT). Data from these registries and from the research literature inform this chapter's descriptions of the pathology of birth defects and their patterns of occurrence in developing countries.

CAUSES OF BIRTH DEFECTS

Birth defects can be divided into three classes, based on their known or suspected causes: genetic birth defects, which include chromosomal abnormalities and single-gene disorders; birth defects of environmental origin, caused solely by teratogens such as infectious agents, drugs, and nutritional deficiencies; and complex genetic or unknown causes, which may result from interactions among a few or several genes and may be influenced by environmental factors (see Table 7-1). Chromosomal abnormalities and single gene mutations are important demonstrable causes of birth defects (Nelson and Holmes, 1989).

The specific conditions included in this chapter were chosen because of

TABLE 7-1 The Cause and Classification of the Birth Defects Included in This Report[a]

Cause	Classification	Selected Birth Defects
Genetic	Chromosomal	Down syndrome
	Single gene	α-and β-Thalassemias Sickle cell disorder G6PD[b] deficiency
Environmental (teratogenic)	Infectious diseases	Congenital rubella syndrome
	Insulin-dependent diabetes mellitus	Cardiovascular and nervous system damage
	Hyperthermia	Neural tube defects
	Maternal nutritional deficiencies	
	Folic acid	Neural tube defects
	Iodine	Iodine deficiency disorders
	Medications	
	Thalidomide	Limb reduction deformities
	Misoprostol	Several
	Anticonvulsants	Several
	Anticoagulants	Neurologic damage
	Recreational drugs	
	Alcohol	Fetal alcohol syndrome
	Pollutants	
	Organic mercury	Neurological damage
	Ionizing radiation	Neurological damage
Complex genetic and unknown	Congenital malformations involving single organ systems	Congenital heart disease Neural tube defects Cleft lip and/or cleft palate Talipes or clubfoot Developmental dysplasia of the hip

[a]The birth defects included in this report were selected for their severity, prevalence in developing countries, and having effective, affordable interventions to reduce their impact. Additional birth defects are included in the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* (Institute of Medicine, 2003).
[b]G6PD = Glucose-6-phosphate dehydrogenase.

their severity and prevalence in developing countries, and because of the availablity of affordable, effective interventions that can reduce their impact. What is known, and not known, about these birth defects—their prevalence, burden of disease, biological origins, associated risk factors, prevention, and treatment—informs the committee's overall recommendations.

Genetic Birth Defects

Chromosomal disorders

Sporadic (nonhereditary) losses or rearrangements of genetic material affect at least 10 percent of conceptions, 90 percent of which end in spontaneous abortion. Surviving infants may have a congenital malformation, mental retardation, or disorders in sexual differentiation (World Health Organization, 1999). Advanced maternal age is the only well-documented risk factor (Nicolaidis and Petersen, 1998), and this is relatively constant across races and ethnic groups (Carothers et al., 2001).

Down syndrome is caused by abnormalities involving chromosome 21. The most common form is the presence of an extra chromosome 21 (trisomy 21) in cells of the fetus or infant, the extra chromosome usually coming from the mother. The risk of trisomy 21 increases with maternal age, first slowly then more rapidly above 35 years of age. Affected infants have many problems, including life-threatening cardiac and gastrointestinal abnormalities, susceptibility to infection, and unpredictable and varying degrees of mental impairment, from profound to moderate or even mild (Bishop et al., 1996). Even with the best care, including antibiotics and corrective heart surgery, many die in early infancy or childhood and very few survive middle age. Congenital heart disease associated with Down syndrome is the major cause of death. In resource-poor situations, mortality is very high. Down syndrome can also result in a spontaneous abortion.

The estimated incidence of Down syndrome at birth in developing countries is considerably higher than in developed countries (Kuliev and Modell, 1990; United Nations Population Fund, 1998; World Health Organization, 1996). This is consistent with the proportion of births to women over 35 years of age, which averages 11 to 15 percent in developing countries compared with 5 to 9 percent in developed countries (World Health Organization, 1999).

Single-gene disorders

More than 6,000 different single-gene (Mendelian or monogenic) conditions have been described (World Health Organization, 1997). Although individually rare, together they are estimated to account for a global birth prevalence of 10 per 1,000 (World Health Organization, 1999). Single-gene disorders are classified by mode of inheritance as autosomal recessive, autosomal dominant, or X-linked recessive. For autosomal recessive traits to be expressed, two copies of the mutated gene must be present; if both parents are carriers of the same disease-causing recessive gene, each child has a 25 percent chance of having the disease and a 50 percent chance of being a carrier.

Consanguineous marriage increases the birth prevalence of autosomal recessive diseases. For example, 93 percent of Palestinian Arabs who are parents of children with rare autosomal disorders have been shown to be related, while in the general population only 44 percent of couples are consanguineous (Zlotogora, 1997). Central nervous system anomalies were associated with consanguinity in studies conducted in the United Arab Emirates (al-Gazali et al., 1999) and Saudi Arabia (Murshid, 2000). Major malformations (including, but not limited to, nervous system anomalies) were found at significantly higher rates among children of consanguineous parents in south India (Kulkarni and Kurian, 1990) and in an Israeli Arab community (Jaber et al., 1992).

Thalassemias are autosomal recessive conditions that result from mutations in genes that synthesize the α- and β-globin chains of the hemoglobin molecule. β-Thalassemias occur most often in Mediterranean populations and are due to the absence or malfunction of the β-globin chains. Children with β-thalassemia major do not present symptoms in the first month of life; then in the second six months they often fail to thrive and may suffer from recurrent bacterial infections, severe anemia, hepatosplenomegaly, and bone expansion, which gives rise to classical thalassemia facies. Left untreated, which is the case in many low-income settings, severe β-thalassemia is fatal in childhood or early adolescence (Weatherall and Clegg, 2001); with regular transfusions, patients live into their twenties and longer if treated to prevent iron overload. α-Thalassemias, which are most prevalent in Asia, may involve mild anemia in some heterozygotes or fetal mortality for severe homozygous states.

Thalassemia has a high incidence in the geographical area extending across the Mediterranean and parts of Africa, through the Middle East, India, and Southeast Asia, and into the Pacific Islands. In these areas, the carrier frequency for β-thalassemia varies from 1 to 20 percent. Carriers for the milder form of α-thalassemia range from 10 to 20 percent of the population in parts of sub-Saharan Africa to 40 percent or more in parts of the Middle East, India, and Papua New Guinea. Carriers of the more severe form of β-thalassemia occur at high frequencies but in a more limited area, which includes parts of Southeast Asia and the Mediterranean (Weatherall and Clegg, 2001).

Sickle cell disease, an autosomal recessive structural hemoglobin abnormality, occurs with increased incidence in populations of Africa and the Mediterranean. The high frequency of sickle cell disease in these populations is attributed to the lower mortality from malaria among heterozygotes (carriers of the sickle cell trait) compared with noncarriers (Ashley-Koch et al., 2000). Relatively high rates of consanguineous marriage in the Eastern Mediterranean region have increased the prevalence of sickle cell disease in that population (World Health Organization, 1997).

Children with sickle cell disease are susceptible to episodes of painful vaso-occlusive crises and chronic anemia and are at increased risk for developing infections, including meningitis and pneumonia, which can be fatal. In sub-Saharan Africa, many children with sickle cell disease die early in life (Weatherall and Clegg, 2001).

Epidemiological studies of sickle cell disease suggest a range in the birth prevalence among and within developing countries. The combined carrier rates for sickle cell disease and hemoglobin C disease would be expected to result in about 90,000 affected births per year in Nigeria alone, but the prevalence of the disorder in the general population is low because a large majority of patients with sickle cell anemia (HbSS) die undiagnosed in childhood (Akinyanju, 1989; Angastiniotis et al., 1995).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency results from recessive mutations in the X-linked gene for the enzyme G6PD. More than 100 variants of G6PD deficiency have been identified among the millions of affected people throughout the world. The disorder is most prevalent in Central, West, and East Africa, the Eastern Mediterranean, and South and East Asia (World Health Organization, 1997; El-Hazmi and Warsy, 1996). Individuals deficient in G6PD can develop acute hemolytic anemia as a result of infections, exposure to oxidants, or consumption of fava beans. Severe hemolysis in these cases can be fatal (Steensma et al., 2001). As with the thalassemias and sickle cell disease, carriers of G6PD deficiency have a selective advantage against infection by malaria (Roth et al., 1983).

Birth Defects of Environmental Origin

Maternal illness

The majority of infections during pregnancy do not affect the fetus; those that do, however, can cause fetal loss or severe birth defects. Teratogenic pathogens may exert an immediate effect or initiate complex processes that cause damage throughout gestation and into infancy (Alford and Pass, 1981). Although infections cause only a fraction of total birth defects, they are an important preventable cause.

Congenital rubella syndrome (CRS) results from maternal infection with rubella virus in early gestation. The condition interferes with critical organ development in the fetus and can cause a spectrum of birth defects including blindness, deafness, cardiovascular anomalies, and mental retardation. The prognosis for infants with severe CRS is poor. For those diagnosed in the first year, mortality is high and most survivors are seriously impaired (Bos et al., 1995).

In unimmunized populations, rubella epidemics occur about every 4 to 7 years (Cutts et al., 1997). Over the last 25 years, surveillance of these epidemics has documented CRS birth prevalence rates of 0.6-2.2 (Banatvala, 1998) and 0.6-4.1 (World Health Organization, 2000a) per 1,000 live births. Higher rates are found when follow-up is after two or more years, as deafness or psychomotor retardation are more likely to be detected after infancy.

Noninfectious maternal conditions. Several conditions can cause birth defects. Pregnant women with preexisting insulin-dependent diabetes mellitus (IDDM) have a higher risk for fetal loss (American Diabetes Association, 2000); surviving infants are prone to central nervous system, cardiovascular, renal, and limb defects (Khoury et al., 1989).

Hyperthermia (fevers of 39°C or higher for at least 24 hours) during the first 4 weeks of pregnancy is associated with higher rates of neural tube defects (NTDs) and other birth defects (Chambers et al., 1998; Warkany, 1986; Kalter and Warkany, 1983).

Maternal nutrition

Folate deficiency early in pregnancy is associated with NTDs such as spina bifida, encephalocele, and anencephaly (see description of NTDs in section on birth defects of complex and unknown origin.). Supplementation of the maternal diet with 400 micrograms of folic acid per day before conception and during the next 28 days protects the fetus against NTDs (Berry et al., 1999; MRC Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992).

Iodine deficiency disorders (IDD) include mental retardations, hypothyroidism, goiter, cretinism, and varying degrees of other growth and developmental abnormalities, which result from inadequate thyroid hormone production as a result of an insufficient iodine intake. Cretinism, the most severe form of iodine deficiency, causes profound mental retardation (Sankar et al., 1998). Severe maternal iodine deficiency begins to affect the fetus in the second trimester of pregnancy, and the damage becomes irreversible at the end of that trimester (DeLong et al, 1985). In endemic areas, where up to 100 percent of the population does not consume adequate iodine (Ali, 1995; Yusuf et al., 1996; Wyss et al., 1996; Geelhoed, 1999; Kouame et al., 1998), nearly every developing fetus is at high risk for IDD (Mittal et al., 2000). In 1990, it was estimated that 43 million people worldwide are suffering from varying degrees of brain damage due to IDD (United Nations Children's Fund, 1998). In several countries, the prevalence of cretinism is between 0.5 and 11 percent of the population (Bellis et al., 1998; Geelhoed 1999; Jalil et al., 1997; Kouame et al., 1998; Sankar et al., 1998; Wyss et al., 1996; Yusuf et al., 1996).

Medications

Several drugs taken during pregnancy can pose a risk to the fetus (Briggs et al., 1994; Koren et al., 1998). This is of particular concern in the developing world since most women do not know for several weeks that they are pregnant, and there may be access to drugs without a formal prescription.

Thalidomide was withdrawn from global markets in the early 1960s when it was determined that the sedative, then commonly prescribed for morning sickness, had caused severe limb and organ defects in more than 8,000 infants in 46 countries (Koren et al., 1998; Vanchieri, 1997; Grover et al., 2000). Thalidomide is once again available in many countries for indications including leprosy and HIV (Castilla et al., 1996). As a result, 34 infants have been reported to be born with thalidomide embryopathy in areas of South America where leprosy is endemic (Castilla et al., 1996).

Misoprostol, used to treat peptic ulcer and postpartum hemorrhage, has also been used to induce early abortion (Gonzalez et al., 1998; Orioli and Castilla, 2000) The drug is not always effective for this purpose, and surviving newborns have exhibited birth defects attributed to vascular disruption (Gonzalez et al., 1998; Orioli and Castilla, 2000).

Anticonvulsants are estimated to be used by about 1 in 250 pregnant women (Lindhout and Omtzigt, 1992). Phenobarbital, phenytoin, and primidone have each been associated with congenital heart defects or facial clefts, and carbamazepine and valproate with neural tube and other birth defects (Samren et al., 1999). These birth defects do not appear to be associated with maternal epilepsy itself (Holmes et al., 2001). Polytherapy with anticonvulsant drugs has been shown to carry a higher risk than monotherapy for causing birth defects (Samren et al., 1999).

Anticoagulants. Exposure during the first trimester of pregnancy to coumarin derivatives such as Coumadin (warfarin) can cause nasal hypoplasia, stippling of bones, and neurological damage. Exposure in the second trimester has been associated with brain damage (Vitale et al., 1999).

Alcohol

A safe level of alcohol has not been established for pregnant women. The teratogenic risk of maternal binge drinking during pregnancy is uncertain, but studies suggest that a single heavy binge at a critical period of embryonic development can cause fetal damage (Gladstone et al., 1996). Used regularly and heavily during pregnancy, alcohol is associated with fetal alcohol syndrome (FAS) and alcohol-related neurodevelopmental disorder (ARND). This syndrome is characterized by altered facial features, fetal growth reduction, and behavioral and cognitive effects (Institute of Medicine, 1996). With or without FAS, mental retardation is the most serious and common effect of alcohol use during pregnancy. (See chapter 4.)

Teratogenic pollutants

Teratogens including heavy metals, pesticides, and solvents are associated with a variety of birth defects (Jacobson and Jacobson, 1996; Ramsay and Reynolds, 2000), but there is little information on exposure in developing countries.

Methylmercury, an organic form of mercury, causes birth defects in the central nervous system and, to a lesser extent, the liver and kidneys (Institute of Medicine, 2000). Mass methylmercury poisoning, which occurred in Japan in the 1950s (Eto et al., 2002) and in Iraq in the 1970s (Marsh et al., 1987), resulted in severe neurological dysfunction and developmental abnormalities among children exposed *in utero*. The adverse effects include mental retardation, cerebral palsy, deafness, blindness, and dysarthria.

Ionizing radiation

Studies of atomic bomb survivors demonstrated that ionizing radiation during gestation can damage the developing brain, particularly when exposure occurs 8 to 25 weeks after ovulation (Schull and Otake, 1999). Diagnostic radiography involves a low level of X-ray exposure of the fetus so that, with protection, the risk of a birth defect is small (Fattibene et al., 1999; Fenig et al., 2001).

Birth Defects of Complex and Unknown Origin

The origins of most birth defects have not been established; many of them are thought to be due to the additive effects of a few (oligogenic) or many (polygenic) genes, which may interact with nongenetic (environmental) factors. These conditions are usually limited to a single organ system and include the following examples: NTDs, congenital heart disease, cleft lip and/or cleft palate, talipes, and developmental dysplasia of the hip.

Neural tube defects (NTDs)

These include a range of congenital malformations that result from incomplete development of the brain and spinal cord or their protective coverings. Worldwide, NTDs (particularly the two major types, anencephaly and spina bifida) are estimated to affect 300,000 or more infants each year (Murray and Lopez, 1998). The birth prevalence of NTDs varies widely among countries, due in part to genetic and environmental factors and to differences in the availability of antenatal screening and termination of severely affected pregnancies (Shibuya and Murray, 1998). Epidemiological studies show a strong association between NTDs and inadequate maternal consumption of folic acid during the preconceptional and periconceptional periods.

Spina bifida is a birth defect in which closure of the neural tube (predecessor of the spinal cord) is incomplete. The birth outcome varies with the location of the defect and whether it affects neural tissue, skeletal components, and/or skin. In some cases, the affected infant is born with the spinal cord exposed on the surface as a neural plaque and it may include meningeal tissue. This interrupted development of the spinal cord occurs in the first 4 to 5 weeks of fetal development and causes serious clinical problems that may include paralysis, incontinence, or skeletal deformities, depending on the location and nature of the defect. There may be associated hydrocephalus. Surgery at birth helps and saves some infants, but they may be significantly handicapped (Shibuya and Murray, 1998). In resource-poor situations, the future of an affected child is severely compromised.

Anencephaly is the congenital absence of the cranial vault with cerebral hemispheres missing or reduced to small masses attached to the base of the skull. This fatal condition causes significant mortality before and soon after birth.

Congenital heart disease

These disorders, which occur in about 1 percent of live births, are the leading cause of birth-defect-related deaths despite improvements in diagnostic and life-saving surgical treatments over the last 40 years (Pradat, 1992). A variety of conditions—maternal rubella infection, alcohol abuse, genetic abnormalities, and chromosomal disorders such as Down syndrome—are associated with congenital cardiac malformations.

Typical symptoms and signs of congenital heart disease include cyanosis, pulmonary hypertension, growth retardation, and syncope. In developing countries, many cases cannot be diagnosed at birth. Left untreated, many lesions prove fatal before age 20 (Rygg et al., 1971; Kirklin and

Barrat-Boyes, 1993; Cartmill et al., 1966). Echocardiography, a diagnostic procedure available to urban populations in developing countries, provides a reliable anatomical diagnosis for cases where a cardiac defect is suspected from clinical data.

Cleft lip and/or cleft palate

Congenital malformations of the lip and hard or soft palate may occur individually at each site or together. Affected infants have difficulty first with feeding, then with speech development; stigmatization and discrimination pose lifelong problems. If cleft lip or palate are left untreated, resulting malnutrition and infection can be fatal (Shibuya and Murray, 1998). Cleft lip and/or cleft palate are often associated with additional birth defects that co-occur with a genetic syndrome (Shibuya and Murray, 1998). Birth prevalence rates for oral clefts from several countries are between 1 and 2 per 1,000 live births. Facial cleft is associated with maternal or environmental factors and with birth order (Cooper et al., 2000).

Talipes or clubfoot

This condition includes a spectrum of abnormalities in the ankle joints and bones, muscles, and ligaments of the foot, which is twisted out of shape. In severe cases, bones may be smaller than normal, with displacement of the joint. When bones are normal in shape and size, the deformity is maintained by contracted muscles, tendons, and ligaments (Sinha, 1987). The incidence of talipes at birth is approximately 1 in 1,000, but in some populations the incidence might be greater. Talipes is often associated with other severe congenital malformations, particularly spina bifida.

Developmental dysplasia of the hip (DDH)

This condition is due to the abnormal position of the head of the femur relative to the acetabulum (American Academy of Pediatrics, 2000), which causes pain and osteoarthrosis (Leck, 2000). Swaddling or diapering infants with their thighs extended increases the risk for DDH, because this position separates the head of the femur from the acetabulum. The prevalence reported for DDH also varies with the diagnostic criteria used (Bialik et al., 1999; Dunn et al., 1985; Herring, 1990). Hospital-based studies in Singapore (Ang et al., 1997) and Israel (Bialik et al., 1999) have reported birth prevalence rates of DDH of about 5 per 1,000 live births. Females with DDH outnumber males 5 to 1, presumably due to sexually-related differences in the shape of the acetabulum and the pelvis.

REDUCING THE IMPACT OF BIRTH DEFECTS

A Multistage Process

The path to reducing the impact of birth defects may be viewed as a multistage process: (1) low-cost preventive strategies, (2) early diagnosis and treatment, and (3) screening for genetic disorders. This report includes recommendations from the first stage of this process. Recommendations for stages two and three, and older infants, children, and adults, are described in the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World*.

Stage One: Low-Cost Preventive Strategies

Basic reproductive care provides the foundation for improving neonatal and infant mortality and reducing birth defects. It includes:

- Family planning to educate young adults regarding pregnancy timing, spacing, and contraceptive methods so that they can make informed choices on childbearing.
- Preconceptional care to address risk factors for birth defects and provide the means to minimize those risks.
- Antenatal care to reinforce preconceptional care and treat maternal illnesses that can cause birth defects in the developing embryo and fetus.
- Neonatal care to permit early diagnosis and timely treatment of birth defects, thereby minimizing or preventing complications and reducing disability due to birth defects.

This basic, yet effective framework of care can be established in countries with high infant mortality rates and limited health care resources. Once in place, and as resources and needs dictate, this framework can be augmented with additional interventions that address the risks that underlie many birth defects.

Folic acid vortification

Provision of adequate dietary folic acid periconceptionally or very early in pregnancy protects infants against NTDs. Folates are present in leafy vegetables, legumes, and citrus, but it is unlikely that dietary advice alone can assure the consumption of sufficient amounts of these foods. Fortification of staple foodstuffs at a level estimated to provide women with 400 micrograms of folic acid per day overcomes the logistical problems of supplementation: provision of folic acid before and very early in pregnancy, and compliance with the complete regimen. Almost universal folic acid coverage is possible and relatively inexpensive (Oakley, 2002). Supplementation is useful in settings where fortification is not possible or is below the recommended level (United Kingdom, Committee on Medical Aspects of Food and Nutrition Policy, 2000).

Iodine fortification

Correction of maternal iodine deficiency before conception is necessary to avoid adverse effects on the fetus. The daily adult requirement for iodine is met with 100 to 150 micrograms and an additional 50 micrograms during pregnancy and lactation (Stanbury, 1998). The accepted strategy for eliminating iodine deficiency is through universal iodization of salt (Stanbury, 1998). This has been implemented in many developing countries (United Nations Children's Fund, 2001); the coverage of households in iodine-deficient areas of the world has increased over the past decade from 10 to 68 percent (Delange et al., 2001).

Fortification is generally 25-50 mg of iodine per kilogram of salt. Fortified salt costs only slightly more ($0.02-$0.06 per person annually) than the unfortified product, and salt manufacturers generally cooperate in the iodination process once they understand its importance. An alternative strategy for populations with severe iodine deficiency complicated by endemic cretinism is the administration of iodized oil (Delange, 1996; Geelhoed, 1999).

Discouraging pregnancy in older women

The simplest means of preventing chromosomal disorders, such as Down syndrome, is to decrease the number of pregnancies among women older than 35 years. This strategy requires that family planning is widely available, along with appropriate information about Down syndrome and risk factors.

Limiting alcohol consumption

A safe level of maternal alcohol use has not been established. The lack of clear evidence complicates the choice between no use of alcohol and restricted use of alcohol during pregnancy. All women should be informed before and during pregnancy about the hazards of alcohol. (See chapter 4.)

Rubella immunization

Rubella infections are common worldwide. The effectiveness of rubella vaccination in reducing congenital rubella syndrome (CRS) depends on the susceptibility of women of childbearing age, the burden of disease due to CRS, the strength of the immunization program, the infrastructure and resources for immunization, record of injection safety, and other disease priorities (World Health Organization, 2000a). Rubella should be included in immunization programs that reach more than 80 percent of the population. Where immunization coverage is lower, it should be increased before introducing rubella immunization because low coverage can interrupt natural transmission during childhood and actually increase the number of women who are not immune during their childbearing years (Banatvala, 1998). The most rapid reduction in CRS is achieved through mass immunization campaigns that reach children so that immunity is reached by adolescence. Where resources permit, testing for rubella antibodies before conception allows those who test negative to be immunized provided they can prevent pregnancy during the immunization process.

Avoiding teratogenic medications during pregnancy

Avoidance of birth defects due to teratogenic medications such as thalidomide, misoprostol, anticonvulsants, and anticoagulants requires awareness on the part of medical workers and women of childbearing age. Educational campaigns, health messages, and preconceptional counseling on the prevention of birth defects should include information on medications to be avoided.

Stage Two: Early Diagnosis and Treatment of Birth Defects

Even where health care resources are limited, there are affordable, effective treatments[1] for some birth defects. Early diagnosis of the following conditions permits therapeutic or surgical interventions before the condition becomes more severe.

Talipes or clubfoot

In some infants, this can be resolved through manipulation and passive stretching, followed by well-molded plaster casts, while others may require surgery (Porter, 1987). In any case, early intervention is critical to obtain a foot that is supple, painless, and of normal shape and function. Serial manipulation to elongate the contracted tissues should begin within a day or two of birth (Sinha, 1987). By 12 weeks of age, the soft tissues of the

[1]The companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* also addresses rehabilitiation of individuals with birth defects.

infant foot are less pliable and surgery may be required to correct the condition (Sinha, 1987).

Cleft lip and/or cleft palate

Early establishment of feeding is a top priority for infants with cleft lip and/or cleft palate. Primary surgery must wait until the infant is 3 months old for repair of the lip and 6 months old for repair of the palate (Smith et al., 1991). International foundations such as Operation Smile provide such surgery during periodic missions to low-income countries.

Congenital heart disease

Developing countries do not have the infrastructure to treat most cases of congenital heart disease (CHD). Researchers estimate that hundreds of thousands of children are born each year with surgically treatable CHD. Without treatment, most will die as children (Pezzella, 1998; McGrath, 1992; Rygg et al., 1971, Kirklin and Barrat-Boyes, 1993).

Developmental dysplasia of the hip (DDH)

Diagnosis and treatment of DDH is more successful for children under two years of age (Kim et al., 1990). Early treatment maintains the thighs in a flexed and partly abducted position so that the head of each femur remains deep within the acetabulum, more completely encompassed by the acetabulum. Dislocated hips that fail to respond to early splinting, and those detected and treated in older children, can be corrected by surgical procedures (Kim et al., 1990).

Stage Three: Screening for Genetic Disorders

In countries where good reproductive health care is in place and infant mortality has been decreased, screening for genetic disorders becomes the next important step to further decrease infant mortality (World Health Organization, 2000b). These programs require more resources and more highly trained staff than programs for basic reproductive health care, but they too can be cost-effective.[2]

[2]See the companion report, *Reducing the Impact of Birth Defects: Meeting the Challenge in the Developing World* (IOM, 2003), for more in depth coverage of this topic.

Genetic screening

Whereas diagnosis of a birth defect involves accurate testing of individual patients, genetic screening involves testing of a clinically normal population and identifies most, but not all, persons at high risk for a specific disorder or condition or of producing offspring with a defect. Priority should be given to genetic testing for the birth defects that impose the heaviest burdens on the population as a whole. Genetic data should only be used to benefit members of a family or ethnic group and should be treated as confidential at all times (World Health Organization, 1997).

β-Thalassemia major is easy to diagnose and effective—but costly—treatment is available. Without diagnosis and treatment, those with β-thalassemia major usually die early in childhood; thus the population prevalence is a fraction of the birth prevalence. Where diagnosis and treatment are available, patients survive longer, the population prevalence increases, and treatment costs increase. In Greece (Loukopoulous, 1996), Sardinia (Cao et al., 1991, 1996), Iran (Habibzadeh et al., 1999), and Cyprus (Modell et al., 1991), screening programs have significantly reduced the birth prevalence of β-thalassemia.

Sickle cell disease (SCD) can be addressed through preconceptional genetic screening to identify and counsel couples at risk for having a child with SCD and antenatal screening followed by diagnosis and counseling regarding sickle cell in childhood. Where appropriate, families should be offered the option of termination of pregnancy. In some populations, neonates, rather than adults, are screened (Lees et al., 2002) to allow early treatment of SCD (such as penicillin prophylaxis and pneumococcal vaccination to prevent potentially fatal infections), early education of parents on the care of affected children, and education about the risk for future pregnancies.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency screening is primarily used to detect the disorder after birth in order to control the occurrence and severity of hematological crises. It also alerts carriers of their status (Verjee, 1993; Meloni et al., 1992). Several screening tests are quick, easy, inexpensive and suitable for large populations. Positive screening results are generally confirmed by enzyme assay. The definitive assay requires laboratory equipment generally not available in those countries where G6PD deficiency is common.

Preconceptional screening

Preconceptional screening of national populations or groups at high risk for carrier status can be undertaken for serious recessive birth defects where they are prevalent, a reliable test is available, and the condition is amenable to prevention. Iran and Cyprus screen nationally for β-thalassemia, while Cuba screens nationally for SCD. Preconceptional screening has three components: recording and evaluating a genetic history, laboratory testing where indicated, and counseling. Genetic histories can identify clinically normal couples at risk for passing an inherited birth defect to their offspring. If these couples are determined to be at risk, they should receive counseling and appropriate care.

Antenatal screening and diagnosis

Antenatal screening can identify most pregnancies at high risk for Down syndrome, NTDs, and single gene disorders (Baird, 1999). Screening and a follow-up diagnosis for those who screen positive are generally done before 20 weeks gestation. This timing allows parents to plan for the care of an affected child, the time and place of delivery if surgery is needed at birth, or to consider termination of the pregnancy in the case of severe birth defects. There is agreement in many countries that termination of pregnancies must not be offered for the purpose of gender selection (Wald et al., 2000).

Neonatal screening and diagnosis

Early diagnosis and prompt, appropriate treatment of some birth defects can reduce some life-threatening or disabling sequelae. Even when little can be done to assist the infant, accurate diagnosis of birth defects alerts parents to their risk in future pregnancies. Early neonatal screening is important for G6PD deficiency to treat jaundice and prevent kernicterus, for phenylketonuria to allow early dietary intervention, and for hypothyroidism to allow thyroid replacement therapy (Wald and Leck, 2000). The diagnosis of Down syndrome can be made clinically at birth and confirmed by chromosome analysis (karyotyping).

Counseling on genetic risks

Parents have the right to be appropriately informed and counseled about screening services, to choose whether to accept them, and to receive continuing support independent of that choice. When antenatal screening and diagnosis reveal a birth defect, counselors should provide information and support to parents. When a birth defect is severe and termination of the pregnancy is a consideration, counseling and health care should support the decision of the parents.

Genetic counselors, whether physicians or primary care workers, need to be trained and tested in the content and delivery of the information they provide. In addition, the content of consultations with parents should be documented and monitored. Counselors provide the link between the health care system and the social, religious, and legal foundations of society, which together determine the availability of reproductive choices.

RECOMMENDATIONS

Despite incomplete data on birth defects, several studies have established that birth defects are an important public health problem in developing countries. Basic reproductive health care, an essential component of primary health care, can prevent or reduce the impact of birth defects by providing education for parents regarding avoidable risks for birth defects, effective family planning, effective preconceptional and antenatal care and educational campaigns to stress their importance, and neonatal care that permits the early detection and management of birth defects.

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- **Discouragement of women from childbearing after age 35 to minimize the risk of chromosomal birth defects such as Down syndrome.**
- **Immunization against rubella for women before they reach reproductive age.**
- **Routine and continuous provision of 400 micrograms of folic acid per day for all women of reproductive age**
- **Universal iodine fortification of salt (25-50 milligrams of iodine per kilogram of salt).**
- **Counseling of women to limit alcohol consumption during pregnancy.**
- **Counseling of women and their health care providers on locally relevant teratogenic medications to be avoided during pregnancy.**

(See Chapters 2, 3, 6, and 8 for other components of this recommendation.)

RESEARCH NEEDS

The priorities for research to improve existing interventions against birth defects and to create and implement additional interventions include:

- Operational research to monitor, evaluate, and adjust interventions for maximal clinical- and cost-effectiveness. Because there is considerable variability in the settings in which interventions are undertaken, an intervention proven effective in one setting will still require tailoring in the delivery of services to be fully effective in another setting. The first stage of transferring an "effective" intervention may involve a pilot study that is monitored, evaluated, and adjusted before wider implementation.

- Surveillance to provide basic planning information on maternal, neonatal, and fetal mortality and on infants born with birth defects
- Effective strategies for changing maternal behaviors to minimize the risks for birth defects, including childbearing before age 35 and limiting alcohol consumption during pregnancy.

CONCLUSION

Birth defects have enormous personal and societal consequences in developing countries. Reducing their impact can be accomplished in a multi-stage process in line with the needs, infrastructure, and resources of countries:

- The first stage is the introduction of practical, low-cost interventions to reduce the occurrence of NTDs, iodine deficiency disorders, Down syndrome, FAS, and CRS. Prevention of these birth defects is affordable in almost all settings and can be pursued with little need to gather additional information.
- The second stage of reducing the impact of birth defects is early diagnosis and treatment of infants with birth defects such as cleft lip and/or cleft palate, talipes, and developmental dysplasia of the hip. The conditions treated and level of care will vary with the setting, but should be the best locally available. Undertaking this stage may require an assessment of the burden of different birth defects in the local setting and of the resources available.
- The third stage of reducing the impact of birth defects is genetic screening and counseling on severe birth defects, possibly followed by termination of a severely affected pregnancy. Such programs can be cost-effective in populations where the basic strategies for reducing infant mortality and birth defects have already been implemented, infant mortality rates have been reduced to about 20 to 40 per 1,000 live births, and adequate new resources have been committed. Increased surveillance may be needed to guide health leaders on the genetic disorder(s), such as thalassemias, SCD, and G6PD deficiency, to be screened.

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**Summary of Findings:
Preventing Perinatal Transmission of HIV**

- To date, an estimated 3.8 million children have died of HIV/AIDS. The vast majority of these children acquired HIV from their mothers during pregnancy, childbirth, or breastfeeding.

- In parts of southern Africa, 30 percent or more of pregnant women are infected with HIV, and 25 to 35 percent of their children become infected.

- Considerable evidence indicates that treating pregnant women who are HIV-positive and their infants with simple low-cost regimens of antiretroviral drugs is the most feasible and cost-effective means to prevent perinatal HIV transmission in developing countries.

- The stigma and discrimination borne by women who test positive for HIV/AIDS present significant additional problems to their physical illness.

- Counseling women on the risks and benefits of antenatal HIV screening and treatment must be incorporated into antenatal care, along with options for HIV screening and antiretroviral prophylaxis.

8

Preventing Perinatal Transmission of HIV

The transmission of HIV from mother to fetus or infant presents a pressing challenge to improving birth outcomes in many developing countries. Since the start of the AIDS epidemic, an estimated 3.8 million children have died of the disease. The vast majority of these children acquired HIV from their mothers during pregnancy, at the time of childbirth, or during breastfeeding. Antiretroviral drugs that can be delivered to the mother during pregnancy and labor and to the child after birth, and which are widely used in the United States and other developed countries, have the potential to reverse the epidemic of pediatric AIDS in developing countries (Mofenson and McIntyre, 2000; Coll et al., 2002). Despite their promise, however, such interventions are not common in the developing world.

This chapter describes the scope of the HIV/AIDS epidemic, focusing on heavily infected populations where mother-to-child transmission occurs most frequently, and reviews the evidence for a variety of potential interventions to prevent perinatal transmission of HIV. It concludes with a description of an approach that would prevent new infections. Treatment of pregnant women for their own disease is clearly important, but beyond the scope of this report. The program of interventions described here can be accomplished ethically and at a reasonable cost compared with alternative treatments.

THE HIV/AIDS EPIDEMIC

Since HIV/AIDS was recognized only two decades ago, the disease has reached epidemic proportions in many countries, especially in sub-Saharan

Africa (see Figure 8-1). Worldwide, approximately 3 million people died of AIDS during 2001. By the end of that year, an estimated 40 million people were living with HIV/AIDS—28 million in sub-Saharan Africa alone (Joint United Nations Programme on HIV/AIDS, 2001). In parts of southern Africa the prevalence of HIV in childbearing women may exceed 30 percent. The Joint United Nations Programme on HIV/AIDS estimates that about half of the 15-year-olds now living in the most heavily infected countries in Africa will eventually die of the disease and that it will reduce life expectancy in Southern Africa, which reached a high of 59 years in the early 1990s, to 45 years between 2005 and 2010 (Joint United Nations Programme on HIV/AIDS, 2000a, 1999). This represents a return to life expectancy rates not seen in the region since the early 1950s.

HIV/AIDS is killing large numbers of men and women in developing countries at the most productive time of their lives. They include doctors, farmers, and workers in agriculture, mining, and industry who not only support their families and raise children, but who make important contributions to the social and economic welfare of their countries. The loss of many teachers profoundly affects economic productivity, as it interferes with the development of human capital. Absenteeism, decreased productivity, worker turnover, training costs, funeral and death benefits are increasing across all sectors in many African countries, draining scarce public resources and impeding job creation and foreign investment (Joint United Nations Programme on HIV/AIDS, 2001). Many parents who have died of HIV/AIDS have orphaned children, some of them infected with HIV themselves, who are typically cared for by extended families (Mukwaya, 1999). UNAIDS estimates that there have been 13.2 million AIDS orphans in the world through 2000, 12.1 million in Sub-Saharan Africa (Joint United Nations Programme on HIV/AIDS, 2000a).

HIV in Women of Childbearing Age

In many developing countries, a high proportion of the female population is infected with HIV as compared with the global average. In sub-Saharan Africa, where heterosexual transmission predominates, women constitute 55 percent of the adults living with HIV/AIDS. In South and Southeast Asia and the Caribbean, women make up 30 percent to 50 percent of the HIV-infected adults. By comparison, women constitute about 20 to 40 percent of HIV-infected adults in North America, Western and Central Europe, Latin America, North Africa and the Middle East. The relatively high prevalence of HIV in women of childbearing age in developing countries increases the risk of perinatal transmission (Joint United Nations Programme on HIV/AIDS, 2001; Newell, 2000).

Biological and cultural factors help to explain the high prevalence of

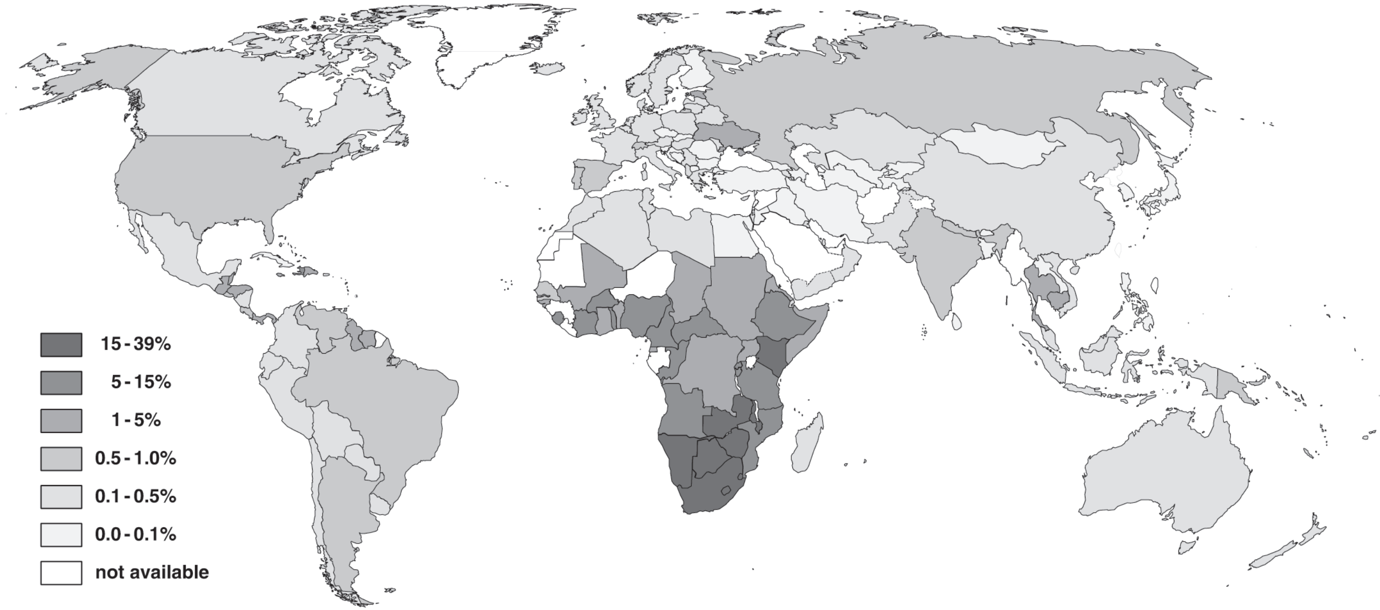

FIGURE 8-1 Worldwide HIV prevalence rates in adults at the end of 2001. Estimates are based in large part on anonymous seroprevalence surveys of women in antenatal care.
SOURCE: Joint United Nations Programme on HIV/AIDS, 2002.

HIV infection among women in the developing world. The subordinate sexual and economic status of women in many cultures contributes to the acquisition of HIV as well as of other sexually transmitted diseases, which also increase susceptibility to HIV infection (Joint United Nations Programme on HIV/AIDS, 2001). In Africa and South Asia, for instance, it is not uncommon for women to be coerced or seduced by older men into having sex. In some cultures there is a myth that if a man infected with an STD including HIV has sexual relations with a virgin, he can cure himself of his disease (Mukwaya, 1999).

In some populations, especially in sub-Saharan Africa, the estimated prevalence of HIV among pregnant women reaches 36 percent (Walker et al., 2002) (see Figure 8-1). In South and Southeast Asia, the overall prevalence in childbearing women is likely to be much lower than in Africa; there, HIV prevalence rates of up to 5 percent have been documented in antenatal clinics. The effects of high HIV prevalence on child mortality can be roughly estimated as follows: if one-third of the childbearing women in a population were infected with HIV, and the risk of mother-to-child transmission was one in three (as has been documented in some developing countries), then about 10 percent of children born in that population would be infected with HIV. Because nearly all HIV-infected children will die before they reach adulthood, these deaths would therefore raise child mortality by approximately 100 per thousand live births. And since maternal mortality negatively affects children's survival, children who were not infected at birth would still face an increased risk of death after losing their mothers to AIDS.

Perinatal Transmission of HIV

Transmission of HIV from mother to child can take place in utero, intrapartum, or postpartum through breastfeeding (Mofenson, 1997). In sub-Saharan Africa and other developing countries, 25 to 35 percent of children born to HIV-infected mothers become infected at birth or shortly thereafter (De Cock et al., 2000; Brocklehurst, 2002). By contrast, the transmission rate in industrialized countries has been reduced to 5 percent or less through programs of antenatal counselling, testing, and antiretroviral treatment for infected women (Mofenson and McIntyre, 2000; Coll et al., 2002).

A series of maternal, obstetrical, and postpartum risk factors can affect the probability and the timing of mother-to-child transmission of HIV. The results of the European Collaborative Study demonstrated a linear relationship of transmission with decreasing maternal CD4+ cell counts, seemingly independent of other factors (European Collaborative Study, 1992). Other studies associate high maternal plasma HIV RNA levels with a significant risk of perinatal HIV infection (Garcia et al., 1999; Mofenson et al., 1999), although transmission may occur even when the virus is undetectable. Separate studies of cohorts of pregnant women in Malawi and the United States have also found an association between low maternal vitamin A levels in pregnancy and increased risk of transmission (Semba, 1997; Greenberg et al., 1997). Other studies (Burns et al. 1999; Fawzi, 2000) did not detect such a trend, however.

Several obstetric factors also influence the rate of perinatal HIV transmission. Prolonged rupture of membranes, instrumentation, vaginal delivery, and birth trauma all increase the child's risk of infection (International Perinatal HIV Group, 2001; Mofenson, 1997). Studies in both humans and primates demonstrate the transmission of HIV through maternal blood or secretions; thus if membranes rupture prematurely or if the mother hemorrhages, the child is at increased risk for infection (Mofenson, 1997). In the postpartum period, breastfeeding is the primary mode of mother-to-child HIV transmission. A randomized trial in Nairobi, Kenya, that compared breastfeeding and formula feeding found that breastfeeding increased the risk of HIV transmission by 16.2 percent, which accounted for 44 percent of HIV infection in the breastfeeding arm of that study. Most—75 percent—of the risk difference between the two arms of the study occurred in the first 6 months, but transmission continued throughout the duration of exposure (Nduati et al., 2000). Coutsoudis and colleagues (2001) have shown that mixed infant feeding (breast milk plus other liquids) is associated with higher rates of transmission than exclusive breastfeeding.

Children in developing countries who contract HIV at birth or shortly thereafter rarely live more than a few years. In several studies in Africa, the probability of death by the age of 12 months in HIV-infected children was found to be about 30 percent, and by the age of 5 years 60 to 90 percent had died (Joint United Nations Programme on HIV/AIDS Reference Group on Estimates, Modelling, and Projections, 2002; Adetunji, 2000; Tudor-Williams, 2000). A study in Malawi concluded that nearly 90 percent of African children infected with HIV do not survive beyond their third birthday (Taha et al., 2000).

INTERVENTIONS TO PREVENT HIV TRANSMISSION

Antiretroviral Strategies

Antiretroviral drugs that have proved effective in the treatment of adults and children with AIDS when administered either individually or in combination have also been tested and compared for their ability to prevent mother-to-child transmission of HIV. These medications include zidovudine (ZDV or AZT); ZDV in combination with lamivudine (3TC); and nevirapine (NVP) (Nolan et al., 2002). Research indicates that with appropriate antiretroviral therapy and elective cesarean delivery, perinatal HIV transmission rates can be reduced to less than 2 percent (Mandelbrot et al., 2001). Table 8-1 summarizes the conditions and results of several key trials described below, many of which were conducted in developing countries.

Zidovudine (ZDV or AZT). A seminal study by the AIDS Clinical Trials Group (ACTG) in 1994 concluded that the antiretroviral drug zidovudine (ZDV), previously known to delay the progression of AIDS in persons with relatively advanced disease, was effective in reducing the risk of perinatal transmission (Connor et al., 1994). Based on these and subsequent results, the protocol used in that study—known as the ACTG 076 regimen—has become the minimum standard of care in industrialized countries (Institute of Medicine, 1999). In the United States, mother-to-child transmission of HIV has fallen by about 70 percent from its peak in the early 1990s (Centers for Disease Control and Prevention, 1999). However, while the ACTG 076 regimen is considered cost-effective in the industrialized world, it is considered too expensive and logistically difficult to establish in most developing countries.

As an alternative to the ACTG 076 regimen, a series of clinical trials of a shorter course of ZDV, which includes daily doses of the drug beginning late in pregnancy, have been carried out in Southeast Asia and sub-Saharan Africa. One of two short-course ZDV trials that have been conducted in Thailand, the Bangkok trial, found that a short-course regimen reduced mother-to-child HIV transmission by 50 percent, at a cost of about $200 to $400 per person (Shaffer et al., 1999; Mofenson and McIntyre, 2000). A follow-up study found that 81 percent of the children who received ZDV had no significant adverse events associated with treatment by 18 months (Chotpitayasunondh et al., 2001). The second Thai study, the Perinatal HIV Prevention Trial (PHPT), compared several different ZDV regimens using the same doses as one of the regiments in the Bangkok trial. A short prenatal/short postnatal arm of the trial was stopped early because the transmission rate was significantly higher than in the long prenatal/long postnatal arm. At 18 months, the transmission rate was found to be significantly lower in the long prenatal treatment arms (Lallemant et al., 2000; Mofenson and McIntyre, 2000).

Both African ZDV studies, which took place in Ivory Coast and Burkina Faso, were placebo-controlled trials in which the mothers breastfed. The Ivory Coast trial yielded a 37 percent reduction in the rate of transmission (Wiktor et al., 1999), while the DITRAME ANRS 049 study, conducted in Ivory Coast and Burkina Faso reported a 38 percent reduction in transmission (Dabis et al., 1999).

A recent Cochrane Review (Brocklehurst and Volmink, 2002) concluded that the effectiveness of zidovudine therapy from 28 weeks in pregnancy for the mother through 3 days for the infant (the long-short term course) and from 35 weeks in pregnancy for the mother to 6 weeks for the infant (the short-long term course) provided the same protection as the long-long course.

Combination therapy. With the advent of two- and three-drug combinations to reduce viral loads in people with AIDS, researchers began to evaluate benefits of combining ZDV with other antiretroviral agents to prevent perinatal HIV transmission. Mandelbrot and colleagues (2001) found, using retrospective controls, that a combination of ZDV and lamivudine (3TC) reduced the risk of HIV transmission by almost 80 percent in non-breastfeeding women compared with women taking only ZDV. However, concerns about possible side effects (see toxicity discussion below) and the fact that current treatment guidelines typically call for a three-drug regimen that includes a costly protease inhibitor limit the practical impact of this finding.

The PETRA trial in South Africa, Uganda, and Tanzania tested less intensive ZDV plus 3TC regimes than those used by Mandelbrot and colleagues (2001), and did so in women who mostly breastfed their infants (Petra Study Team, 2002). The study compared a three-part regimen (prepartum, intrapartum, and postpartum) to a combination of intrapartum and postpartum therapy and intrapartum therapy only. At 6 weeks postpartum, the rate of transmission was reduced by 50 percent in the three-part treatment group; the two-part regimen achieved a 37 percent reduction; and the intrapartum-only group was not significantly different from the placebo group. At 18 months the differences between the groups were less pronounced, probably due to the effects of breastfeeding.

A recent Cochrane Review (Brocklehurst and Volmink, 2002) concluded that the combination therapy using zidovudine and lamivudine (3TC) decreased the risk of transmission when the combination is given during the antenatal and intrapartum periods or the intrapartum and postpartum periods, but not when given only in the intrapartum period alone.

Nevirapine. The 1999 HIVNET 012 randomized controlled trial in Uganda found that nevirapine (NVP), a nonnucleoside reverse-transcriptase inhibitor that is rapidly absorbed orally, reduced the risk of perinatal transmission by 47 percent (Guay et al., 1999). This result, which is comparable to results achieved with a short course of ZDV, followed a single intrapartum dose of NVP for the mother and a single dose for the infant after birth. That regime costs about $4—a tiny fraction of the cost of ZDV treatment (Marseille et al., 1999).

The SAINT trial in South Africa compared NVP to a combination of ZDV and 3TC, both regimens administered intrapartum and postpartum. Preliminary results indicate that there was no significant difference in HIV infection in the two groups at 8 weeks postpartum (Moodley, 2000).

TABLE 8-1 Trials of Antiretroviral Treatments to Prevent Mother-to-Child HIV Transmission

Study Name and Reference	Population Characteristics	Treatment (Pre- and Intrapartum to Mother, Postpartum to Child)
ACTG 076 (Connor et al., 1994)	Nonbreastfeeding women in US and France	Pre: 100 mg ZDV orally 5x daily starting at 14-34 weeks gestation Intra: 2 mg/kg ZDV IV for 1 hour, then 1 mg/kg ZDV IV per hour until delivery Post: 2 mg/kg orally 4x daily for 6 weeks
Bangkok trial (Shaffer et al., 1999)	Nonbreastfeeding women in Thailand	Pre: 300 mg ZDV orally 2x daily starting in 36th week of pregnancy Intra: 300 mg ZDV every 3 hours
Perinatal HIV Prevention Trial (PHPT) (Lallemant et al., 2000)	Nonbreastfeeding women in Thailand	Short Pre: 300 mg ZDV orally 2x daily starting at 35 weeks gestation Intra: 300 mg ZDV every 3 hours Short Post: 2 mg/kg ZDV orally every 6 hours for 3 days
		Long Pre: 300 mg ZDV orally 2x daily starting at 28 weeks gestation Intra: 300 mg ZDV every 3 hours Short Post: 2 mg/kg ZDV orally every 6 hours for 3 days
		Short Pre: 300 mg ZDV orally 2x daily starting at 35 weeks gestation Intra: 300 mg ZDV every 3 hours Long Post: 2 mg/kg ZDV orally every 6 hours for 6 weeks
		Long Pre: 300 mg ZDV orally 2x daily starting at 28 weeks gestation Intra: 300 mg ZDV every 3 hours Long Post: 2 mg/kg ZDV orally every 6 hours for 6 weeks
RETROCI (Wiktor et al., 1999)	Breastfeeding women in Ivory Coast	Pre: 300 mg ZDV orally 2x daily starting at 36 weeks gestation Intra: 300 mg ZDV every 3 hours
DITRAME ANRS 049 (Dabis et al., 1999)	Mostly breastfeeding women in Ivory Coast and Burkina Faso	Pre: 300 mg ZDV orally 2x daily starting at 36-38 weeks gestation Intra: 600 mg ZDV at onset of labor Post (maternal): 300 mg ZDV orally 2x daily for 1 week

HIV Status Evaluated	Risk of Transmission (% of Children)		Relative Reduction in Risk (in %)
	Control	Treatment	
18 mo.	25.5	8.3	67
6 mo.	18.9	9.4	50.0
6 mo.	—	10.5	Stopped early
18 mo.	—	4.7	In utero transmission higher with short maternal treatment
	—	8.6	
	—	6.5	
3 mo.	24.9 26.1	15.7 16.5	37 37
6 mo.	27.5	18.0	35

(continued)

TABLE 8-1 Continued

Study Name and Reference	Population Characteristics	Treatment (Pre- and Intrapartum to Mother, Postpartum to Child)
RETROCI and DITRAME pooled analysis (Peiperl, 2001)		As above
	Nonbreastfeeding women in France	ACTG 076 regimen (historical controls)
		ACTG 076 regimen plus 150 mg 3TC orally 2x daily starting at 32 weeks gestation and 2 mg/kg orally 2x daily for 6 weeks to child
PETRA (Petra Study Team, 1999)	Mostly breastfeeding women in South Africa, Tanzania, and Uganda	Intra: 300 mg ZDV every 3 hours and 150 mg 3TC orally every 12 hours
		Intra: as above Post (maternal): 300 mg ZDV and 150 mg 3TC orally 2x daily for 1 week
		Pre: 300 mg ZDV and 150 mg 3TC orally 2x daily starting at 36 weeks gestation Intra: as above Post (maternal): as above
		Intra: 300 mg ZDV every 3 hours and 150 mg 3TC orally every 12 hours
		Intra: as above Post (maternal): 300 mg ZDV and 150 mg 3TC orally 2x daily for 1 week
		Pre: 300 mg ZDV and 150 mg 3TC orally 2x daily starting at 36 weeks gestation Intra: as above Post (maternal): as above

HIV Status Evaluated	Risk of Transmission (% of Children)		Relative Reduction in Risk (in %)
	Control	Treatment	
15 mo.	30.6	21.5	30
6 mo.	26.1	16.9	
12 mo.	28.5	18.5	
18 mo.	30.1	21.6	
24 mo.	30.1	22.1	27
18 mo.	6.8		
		1.6	78
6 wk.	17.2	17.1	0
	17.2	10.8	37
	17.2	8.6	50
18 mo.	26.6	25.7	3
	26.6	24.4	8
	26.6	20.7	22

(continued)

TABLE 8-1 Continued

Study Name and Reference	Population Characteristics	Treatment (Pre- and Intrapartum to Mother, Postpartum to Child)
HIVNET 012 (Guay, 1999)	Breastfeeding women in Uganda	Intra: 600 mg ZDV orally at onset of labor and 300 mg ZDV every 3 hours Post: 4 mg/kg orally 2x daily for 1 week
		Intra: 200 mg NVP orally at onset of labor Post: 200 mg/kg NVP orally at 48-72 hours postpartum
		Intra: 600 mg ZDV orally at onset of labor and 300 mg ZDV every 3 hours Post: 4 mg/kg orally 2x daily for 1 week
		Intra: 200 mg NVP orally at onset of labor Post: 200 mg/kg NVP orally at 48-72 hours postpartum
SAINT (Moodley, 2000)	Mostly breastfeeding women in South Africa	Intra: 600 mg ZDV and 150 mg 3TC orally at onset of labor and 300 mg ZDV and 150 mg 3TC orally every 3 hours Post: 12 mg ZDV and 6 mg 3TC orally 2x daily for 1 week Post (maternal): 300 mg ZDV and 150 mg 3TC orally 2x daily for 1 week
		Intra: 200 mg NVP orally at onset of labor Post: 6 mg NVP orally at 24-48 hours postpartum Post (maternal): 200 mg NVP orally at 24-48 hours postpartum

A recent Cochrane Review (Brocklehurst and Volmink, 2002) stated that one large randomized trial demonstrates that nevirapine given to the mother as a single dose at the onset of labor and to the infant as a single dose within 72 hours of birth is more effective than an intrapartum and post partum regime of zidovudine.

Toxicity and risks associated with antiretroviral therapy. Given the

HIV Status Evaluated	Risk of Transmission (% of Children)		Relative Reduction in Risk (in %)
	Control	Treatment	
14-16 weeks	25.1	—	47
	—	13.1	
1 yr.	24.1	—	35
	—	15.7	
8 weeks	10.8	—	Difference not significant
	—	14.0	

known vulnerability of the developing fetus to toxicity, the potential side effects of any drug used in utero must be investigated. While some antiretroviral drugs have been shown to be carcinogenic in rodents, no such effects have been detected in short-term human studies or reported to a registry maintained by the drugs' manufacturers (Culnane et al., 1999; Mofenson and McIntyre, 2000). Overall, it is likely that the risk of serious drug-associated side effects to the child is small compared with the averted risk of HIV infection and death.

Based on eight cases in France, researchers have postulated a link between mitochondrial dysfunction and exposure to ZDV or a combination of ZDV and 3TC (Blanche et al, 1999). These authors have recommended that antiretroviral treatment to prevent perinatal HIV transmission be limited to ZDV alone to minimize the dangers of mitochondrial damage or toxicity. Recent evidence of toxic side effects from NVP, including severe liver damage in health care workers who took the drug for postexposure prophylaxis, has been attributed to taking multiple doses of the drug; a single dose is typically used to prevent perinatal HIV transmission. Having compared the costs and benefits of NVP use in both situations, the Centers for Disease Control and Prevention (CDC) has advised against using the drug for postexposure prophylaxis while continuing to recommend it for the prevention of perinatal transmission (Centers for Disease Control and Prevention, 2001).

There are also concerns about the development of resistance to antiretrovirals (Mandelbrot et al., 2001; Morris et al., 2001; Hirsch, 2002; Euroguidelines Group for HIV Resistance, 2001). It is unlikely that NVP-resistant strains of the virus would be tramsmitted during labor or delivery (Joint United Nations Programme on HIV/AIDS, 2000b). Transmission during breastfeeding is a greater concern, however, as NVP-resistant virus has been observed in adults receiving chronic NVP treatment as a single agent and after single dose prophylaxis (Eshelman and Jackson, 2002). This possibility would be minimized through the use of combination therapies which include NVP or another nonnucleoside reverse transcriptase inhibitors (NNRTIs) (Mandlebrot et al., 2001).

Cost of antiretroviral drugs. Recently, pharmaceutical companies that produce anti-AIDS medicines responded to concerns about the prices of these drugs. The companies agreed to offer ZDV, NVP and other AIDS drugs—at prices discounted by up to 90 percent—to developing countries that have been severely affected by the AIDS epidemic, and Roxane Laboratories, the manufacturer of NVP, has offered to provide it free to some countries. The governments of some African nations were originally reluctant to accept these offers, however, due to the cost of developing the necessary infrastructure for drug distribution, patient education, and laboratory monitoring. Moreover, a *Washington Post* article (Gellman, 2000) reports that Secretary-General of the United Nations Kofi Annan's advisers said in a memo that even at a 90 percent discount, treatments to save the lives of people with AIDS can cost hundreds to thousands of dollars per person, an amount that is unrealistic in developing countries. However, the simple courses of ZDV and NVP that are necessary to prevent perinatal transmission are far less costly than treatment regimens for HIV-infected adults and children.

Cost of programs to administer ART. Introducing and sustaining programs to administer antiretroviral therapy in resource poor countries, even short-term therapies, involves resources well beyond the cost of the drugs. These programs involve the counseling and testing of pregnant women: those who are infected with HIV need information and support in dealing with their own infection, while those who are not infected should be provided with information and support to avoid future infection. Although the cost of the drugs has become more affordable, development of appropriate infrastructure including trained staff is a separate and substantial challenge.

Nonantiretroviral Strategies

Cesarean section. A meta-analysis of North American and European studies found that elective cesarean section reduces the risk of mother-to-child transmission of HIV by more than 50 percent, independent of treatment with ZDV (International Perinatal HIV Group, 1999). It is postulated that the reduced risk of perinatal HIV transmission is the result of minimizing the infant's exposure to body fluids in the maternal genital tract. However, safe and effective cesarean sections are not available to many women in the developing world, and some studies in both developing and industrialized countries have found an increased rate of maternal complications in HIV-infected women who have undergone the procedure (Mofenson and McIntyre, 2000). Thus, cesarean section may be an appropriate strategy for preventing perinatal transmission of HIV, but only when performed in appropriately staffed and equipped health facilities, where the risks associated with cesarean section are low.

Vaginal lavage. Viricidal cleansing of the birth canal and the infant's skin immediately after delivery has been examined as a potentially inexpensive, low-technology method of reducing perinatal HIV transmission. To date, its efficacy has not been demonstrated. Therefore, additional research and well designed randomized, controlled trials are needed.

Vitamin A therapy. Therapeutic doses of vitamin A have been shown to be ineffective in preventing perinatal transmission of HIV, so vitamin therapy is not recommended at this time (Kumwenda et al., 2002; Fawzi et al., 2002b).

Breast milk substitutes. The HIV epidemic has raised difficult questions about breastfeeding in areas where there is a high prevalence of HIV among lactating women and where infants are at high risks for diarrhea and malnutrition (Fowler et al., 1999). The rate of postnatal transmission of HIV through breastfeeding is high (Fawzi et al., 2002a). While early weaning may reduce transmission, this must be balanced against risks of malnutrition and diarrhea in a particular setting. Antiretroviral drugs to the mother may also reduce risk of breast milk transmission. Breastfeeding by HIV-positive mothers is discouraged in industrialized countries, where safe and affordable alternatives to breast milk are available. The choice is complicated in developing countries, where breastfeeding has proven benefits and artificial feeding has established risks. In 1998, UNAIDS, WHO, and UNICEF issued a joint statement that supports breastfeeding, but also encourages voluntary and confidential testing for both men and women of reproductive age, and promotes education regarding the implications of their HIV status for the health and welfare of their children. "When children born to women with HIV can be ensured uninterrupted access to nutritionally adequate breast milk substitutes that are safely prepared, they are at less risk of illness and death if they are not breast fed. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases children's risk of illness or death" (World Health Organization, Joint United Nations Programme on HIV/AIDS, 1998).

Breastfeeding has been promoted for many years for its reduction of mortality due to infectious diseases including neonatal sepsis, acute respiratory infections, and diarrhea (Arifeen et al., 2001; Ashraf et al., 1991; World Health Organization Collaborative Study Team, 2000). Discouraging breastfeeding now may be both unsafe and socially unacceptable in certain settings. Programs to reduce breastfeeding or limit its duration among HIV-infected women (and thus decrease transmission to their infants) must not reduce breastfeeding among women who are not infected with HIV, and must ensure that safe and affordable breast milk substitutes are available as long as needed (World Health Organization, 2000). In addition, maternal antibodies in breast milk confer immunity to the child (Nicoll et al., 1995), so breastfeeding can protect against infectious diseases. Finally, since breastfeeding is the norm for infant feeding in the developing world, a woman who does not breastfeed tacitly admits that she is HIV-positive, which in turn may cause her to be rejected by her mate and community.

Comparing Preventive Interventions

Of all of the options discussed, it appears that treating pregnant women who are HIV-positive, and their infants, with simple low-cost regimens of antiretroviral drugs is the most effective and feasible means to prevent perinatal transmission in developing countries. The success of this strategy depends upon access to antenatal care, so that HIV-positive women can be identified before (or at least by) the time of delivery. To increase the effectiveness of antiretroviral treatment, infants of HIV-positive mothers should be fed a breast milk replacement where safe, appropriate, and feasible.

A number of available antiviral regimens for preventing perinatal HIV transmission are known to be safe and effective (World Health Organization, 2000). Although less effective than the ACTG 076 regimen used in developed countries (see Table 8-1), short-course ZDV and intrapartum NVP have both been shown to reduce the HIV transmission rate by up to 50 percent at a much lower cost. The choice of regimen should be determined according to local circumstances on the grounds of costs and practicality, particularly as related to the availability and quality of antenatal care (World Health Organization, 2000).

Unlike most types of interventions that could improve birth outcomes in developing countries, AIDS prevention programs—including those to prevent perinatal HIV transmission—have been the subject of many cost-benefit analyses. Table 8-2 summarizes the results of several studies that examine antenatal HIV screening and the subsequent treatment of women who test positive, as well as their infants, to prevent HIV infection. Although the details of these studies differ, all indicate that perinatal HIV prevention programs can be effective at a relatively low cost. Given the high opportunity cost to the economy of losing a life at a young age, antenatal HIV screening appears to cost-effective even at low prevalence rates. Where prevalence is high, the cost-effectiveness of antenatal HIV prevention programs can be substantially less than $100 per disability-adjusted life years (DALY) saved, and may actually save money for the health care system (Stoto and Goldman, 2003). This compares favorably with the four most effective public health interventions for children under 5 years of age in developing countries: control of respiratory and perinatal infections, diarrheal diseases, and vaccine-preventable diseases (World Bank, 1993).

A number of caveats, however, must be heeded when interpreting such economic analyses. First, because many assumptions must be made without hard data, there is a large amount of uncertainty in the results. These educated guesses, however, do establish the order of magnitude of the results, which sometimes is enough for policy comparisons. Second, new developments with respect to the cost and efficacy of the medication, as well as efficiencies in counseling and testing and other aspects of screening and treatment, are likely to make the economic comparisons more favorable, so the cost estimates presented here should be seen as conservative.

Barriers to Implementing Antenatal Screening

Despite evidence of the cost-effectiveness of antenatal HIV screening, few developing countries have decided to implement national screening programs. Some countries have pilot programs underway; others have con-

TABLE 8-2 Cost-Effectiveness Analyses of Antenatal HIV Screening Programs

Several published cost-effectiveness analyses have evaluated antenatal HIV screening programs on the individual, health sector, and social level. Program costs include counseling women in antenatal care, testing them for HIV, and treating those who are found to be positive to prevent transmission to their children (except for one study of NVP treatment provided to all pregnant women). All costs are based upon actual local costs for program administration, but are expressed in terms of U.S. dollars.

Population Characteristics	HIV prevalence in pregnant women (percent)	Treatment regimen(s)	Cost per case averted	Reference
Sub-Saharan Africa	12.5	Two doses of 300 mg ZDV/day beginning 2 to 6 weeks before delivery and 300 mg per 3 three hours in labor	$1,269 (a savings of $1.06 million per 100,000 births)	Mansergh et al. (1996, 1998)
Sub-Saharan Africa	15	ZDV and 3TC daily starting at the 36th week of pregnancy and continuing for 1 week postpartum	$5,134	Marseille et al. (1998)
Sub-Saharan Africa	15	ZDV and 3TC starting at delivery, continuing through 1 week postpartum	$2,680	Marseille et al. (1998)

Sub-Saharan Africa	15	ZDV and 3TC administered intrapartum only	$1,129	Marseille et al. (1998)
Rural South Africa (KwaZulu/Natal district)	26	ACTG 076 (see Table 8-1)	$5,806 ($5,591 with enhanced service infrastructure)	Wilkinson et al. (1998)
Rural South Africa (KwaZulu/Natal district)	26	Short course of ZDV with 3TC	$2,492	Wilkinson et al. (1998)
Sub-Saharan Africa	15, 30	NVP administered 200 mg oral dose given to all women in labor and 2 mg given to infant after birth	$276, $138	Marseille et al. (1999)
Sub-Saharan Africa	15, 30	NVP administered 200 mg oral dose given to HIV-positive mother (identified through counseling and testing) in labor and 2 mg given to infant after birth	$506, $298	Marseille et al. (1999)
Urban, working-class South Africa (Soweto)	15	Short course ZDV before and during birth plus formula supplied	less than $100 (formula recommended); $669 (formula supplied)	Söderlund et al. (1999)

sidered implementing such programs but have declined to do so, citing their cost as well as social, cultural, and ethical concerns.

Cost. The cost of treating individuals with HIV may exceed a developing country's national health budget on a per capita basis. In sub-Saharan Africa, for instance, the annual budget for health care averages $24 per capita (World Bank, 1993). Antenatal screening and treatment with NVP costs less than $10 per pregnant woman, most of which pays for counseling and HIV testing; however, only pregnant women (not the whole population) incur costs. A more relevant comparison, therefore, might be made with antenatal and delivery care, which typically costs $90 per woman in the poorest developing countries (World Bank, 1993); that figure would increase by less than 10 percent were it to include the cost of HIV screening.

Social, cultural, and ethical concerns. In light of the evidence that a program of antenatal HIV screening and prophylaxis of infected mothers to prevent transmission is both effective and cost-efficient under most if not all circumstances, one might argue that not to implement antenatal HIV screening is unethical. However, acceptability of HIV counseling and testing has limited implementation for treatment programs in some settings (Meda et al., 2002). If stigma and discrimination associated with HIV infection is high—if women who are known to have AIDS or HIV infection endure beatings and may be disowned by their families (Berer, 1999; Mukwaya, 1999)—it is understandable that women might want to avoid HIV testing, especially during pregnancy, a time of great vulnerability. Concerns about stigma and discrimination also interfere with women's ability to accept antiviral treatment for themselves and bottle-feeding for their infants. A study in Rwanda suggested that women 35 years and older and those whose partners had skilled and well-paid jobs were more likely to accept HIV testing (Kowalczyk et al., 2002). Clearly, the stigma associated with HIV status must be removed through extensive social programs if efforts to prevent transmission are to succeed, but such changes will take time. Women must meanwhile be counseled frankly about the costs and benefits of HIV testing and treatment if necessary for themselves and their children and be allowed to make their own decisions.

Policy makers in developing countries have also questioned the appropriateness of treating women to prevent transmission of HIV at birth if (a) there is a high risk of transmission later through breastfeeding and (b) parents are likely to die of HIV disease before the infant reaches adulthood. Many observers believe that a life is worth saving whatever the risks that the child faces later in life, and that antenatal HIV screening with prophylaxis offers many children a chance to live into adulthood. Moreover, it can be argued that the main risks facing children saved from HIV infection can themselves be mitigated. The risk of transmission through breastfeeding can be eliminated or reduced through the provision of alternatives such as formula, and most AIDS orphans can be raised by extended families, as they are today in many developing countries. Children saved from HIV infection through antenatal screening programs may represent a burden on society and especially their relatives during early life, but they have the potential to contribute significantly to society and the economy, as well as to the welfare of their extended families. If resources are not sufficient to provide treatment to all HIV-infected citizens, treatment of pregnant women should be considered seriously in setting priorities, because of transmission from mother to baby.

One might also ask whether it is ethically appropriate to treat a mother with a short course or a single dose of drugs that would benefit her child, but not the mother herself. Many observers have argued that it is, given the inability of many developing countries to pay for lifelong therapy for people with HIV, the tangible benefits to the child, and the satisfaction that many women get from selflessly protecting their children. Prophylaxis of pregnant women also can be distinguished from other treatment programs in that it aims to prevent new AIDS cases, and is far more effective in doing so than other measures.

In the United States, where HIV prevalence rates in childbearing women are low and many women are well informed about HIV and AIDS, the Institute of Medicine has recommended that prenatal care for all women include HIV testing, with notification of results to the patient (Institute of Medicine, 1999). In developing countries, where women might be less aware of HIV/AIDS, for example among women in India (Chaterjee, 1999), and where prevalence rates may be higher, counseling and informed consent for HIV testing in antenatal care should be more intensive and focused on helping women make informed choices for themselves.

Guidelines for Antenatal HIV Screening

A recent summary of the characteristics of a well-organized perinatal public health screening program (Institute of Medicine, 1999), which draws upon earlier principles developed by WHO (Wilson and Jungner, 1968), is relevant to countries considering antenatal HIV screening programs:

- The goals of a screening program must be clearly specified and achievable.
- The natural history of the condition should be adequately understood, treatment for those found positive must be widely accepted by the medical community, and there should be evidence that early intervention improves health outcomes.
- The screen should be able to distinguish individuals likely to have the condition from those not likely to have it.

- There must be adequate resources to diagnose and treat every person with the condition.
- The test and intervention should be acceptable to the affected population.

Given the evidence discussed in this chapter, and understanding "treatment" as short-course ZDV or intrapartum NVP intended to prevent transmission to the infant, antenatal HIV screening programs would likely be judged to be ethically appropriate in most developing countries where the prevalence of HIV in childbearing mothers is high and where resources exist to treat them.

RECOMMENDATIONS

Antenatal screening and prophylaxis programs represent the most immediate means to reducing perinatal HIV transmission. The reduced cost of drug therapy makes them more comparable with other health and economic investments. The most significant cost is, however, that associated with building the health care infrastructure needed to deliver testing, counselling, and drugs.When the social costs of AIDS are considered, especially in populations with a high prevalence of HIV[1] in childbearing women, antenatal screening programs in developing countries appear to be cost-saving; in populations with low prevalence rates, the per capita cost can be low. In order to implement antenatal HIV screening programs as quickly as possible, international support should be organized to supplement limited resources of developing countries.

The social cost of HIV/AIDS is very high in terms of the stigma and discrimination borne by women who test positive, especially those who have little power. Fear of the consequences of a positive test and the lack of resources to treat HIV infection in developing countries turn women away from testing. In addition, relatively few women in developing countries realize that HIV can be transmitted to their children, or that effective measures to reduce the risk of transmission are available. Thus education regarding the risks and benefits of antenatal HIV screening and treatment must be incorporated into antenatal care along with options for HIV screening and antiretroviral prophylaxis.

There are inadequate data on which to base specific recommendations on breastfeeding or formula feeding by HIV-infected women in developing countries. Although formula feeding eliminates the risk of vertical trans-

[1]HIV is generally considered to be a public health problem in populations where the seroprevalence is above 1 percent.

mission of HIV, the use of unsafe water to reconstitute infant formula poses an even greater hazard to neonates in most settings. Accordingly, the benefits and disadvantages of breast and formula feeding need to be assessed simultaneously, and HIV-infected women should receive counseling on infant feeding options appropriate to the woman's cultural, social, and economic circumstances and support for her individual choice.

Recommendation 4. The following strategy is recommended for incorporation into preconceptional and antenatal care in all settings:

- **In areas where HIV is a public health problem** (seroprevalence **exceeds 1 percent), antenatal screening for HIV should be provided to women who, after counseling, give their informed consent. Women who test positive should receive antiretroviral prophylaxis to prevent mother-to-child transmission of the virus, along with appropriate counseling on infant feeding options.**

(See Chapters 2, 3, 6, and 7 for other components of this recommendation.)

The success of programs to prevent perinatal HIV transmission—and indeed of all efforts to reduce the global impact of AIDS—rests on the longer-term prospect of removing the stigma associated with the disease. Countries should use every means possible to reduce this stigma, which presents a major barrier to the prevention and treatment of HIV/AIDS. It is possible that incorporating HIV screening as a routine part of antenatal care for all women will contribute to that goal.

RESEARCH NEEDS

Despite considerable progress over the last decade, optimizing the prevention of perinatal HIV infection, especially in low-resource settings, will require ongoing study. The committee therefore recommends research on the following topics to support the previous recommendation.

- Identifying effective and efficient ways to implement antenatal HIV screening programs in developing country settings.
- Discovering effective counseling techniques that increase women's awareness of the risks and benefits of antenatal HIV screening and encourage them to make informed choices regarding testing.
- Identifying barriers to women accepting HIV testing and discovering means to overcome them.
- Developing and testing rapid HIV diagnostic tests suitable for field settings to be used late in pregnancy or in the intrapartum period.

• Selecting the most effective antiretroviral drugs, doses, and regimens for reducing perinatal HIV transmission, and determining the extent to which the effectiveness of treatments can be preserved while reducing duration of therapy, drug dose, and cost.

• Identifying effective alternatives to antiretroviral medications for reducing the risk of transmission from mother to child, especially during breast feeding.

• Finding effective ways to reduce the stigma associated with AIDS.

CONCLUSION

Preventing perinatal HIV transmission will not substantially reduce mortality in the target populations served by this study (mothers, fetuses, and neonates). However, as the swiftest and most affordable means of reducing the number of new AIDS cases in developing countries, prevention of mother-to-child infection represents a key opportunity for antenatal care in developing countries. Because stigma and discrimination associated with HIV infection may pose a considerable barrier to diagnosis, successful programs to prevent perinatal transmission will need to educate pregnant women about the risks and benefits of antenatal HIV screening and prophylaxis.

Clearly, the most reliable means of preventing perinatal HIV transmission is to prevent infection among women of childbearing age. Achieving this long-term objective will require the implementation of primary prevention strategies, as well as the education and empowerment of women. For the near term, the evidence and analyses reviewed in this chapter demonstrate that the goal of preventing HIV infection in substantial numbers of children born to infected women in developing countries is well within reach.

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9

Summing Up: The Way Forward

How can procreation in developing countries be made a safe event that results in the birth of a healthy baby to a healthy mother? This is the fundamental challenge for this committee and for readers of this report. Over the last 50 years, the survival of young children has been significantly improved; now it is time to address the health of mothers, fetuses, and neonates. The interventions recommended in this report provide a set of tools for the first stage of this formidable task, focusing on the vast—and to a considerable extent, uncounted—numbers of maternal, neonatal, and fetal deaths that occur in developing countries.

The committee's findings and recommendations are supported by broad knowledge. Some of its conclusions draw on rigorous reviews of randomized trials of individual interventions, while some are founded on less rigorous observational studies of the effectiveness of one or several interventions in health systems. Many of the recommended interventions have been undertaken successfully in countries with limited resources, such as Sri Lanka and Cuba.

PRIORITIES

Reproductive health care priorities vary with mortality rates and local needs for obstetric and neonatal care and the resources that can be mobilized to meet these needs. Ideally, each country will identify and implement the interventions to improve birth outcomes that best meet its needs and resources. In many settings, it is not realistic to expect that all or even most of the strategies recommended in this report can be undertaken simultaneously. Highest priority should then be accorded the report's first two recommendations, which call for skilled attendance at delivery and, in the event of complications, timely access to good-quality essential obstetric and neonatal care. These interventions address key weaknesses in the health services of many countries that result in high maternal, neonatal, and fetal mortality. These strategies can be further supported through programs of effective antenatal and postpartum care, as specified in two subsequent recommendations. These four recommendations have the potential to greatly improve birth outcomes and can be implemented now.

The challenge for developing countries, given their limited resources and important health care needs, is how to most effectively and widely undertake these interventions. The implementation of interventions and development of next steps is addressed in the committee's final three recommendations, which establish a framework for long-term improvement of birth outcomes based on promising strategies and committed leadership, surveillance of pregnancy- and birth-related mortality and morbidity, and the public health capacity for implementing interventions and monitoring them for clinical- and cost-effectiveness. Surveillance of adverse birth outcomes enables the identification, prioritization, and evaluation of interventions based on evidence of their effectiveness. This process is key to making wise choices among alternative interventions and programs to improve birth outcomes, and is even more crucial where resources are limited. Each country will also need to conduct operational research, as its resources permit, to identify and improve interventions to meet specific needs and expectations.

THE SKILLED BIRTH ATTENDANT

In this report a "skilled birth attendant" is defined as a midwife, physician, or nurse who has completed nationally recognized professional training and is proficient in basic techniques for clean and safe delivery; recognition and management of prolonged labor, infection, and hemorrhage; and recognition and resuscitation of neonates who fail to initiate respiration at birth. In countries with sufficient resources, the most effective way to reduce maternal, neonatal, and fetal mortality is through education, training, and oversight on clean and safe labor and delivery for qualified health staff and recognition and referral of complicated deliveries. It is important to recognize that past efforts to train and supervise traditional birth attendants (TBAs) have generally not produced birth attendants with the knowledge, skills, and caseload required to manage a normal delivery safely or the ability to promptly address complications by referral to appropriate medical care. As a result, high rates of maternal, neonatal, and fetal mortality have continued unabated in primary care programs that rely on TBAs.

In some countries it is not possible at this time to provide a midwife, physician, or nurse to attend every birth, and researchers continue to look for ways to provide effective, low-cost care for uncomplicated childbirth. Such services could potentially be provided by caregivers with less formal education and training than a skilled birth attendant, if these caregivers are supervised by skilled staff and under conditions where essential obstetric care is readily accessible. However, any savings gained by reducing the educational requirements for attendance at childbirth may be offset by the attendants' greater need for supervision, higher demands on essential obstetric care, or inability to reduce mortality during childbirth.

A promising trial has been conducted in rural India using trained, supervised village health workers to provide home-based neonatal care (see Box 3-1). Countries seeking the least expensive means to improve birth outcomes are encouraged to undertake similar rigorous trials to determine whether the findings for the rural India trial can be extended to include maternal, as well as neonatal care, and to determine whether this model or some modification thereof can be effective for labor and delivery in different settings. It should be emphasized that the Indian village health workers had 5 to 10 years of formal education; received intensive training in neonatal care, including the identification and treatment of neonatal infections; and were well supervised. The intensively monitored setting of this model is likely to have contributed to its effectiveness. By contrast, there is no rigorous evidence that TBAs (who lack the education, close supervision, and sometimes the training of the village health workers) can be effective in substantially reducing maternal, neonatal, and fetal mortality.

ESSENTIAL OBSTETRIC AND NEONATAL CARE

Because complications of childbirth are not predictable and increase the risk for adverse outcomes, timely access to good-quality essential obstetric care must be provided to reduce maternal, neonatal, and fetal mortality. The goal of basic and comprehensive essential obstetric care, and of neonatal care emphasizing the diagnosis and treatment of infection, is the prevention of maternal, neonatal, and fetal death. This is in contrast to routine hospitalization for delivery, which is not affordable in many countries where health care resources are severely limited.

Basic essential obstetric and neonatal care could be provided in clinics that already exist in many countries if personnel received adequate training. However, significant barriers must be overcome to increase the awareness and need for safe deliveries, especially among women living in rural areas. Successful referral systems in these areas must therefore build good-quality essential care that can be available on a 24-hour basis and address care-seeking behavior, communication, transportation, and the cost of services.

CONCLUSION

This report defines the most pressing health care needs of women, neonates, and fetuses in developing countries. While it also demonstrates the potential to effectively and affordably address those needs, the means of achieving this potential within health care systems are multiple and the choices among them complex. Many factors limit the availability of good-quality health care in developing countries. These include limited financial and human resources for health care, particularly the lack of trained staff and adequate facilities; poverty, and its accompanying burden of infectious disease and malnutrition; illiteracy; widely dispersed populations; and certain cultural and traditional practices that impede effective care.

These limitations must be recognized and reflected in the design and implementation of programs to improve maternal, neonatal, and fetal health. Such programs should be tailored to each country's needs and resources, as well as to the social and cultural context of the health care setting. In general, however, the delivery of good-quality preconceptional, antenatal, obstetric, and neonatal services will require the overall strengthening of primary health care and systems of referral. At the same time, development of these services provides a capacity that strengthens the overall quality of health care. The improvement of birth outcomes therefore represents a key step toward the greater goal of health for all.

BOX 9-1 Report Recommendations
Improving Birth Outcomes Now

Recommendation 1. Every delivery, including those that take place in the home, should be assisted by a skilled birth attendant (a midwife, physician, or nurse) who has been trained to proficiency in basic techniques for a clean and safe delivery; recognition and management of prolonged labor, infection, and hemorrhage; and recognition and resuscitation of neonates who fail to initiate respiration at birth. Where necessary, the birth attendant should also be prepared to stabilize and swiftly refer the mother and/or neonate to a facility providing essential obstetric and neonatal care (Chapters 2 and 3).[1]

Recommendation 2. Essential obstetric and neonatal care should be accessible to address all complications of childbirth that cannot be managed by a skilled birth

[1]This issue is also discussed in Appendix E, Dissenting Note by Dr. Abhay Bang.

attendant. This requires a network of good quality essential care facilities that provide basic essential obstetric care: administration of antibiotic, oxytocic, and anticonvulsant drugs; manual removal of the placenta; removal of retained products of conception; and assisted vaginal deliveries. Comprehensive essential obstetric care facilities have the capacity to perform these basic services and also surgery and blood transfusion. Services for essential neonatal care should emphasize the diagnosis and treatment of infection. Access for the majority of a population to the appropriate level of care also requires strong referral systems that include communication with, and transportation to, referral facilities (Chapters 2, 3, and 5).

Recommendation 3. Postpartum care is critical during the first hours after birth and important throughout the first month. Such care should emphasize: for the mother, the prevention, timely recognition, and treatment of infection, postpartum hemorrhage, and complications of hypertensive disease of pregnancy; and, for the neonate, the prevention, timely recognition, and treatment of infection, thermal control, and promotion and support of early and exclusive breastfeeding (Chapters 2 and 3).[2]

Recommendation 4. The following strategies are recommended for incorporation into preconceptional and antenatal care:

- Greater access for women and men of reproductive age to family planning services that provide effective contraception along with counseling on the risks for adverse birth outcomes (Chapter 2).
- Women should be discouraged from reproducing after age 35 to minimize the risk of chromosomal birth defects such as Down syndrome (Chapter 7).
- Immunization against rubella for women before they reach reproductive age (Chapter 7).
- Routine and continuous provision of 400 micrograms of folic acid per day for all women of reproductive age (Chapter 7).
- Universal iodine fortification of salt (20-50 milligrams of iodine per kilogram of salt) (Chapter 7).
- Immunization against tetanus for all women of reproductive age (Chapter 3).
- Intermittent prophylactic and early treatment of malaria especially for primiparae (Chapters 2 and 6).
- Early detection and timely management of syphilis and other STDs, asymptomatic bacteriuria/urinary tract infection, and tuberculosis (Chapter 3).
- Counseling of women to limit alcohol consumption during pregnancy (Chapter 7).
- Intensive counseling and other forms of support to stop smoking during pregnancy (Chapter 6).
- Early detection and timely management of hypertensive disease of pregnancy (Chapter 2).
- Counseling of women and their health care providers on locally relevant teratogenic medications to be avoided during pregnancy (Chapter 7).
- In areas where HIV is a public health problem (seroprevalence exceeds 1 percent), antenatal screening for HIV should be provided to women who, after counseling, give their informed consent. Women who test positive should re-

[2]See also recommendation 4 with respect to HIV.

(continued)

BOX 9-1 Continued

ceive antiretroviral prophylaxis to prevent mother-to-child transmission of the virus, along with appropriate counseling on infant feeding options (Chapter 8).

Improving Birth Outcomes in the Future

Recommendation 5. Each country should develop a strategy to reduce maternal, neonatal, and fetal mortality, a framework of activities by which this can be accomplished, and the commitment of health leaders to accomplish these goals (Chapter 5).

Recommendation 6. To determine the true burden of disease associated with adverse birth outcomes and measure the effectiveness of interventions to address these problems, basic epidemiological and surveillance data must be collected, analyzed, interpreted, and acted upon. Each country should, as resources permit, incrementally develop complete national demographic data and ongoing surveillance of maternal, neonatal, and fetal mortality and morbidity (Chapter 5).

Recommendation 7. Each country should strengthen its public health capacity for recognizing and implementing interventions that have proven effective in reducing maternal, neonatal and fetal mortality in similar populations. This also involves monitoring and tuning interventions for clinical- and cost-effectiveness in the local setting (Chapter 5).

Appendixes

Appendix A

Workshop Agenda

Improving Birth Outcomes in Developing Countries
Board on Global Health
Institute of Medicine

Foundry Building, Room 2004
Washington, DC

OCTOBER 25, 1999

9:00 Opening and Introduction
Welcome
Judith Bale
Kenneth Shine

Study Charge
Christopher Howson, MOD
Gray Handley, NICHD
Ruth Frischer, USAID

Introduction to Workshop
Adetokunbo Lucas, Co-Chair
Barbara Stoll, Co-Chair

9:30 Opening Session:
Moderator: Barbara Stoll

Reducing perinatal and neonatal mortality: Extent of the problem and possible interventions A review of a May 1999 conference
Robert Black

Improving women's health in developing countries: Life cycle and intergenerational issues
Ann Tinker

10:45 Session I: Adolescents and prepregnancy care
Moderator: Barbara Stoll

Adolescent reproductive health
Kathleen Kurz

Abortions—safe and unsafe
Malcolm Potts

Improving the outcomes of pregnancy
Judith Fortney

Committee questions and discussion

12:45 Session Concluded

1:30 Session II: Antenatal care
Moderator: Barbara Stoll

Averting maternal deaths: A program for the millennium
Allan Rosenfield

A nutritional success story: Folic acid in the prevention of birth defects
Godfrey Oakley

Infectious diseases: HIV/AIDS in developing countries
Zeda Rosenberg

Infectious diseases: Sexually transmitted diseases and adverse outcomes of pregnancy: A global perspective
Michael St. Louis

4:00 Drugs and environmental factors: Impact on birth outcomes
Anthony Scialli

Timing of fetal and neonatal death and potential maternal and neonatal interventions
Brian McCarthy

Committee questions and discussion

5:35 Closing comments
Barbara Stoll

OCTOBER 26, 1999

8:30 Session III: Pregnancy, labor and delivery
Moderator: Adetokunbo Lucas*

Content of antenatal care services
José Villar

Low birth weight and IUGR: Nutritional considerations
José Villar

Birth defects and ECLAMC: Congenital anomalies
Eduardo Castilla

10:45 Why women won't come in for services
Jeanne McDermott

Safe labor and delivery in low-resource settings
— Successes and challenges
— Country case-studies
Jeanne McDermott

Improving intrapartum management
Committee and workshop participants

Committee questions and discussion

1:00 Session Concluded

2:00 Session IV: Newborn and infant care
Moderator: Adetokunbo Lucas

* Moderated by Barbara Stoll.

Resuscitation of the newborn: Outcomes of neonatal asphyxia
Kent Bream

Newborn care priorities in developing countries
— Breastfeeding, warming
— Emergency services
— Neonatal infections
Vinod Kumar Paul

A system for newborn care in India—a promising beginning, but a long way to go
Vinod Kumar Paul

Essential commodities for reproductive health services: Adequacy, availability, cost, and appropriate use
Dennis Ross-Degnan

4:15 Costs and financing of improving birth outcomes in developing countries
Charlotte Leighton

Committee questions and discussion

5:15 Closing comments
Adetokunbo Lucas

Appendix B

Defining Developing Countries

The report uses the term *developing countries* to describe those countries with per capita incomes in 2001 that averaged less than $9,206. These countries are further subdivided into four groups: low income, $745 or less; lower middle income, $746-2,975; upper middle income, $2,976-9,205; and high income, $9,206 or more. Developed countries include those in which per capita incomes in 2001 averaged more than $9,206. The different countries are developing at their own rates and have different capacities and challenges in providing health care services to their populations.

Developing countries tend to share a number of the following characteristics:

- *Low GDP per capita*: In most developing countries, a serious disparity exists between increasing population size and low industrial and agricultural productivity. This situation is often aggravated by heavy external indebtedness, restricted access to global markets, and insecure prices of exportable raw commodities.
- *Young populations*: The pyramidal age structure in most developing countries has a very broad base, due to the relative and absolute predominance of young people, and a narrow tip.
- *High infant mortality and low life expectancy*: Although both indicators have moderated over the last decade, the vital statistics of a majority of the developing countries still lag behind the so-called developed world.
- *Epidemiological transition*: While communicable diseases and mal-

nutrition remain prime causes of morbidity in developing countries, the incidence of noncommunicable diseases such as heart disease, stroke, cancer, and diabetes is increasing, creating a double burden of disease.

- *Weak health care infrastructure*: A shortage of skilled health care workers plagues most developing countries, where the relatively few medical professionals tend to be concentrated in urban areas. Health expenditure per capita in developing countries is typically a fraction of that in the developing world.
- *Social unrest and violent conflict*: The subsequent disruption to and loss of infrastructure reduces the availability of health services. Additionally, the attention and funds for social services and health care are diverted to military and defense efforts.
- *Other features*: Many, but not all, developing countries also suffer the following disadvantages: low literacy rates, especially among women; predominantly traditional, rural forms of social organization; extreme climates; frequent natural catastrophes such as drought, floods, and famine; large-scale population displacement; epidemic rates of HIV/AIDS.

BOX B-1 Classification of Countries by Per Capita Income

Developing Countries

Low Income

East Asia & Pacific
- Cambodia
- Indonesia
- Korea, Dem. Rep.
- Lao PDR
- Mongolia
- Myanmar
- Papua New Guinea
- Solomon Islands
- Timor-Leste
- Vietnam

Europe & Central Asia
- Armenia
- Azerbaijan
- Georgia
- Kyrgyz Republic
- Moldova
- Tajikistan
- Ukraine
- Uzbekistan

Latin America & Caribbean
- Haiti
- Nicaragua

Middle East & North Africa
- Yemen, Rep.

South Asia
- Afghanistan
- Bangladesh
- Bhutan
- India
- Nepal
- Pakistan

Sub-Saharan Africa
- Angola
- Benin
- Burkina Faso
- Burundi
- Cameroon
- Central African Republic
- Chad
- Comoros
- Congo, Dem. Rep.
- Congo, Rep.
- Côte d'Ivoire
- Equatorial Guinea
- Eritrea
- Ethiopia
- Gambia, The
- Ghana
- Guinea
- Guinea-Bissau
- Kenya
- Lesotho
- Liberia
- Madagascar
- Malawi
- Mali
- Mauritania
- Mozambique
- Niger
- Nigeria
- Rwanda
- São Tomé and Principe
- Senegal
- Sierra Leone
- Somalia
- Sudan
- Tanzania
- Togo
- Uganda
- Zambia
- Zimbabwe

Lower middle income

East Asia & Pacific
- China
- Fiji
- Kiribati
- Marshall Islands
- Micronesia, Fed. Sts.
- Philippines
- Samoa
- Thailand
- Tonga
- Vanuatu

Europe & Central Asia
- Albania
- Belarus
- Bosnia and Herzegovina
- Bulgaria
- Kazakhstan
- Macedonia, FYR
- Romania
- Russian Federation
- Turkey
- Turkmenistan
- Yugoslavia, Fed. Rep.

Latin America & Caribbean
- Belize
- Bolivia
- Colombia
- Cuba
- Dominican Republic
- Ecuador
- El Salvador
- Guatemala
- Guyana
- Honduras
- Jamaica
- Paraguay
- Peru
- St. Vincent and the Grenadines
- Suriname

(continued)

Middle East & North Africa
- Algeria
- Djibouti
- Egypt, Arab Rep.
- Iran, Islamic Rep.
- Iraq
- Jordan
- Morocco
- Syrian Arab Republic
- Tunisia
- West Bank and Gaza

South Asia
- Maldives
- Sri Lanka

Sub-Saharan Africa
- Cape Verde
- Namibia
- South Africa
- Swaziland

Upper Middle Income

East Asia & Pacific
- American Samoa
- Malaysia
- Palau

Europe & Central Asia
- Croatia
- Czech Republic
- Estonia
- Hungary
- Isle of Man
- Latvia
- Lithuania
- Poland
- Slovak Republic

Latin America & Caribbean
- Antigua and Barbuda
- Argentina
- Barbados
- Brazil
- Chile
- Costa Rica
- Dominica
- Grenada
- Mexico
- Panama
- Puerto Rico
- St. Kitts and Nevis
- St. Lucia
- Trinidad and Tobago
- Uruguay
- Venezuela, RB

Middle East & North Africa
- Lebanon
- Libya
- Malta
- Oman
- Saudi Arabia

Sub-Saharan Africa
- Botswana
- Gabon
- Mauritius
- Mayotte
- Seychelles

High Income: Non-OECD

- Andorra
- Aruba
- Bahamas, The
- Bahrain
- Bermuda
- Brunei
- Cayman Islands
- Channel Islands
- Cyprus
- Faeroe Islands
- French Polynesia
- Greenland
- Guam
- Hong Kong, China
- Israel
- Kuwait
- Liechtenstein
- Macao, China
- Monaco
- Netherlands Antilles
- New Caledonia
- Northern Mariana Islands
- Qatar
- San Marino
- Singapore
- Slovenia
- United Arab Emirates
- Virgin Islands (U.S.)

High Income: OECD

- Australia
- Austria
- Belgium
- Canada
- Denmark
- Finland
- France
- Germany
- Greece

Iceland	Luxembourg	Spain
Ireland	Netherlands	Sweden
Italy	New Zealand	Switzerland
Japan	Norway	United Kingdom
Korea, Rep.	Portugal	United States

SOURCE: World Bank, 2001.

Appendix C

The Essential Competencies of a Skilled Birth Attendant

SKILLS FOR MANAGEMENT OF COMPLICATIONS AT DOMICILIARY/PRIMARY LEVELS

Maternal haemorrhage: A skilled attendant should be able to diagnose various causes of antepartum and postpartum bleeding, including abortion (see below), as well as recognize the possibility of internal haemorrhage due to ectopic pregnancy. For antepartum and internal hemorrhage, a skilled attendant should stabilize and transfer the woman immediately. Skilled attendants can reduce the likelihood of postpartum hemorrhage by promoting the normal mechanisms of placental delivery and by using active management of this stage when appropriate (including administration of a prophylactic oxytocic with or immediately after delivery of the infant, early cord clamping and cutting, and controlled cord traction). Manual removal of placenta, uterine massage, and aortic or bimanual compression are also options. When the bleeding requires emergency care, skilled attendants can stabilize the woman by giving intravenous fluids and can transfer her to a referral facility.

Sepsis: A skilled attendant should prevent infection by ensuring that the woman gives birth in a safe, clean environment, maintaining the highest possible standards of hygiene and infection control, and using clean or sterile equipment, including gloves. For women who develop an increased risk of sepsis during delivery (e.g., if membranes have been ruptured over a prolonged period, or the woman has been exposed to an infectious substance/situation), skilled attendants can also monitor women after delivery, educate women and their families on the signs of infection, and if sepsis develops, administer antibiotics. Skilled attendants can also recognise sepsis due to unsafe abortion

Pre-eclampsia and eclampsia: Skilled attendants can identify elevated blood pressure and proteinuria as signs of pre-eclampsia. Such cases should be provided with emergency care and referred for higher-level care. If eclampsia occurs during delivery, skilled attendants can provide potentially life-saving care: administering anticonvulsant drugs, inducing labor by rupturing membranes, and correctly positioning an unconscious woman for delivery. Skilled attendants should also be able to administer anticonvulsant drugs and stabilize a woman to prevent her condition from worsening, and refer her for higher-level care.

Prolonged or obstructed labor: A skilled attendant can use a partograph to monitor the progress of labor, identify prolonged or obstructed labor, and take appropriate and timely action. If labor is long or difficult, skilled attendants provide supportive care throughout the process. If prolonged labor is due to ineffective contractions, careful augmentation with oxtocin is an option. For other causes, such as shoulder dystocia or prolapsed cord, skilled attendants can provide emergency care. In some cases, experienced providers can use a vacuum extractor to save the lives of both mother and infant. In all cases of prolonged and obstructed labor, skilled attendants must be able to refer severe cases promptly to higher-level care.

Addressing abortion complications: A skilled attendant can play an important role in facilitating women's access to the appropriate measures for managing unsafe abortion. These include providing treatment for or referring women who present with signs of inevitable, incomplete, and septic abortions, according to the attendant's level of skill. In circumstances where abortion is not against the law, skilled attendants have a role to play in protecting women's health. While not promoting abortion as a method of family planning, they may advocate to ensure that services are safe and accessible. Family planning counseling and methods should be provided in the postabortion period, as well as other reproductive health counseling as needed.

Preventing neonatal deaths: A skilled attendant can take appropriate measures to prevent neonatal death: tetanus toxoid immunization during pregnancy, assessing the baby's condition at birth, and resuscitating, if necessary. Preventing neonatal hypothermia, taking appropriate measures to prevent nosocomial infection, and supporting early and exclusive breastfeeding. The skilled attendant can identify and provide initial care for sick and/or low-birth-weight infants, and refer them safely. Skilled attendants can also support the mother in providing appropriate care of a moderately preterm or low-birth-weight infant who does not have a life-threatening condition.

Conditions that can complicate pregnancy and childbirth (e.g., anemia, malaria, HIV/AIDS): Skilled attendants can take a range of appropriate measures to prevent these conditions, including: providing routine iron and vitamin supplementation; providing prophylactic malaria treatment and antihelminthic drugs; and providing nutrition education. In addition, skilled attendants with access to laboratory facilities can diagnose and treat anemia, malaria, and sexually transmitted infections; they can also provide counseling to encourage women to seek voluntary HIV testing, as well as advise mothers who have or suspect they have HIV/AIDS on infant feeding options. Skilled attendants can administer antiretroviral therapies, where available, to women with HIV, before or during delivery.

ADDITIONAL SKILLS AT THE FIRST REFERRAL LEVEL

In addition to those skills outlined above, the attendant at the first referral level should have the following skills:

- Induction of labor
- Surgical intervention (i.e., cesarean section, laparatomy in case of ectopic pregnancy, emergency hysterectomy, dilation and curettage)
- Destructive operations (e.g., craniotomy)
- Diagnosis and management of diabetes, chronic hypertension, cardiac disease, kidney disease, and other common chronic conditions during labor and birth.

ATTITUDINAL AND COGNITIVE SKILLS

Along with technical competency in clinical care, skilled birth attendants need to understand local customs so that they can work with communities in making healthy choices—that is, promote practices that are benign or beneficial and explain why other practices are harmful and discourage their use. In order to support women and their families in making decisions about health, skilled attendants must have the ability to communicate effectively with women and their families (i.e., listen as well as speak, and speak clearly, simply, and respectfully). Indeed, in some contexts, these communication and interpersonal skills can be the determining factor in whether skilled attendants are accepted in communities and their services utilized.

In addition, it is important for skilled attendants to use cognitive skills that facilitate problem solving and quick, decisive action. In the context of identifying essential competencies for skilled attendants, the International Confederation of Midwives has developed a "framework for decision-making." This framework calls on skilled attendants to take the following actions to ensure high-quality care:

- Gather information—through interviews, dialogue, observation, and clinical examination—and decide what is relevant to the situation(s);
- Identify signs and symptoms of serious and/or life-threatening conditions and develop a plan of care, balancing speed with attention to details; and
- Evaluate the effectiveness of actions taken and modify or adapt the plan of care when needed, in individual cases and when a similar situation arises in the future.

Excerpted with permission from Skilled Care During Childbirth Information Booklet. New York: Family Care International, Inc. 2002. Prepared by Mia MacDonald with Ann Starrs.

Appendix D

Committee Biographies

ADETOKUNBO O. LUCAS, M.D. *(Co-chair),* was born in Nigeria and obtained his medical degree at Durham University, England. His postgraduate training in internal medicine, public health, and tropical medicine took him to Belfast, London, and Harvard University. He chaired the Department for Preventive and Social Medicine in Ibadan, Nigeria, until 1976. From 1976 to 1986 he directed the Tropical Diseases Research Programme of the World Health Organization, and from 1986 to 1990 he served as the chair of the Carnegie Corporation's Strengthening Human Resources in Developing Countries grant program. In 1990, Dr. Lucas was appointed professor of international health at the Harvard School of Public Health. He has served on the technical advisory boards of several national organizations and international agencies including the Rockefeller Foundation, the Edna McConnell Clark Foundation, the Carter Center, and the Welcome Trust Scientific Group on Tropical Medicine. He now chairs the Global Forum for Health Research. Dr. Lucas has received academic honors from Harvard University and honorary degrees form Emory, Tulane, and Ibadan Universities. He is a fellow of the Royal College of Obstetricians and Gynaecologists and is one of the first foreign associates of the Institute of Medicine.

BARBARA J. STOLL, M.D. *(Co-chair),* received her medical degree from Yale Medical School, completed a pediatric residency at Babies Hospital, Columbia Presbyterian Medical Center, and a neonatology fellowship at Emory University School of Medicine. She is currently professor of pediatrics at Emory and vice-chair for Research in the Department of Pediatrics. She spent four years working on issues of childhood disease and mortality at the International Center for Diarrhoeal Disease Research, Bangladesh. In 1995-1996 she was a visiting scientist at the World Health Organization (WHO). She is currently a member of the Executive Board of the Atlanta-based WHO Collaborating Center in Reproductive Health, the Advisory Board for the Saving Newborn Lives Initiative of Save the Children, the Society for Pediatric Research, the Perinatal Research Society, the American Pediatric Society, and a fellow of the American Academy of Pediatrics and the Infectious Diseases Society of America. Her extensive research and publications have focused on low birth weight and premature newborns, preventing and treating neonatal infections, and the global impact of neonatal infections. Dr. Stoll is on the Steering Committee of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and is one of the principal investigators of the collaborative network. In addition, Dr. Stoll practices neonatology at Emory University in Atlanta, Georgia.

ANNA ALISJAHBANA, M.D., Ph.D., is professor emeritus of pediatrics in the School of Medicine at Padjadjaran University in Indonesia and director of the World Health Organization Collaborating Center for Perinatal and Maternal and Child Care in Indonesia. She has studied many aspects of perinatal care, including community-based training of traditional birth attendants in rural areas. In addition, Dr. Alisjahbana has served as a technical consultant for the Asian Development Bank, World Health Organization, United Nations Children's Fund (UNICEF), and the government of Indonesia on a number of programs to improve perinatal outcomes and early child development. She has published on a range topics including patterns of birthweight in rural Indonesia, prevention of hypothermia in low weight infants, ways to improve health care services to prevent maternal mortality, and appropriate technology for resuscitation of newborns. She is founder and chairperson of Surya Kanti Foundation, a nonprofit organization working with children 0-5 years of age with developmental disabilities. The foundation clinic provides services to more than 8,000 patients per year.

ABHAY BANG, M.D., M.P.H., received his M.D. in India and an M.P.H. from the Johns Hopkins University School of Public Health. He is currently living, working, and conducting research in Gadchiroli, India, where he has been the director of SEARCH (Society for Education, Action, and Research in Community Health) since 1986. The major areas of action and research are reproductive health of women, monitoring child mortality, alcoholism in men, reproductive health of men, acute respiratory infections in children, and health care for tribal populations. After establishing baseline data on birth outcomes in the Maharashtra region of India, Dr. Bang has developed a feasible and very effective model of home-based neonatal care, which is delivered with the help of trained village health workers and traditional birth attendants in rural settings in India. As a physician, working in tandem with his wife, an obstetrician, he is providing care, training village birth workers, and monitoring the data on improved birth outcomes. Dr. Bang and his organization have received many national and state awards for community health care and research. He is also a member of the National Commission on Population, India.

LAURA CAULFIELD, Ph.D., received her doctorate in international nutrition from Cornell University. In 1990, she joined the faculty of the Johns Hopkins School of Hygiene and Public Health and is currently associate professor in the Division of Human Nutrition, Department of International Health. Dr. Caulfield has studied the role of nutrition in improving birth outcomes in diverse populations, including the United States and Canada, Latin America, and South Asia. Currently, she is conducting research on the role of prenatal iron and zinc supplements for improving infant health in Peru. Dr. Caulfield has served as a consultant to the Pan American Health Organization, the United States Agency for International Development, and numerous private voluntary organizations. She is a member of various societies, including the Society for International Nutrition Research and the Society for Pediatric and Perinatal Epidemiologic Research, and is vice-chair of the Nutritional Epidemiology Research Interest Section of the American Society of Nutritional Sciences.

ROBERT GOLDENBERG, M.D., received his medical training from Duke University. He is professor of public health and Charles E. Flowers Professor and chair of the Department of Obstetrics and Gynecology at the University of Alabama, Birmingham, where he also served as the director of the Center for Obstetric Research for 10 years. He currently directs the Center for Research in Women's Health. Dr. Goldenberg was director of obstetrical services at Cooper Green Hospital in Birmingham from 1986 to 1989 and chairman of the Department of Obstetrics and Gynecology at Cooper Green Hospital from 1987 to 1991. He is a member of the Institute of Medicine and chairman of the Membership Committee for Pediatrics, and Obstetrics and Gynecology. He has served on numerous advisory committees, including the Council for the National Institute of Child Health and Human Development; the National Institutes of Health Expert Panels on the Content of Prenatal Care and on Pregnancy, Birth, and the Infant Research Plan; and the Congressional Office of Technology Assessment Child Health Advisory Panel. Dr. Goldenberg has been the principal investigator on major grants from NICHD, the National Institute of Allergy and Infectious Diseases, the March of Dimes, and the Robert Wood Johnson Foundation. He has published extensively on preterm birth prediction, low birth weight, intrauterine growth retardation, neonatal mortality, and maternal and neonatal infectious disease prevention, diagnosis, and treatment.

MARJORIE KOBLINSKY, Ph.D., received her doctorate in biochemistry from Columbia University and also holds a Certificate of Community Medicine and Health from the Liverpool School of Tropical Medicine. Dr. Koblinsky is project director of MotherCare at the John Snow, Inc., Center for Women's Health, where she is responsible for multiple projects aimed at developing, implementing, and evaluating a community-based approach to improving maternal and neonatal health and nutrition in developing countries, including Indonesia, India, Pakistan, Nigeria, Uganda, Kenya, Zambia, Bolivia, Ecuador, Peru, and Guatemala. She has also been a program officer for the Ford Foundation and the Canadian International Development Research Center and a project director and research scientist at the International Center for Diarrhoeal Disease Research in Bangladesh. Dr. Koblinsky has published on a range of topics related to maternal health and survival, including ways to define and measure maternal mortality and morbidity, methods for achieving healthy pregnancies and safe deliveries, and implementing and evaluating programs in reproductive health and family planning. She is the 1993 recipient of the NCIH International Health Award, and her project, MotherCare, was the 1998 recipient of the World Health Day Award, given by the American Association of World Health.

MICHAEL KRAMER, M.D., received his M.D., pediatrics, and epidemiology training at the Yale University School of Medicine. Since 1978 he has been at the McGill University Faculty of Medicine and, since 1987, he has been a professor in the Departments of Pediatrics and of Epidemiology and Biostatistics. He is currently a distinguished scientist of the Medical Research Council of Canada. His research focuses on perinatal epidemiology and currently includes a multicenter randomized trial of the WHO/UNICEF Baby-Friendly Hospital Initiative to promote breastfeeding; development of new fetal growth standards based on early ultrasound-validated gestational age; international comparisons of fetal and infant mortality; and mechanisms and causal pathways underlying socioeconomic disparities in risk for preterm birth.

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HARSHADKUMAR CHANDULAL SANGHVI, M.B., Ch.B., has more than 15 years of experience in Africa as a clinical service provider and university faculty member and researcher in obstetrics and gynecology. In his current position as the medical director of the Maternal and Neonatal Program at the Johns Hopkins Program for International Education in Gynecology and Obstetrics in Baltimore, Maryland, he is responsible for the development of reproductive health training materials, especially those for maternal and neonatal health care. He is a senior associate at the School of Public Health, Johns Hopkins University. As the chair of his department at the University of Nairobi in Kenya, he played as instrumental role in the promotion of pre-service training for medical students and postgraduates in all aspects of reproductive care. He has been involved in designing and implementing large-scale epidemiological studies, including the Nairobi Birth Survey and the four-country East Central and Southern African Maternal Mortality Study. His many publications include studies on adolescent health, family planning, maternal and neonatal health, and cervical cancer.

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Appendix E

Dissenting Note

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Gadchiroli, India

This report recommends universal availability of skilled birth attendants (SBA) and access to referral care as the two main interventions to improve pregnancy outcome in the developing world. In doing so, the report is following the current opinion in the international organizations. Donor agencies and policy makers in developing countries will invest billions of dollars and could be putting the lives of millions of women at stake. These recommendations have implications of mammoth proportions.

While I agree with the goal of providing better skilled care to all mothers and neonates, some questions need to be asked before a colossal amount of resources are committed to the approach recommended in this report.

1. Certain levels of development and availability of infrastructure—roads, cars, telephones, literacy, skilled manpower and clinics/hospitals—are necessary for implementing this approach. Will this medical approach, which succeeded in the past in developed countries, work in the absence of such societal development in developing countries? Can it be transplanted successfully in the very different economic and cultural settings?

2. Where is the definitive evidence—randomized, controlled field trials—that such an approach reduced the maternal mortality in developing countries? The report says that no such trials have been conducted so far. Mere historical evidence from Sweden or being "sensible" are inadequate evidence. Many earlier policies failed because they were not field tested rigorously. Is a similar error being committed again?

3. What will be the space for personal choice? Who will decide as to where and how women should deliver? Will this decision for every woman in the developed as well as developing countries be made by the professionals and policy makers alone or will women and their families have a choice?

4. Who will finance the enormously costly professional model of maternal-neonatal care? Will the people be willing to pay the cost because the "experts" want them to be served only by the professionals? At the current maternal mortality ratio (MMR) of 5 per 1000 deliveries, people in many developing countries may consider a pregnancy and delivery to be 99.5% safe. Will they like to put their money for making it safer?

5. Is saving mothers by the SBA approach the most cost-effective option to save mothers? A country may like to put its scarce resources in TB or malaria control or tetanus immunization to save mothers. Has a rigorous comparison of the cost-effectiveness of different approaches been made?

The inference that the training of traditional birth attendants (TBAs) did not succeed in reducing maternal mortality is a half-truth. The other half is that TBAs were not backed by emergency obstetric care. In the absence of referral linkages to manage the complicated deliveries the training of TBAs did not succeed in isolation. Not surprising. Even the skilled birth attendance may not result in the reduction of maternal mortality in the absence of access to emergency obstetric care. The disappointment about TBAs is due to a wrong expectation. When the unskilled birth attendants were backed by the access to referral care (Model I), the maternal mortality ratio reduced in rural China and Brazil to 115 and 120, respectively (Table 5-1 in the report).

The report assumes that what is best for mothers is also the best for neonates. Hence SBA + referral care is recommended as the main strategy for neonates as well. This may not be true. The current level of MMR and the causes of maternal deaths may necessitate access to hospital-based professional care for preventing maternal deaths. But neonatal deaths can be prevented and NMR brought down without dependence on hospitals. In 1996 Sri Lanka achieved an NMR of 12.5 per 1000 live births when the entire country had only 40 neonatal intensive care incubators, 54 pediatricians (1:34,000 population) and 77 obstetricians (1:24,000) (de Silva, 1999). The Gadchiroli (India) trial, described in this report (Box 3-1) has shown that training village level functionaries to deliver home-based neonatal care (including some skilled functions) reduced the NMR by 62 percent at a very low cost of $5.30 per neonate, and $97 per averted fetal/neonatal death. Since nearly 60 percent of neonatal deaths occur after the first day of delivery, when the neonates are usually at home, and since prevention of neonatal deaths needs simpler technology, most of the neonates can be managed at home as well. The NMR can be reduced at a very low cost without access to hospital care. Hence the interventions to reduce the MMR and the NMR need not follow the same approach.

Home-based or community-based approach is by far more cost-effective than the estimated cost-effectiveness of providing the recommended package to mothers and neonates, that is, $1,000-3,000 per averted maternal or neonatal death. The World Bank report 1993, Investing in Health, estimated the cost of providing maternal care to be $3.80 per capita or $90 per mother or $30-50 per disability-adjusted life year saved (World Bank, 1993). The total estimated cost of public health and clinical services in low income countries was $12 per capita. Many developing countries may not be able to devote the required resources for this recommended approach, as it may need $3.80/12, or 30 percent of their total estimated cost of health services, but it will avert only 4 percent of their disease burden (World Bank, 1993).

Many less developed countries may be satisfied at this stage to provide the Model I type of care, and reduce the MMR to 115, as in rural China or Brazil (Table 5-1). The incremental gains of the Model III (MMR reduced from 50 to 43 in Malaysia) seem low. Moreover, the operational problems of implementing these models (i.e., training of SBAs, retaining them in rural areas, cost) seem difficult to surmount. The government of India tried to introduce Model II in the rural area in the entire country nearly 20 years ago, and yet, only 15 percent of deliveries are conducted by nearly 100,000 auxiliary nurse-midwives posted in rural areas. After the failure to shift to Model II, the government of India decided 3 years ago to aim for nearly 100 percent institutional deliveries (Model III). Within 2 years, it was found to be unrealistic, and had to be scaled down. The committee report fails to acknowledge or analyze this gigantic failure in India of the policy that this report now recommends.

Even if the developing countries set the long-term goal of SBA and access to referral care to all mothers, what about the immediate future—the next 5 to 10 years? Globally nearly 60 percent of births occur today at home, most often attended by TBAs or family members. This situation, which will not change immediately, demands that an intermediate feasible goal be accepted and we plan to work with both the TBAs and SBAs during the transition period. If the mothers and grandmothers can be involved and educated, why not TBAs, as well, who are the community grandmothers? Though they are not the ideal personnel, they cannot be ignored or bypassed. Even in the United States, 52 percent of the population seeks help from the healers of alternative/complementary systems, inspite of the availability of highly evolved services of modern medicine.

The report discusses the problem of maternal deaths caused by not having access to safe abortions, but it fails to recommend this simple, safe, and effective method to reduce abortion-related and fertility-related maternal deaths. Many countries have legalized the access to safe abortion, and such service should be recommended where it is politically acceptable.

The policy makers and donor agencies need to consider these issues, ask for the evidence that the recommended solution is acceptable to people, feasible to implement, effective in reducing maternal and neonatal deaths, and is more cost-effective than other interventions. Recommendations based on what appears "sensible" but, not tested in large field trials may fail to produce the desired results, leading to one more round of disillusionment. Didn't it happen many times in the past?

Obviously, we can not generalize and push for one universal health care solution. The recommended professional model of maternal-neonatal care is so resource-intensive that it may not be possible to provide that sort of care to 6 billion people. It also may not be the most cost-effective or acceptable option. Hence, I recommend that:

1. No single model of maternal-neonatal care is appropriate for all countries.
2. For some regions and countries the Model I, that is, home delivery by nonprofessionals backed by access to good-quality emergency obstetric care, may be one of the options at present, at least for some period.
3. In the spirit of the Alma-Ata global declaration, and in respect to the social and cultural norms in developing countries, the efforts should be to provide maternal and neonatal care as close to community as possible, preferably at home.
4. The professional/institutional model can be recommended only after its cost-effectiveness, feasibility, and consumer acceptance in developing countries is proved by controlled field trials and countries have resources to implement that model.
5. Access to safe abortion should be available to all women who want it.

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Glossary[1]

Abortion: Abortion is termination of pregnancy (expulsion or extraction of embryo/fetus) before 22 weeks of gestation or below 500 grams.

Abruptio placentae: Premature detachment of the placenta, often accompanied by shock, oliguria, and fibrinogenopenia.

Anencephaly: Congenital absence of the cranial vault with cerebral hemispheres missing or reduced to small masses attached to the base of the skull.

Anemia in pregnancy: Anemia in pregnancy is defined as a hemoglobin concentration of less than 110 g/L. The degree of anemia is classified as moderate (70-109 g/L), severe (40-69 g/L) and very severe (<40 g/L). The corresponding hematocrit values are 24-37 percent, 13-23 percent, and <13 percent respectively.

Antepartum fetal deaths: Fetal deaths that occur before labor.

Antepartum hemorrhage: Bleeding from the genital tract occurring after the 20th week of pregnancy but before the delivery of the baby.

Basic essential obstetric care: The ability of a health institution to perform manual removal of retained placental pieces; assisted vaginal delivery (i.e.,

[1]Several definitions have been adapted from WHO definitions.

vacuum extraction), as well as the ability to administer antibiotics, sedatives (Valium, magnesium sulfate) and oxytocics (Ergometrine, Pitocin) IM or IV and IV fluids. It is recommended that there should be four basic obstetric care facilities per 500,000 people.

Basic essential obstetrical care facility: Such a facility should manage major obstetric complications (e.g., eclampsia, severe anemia, and diabetes mellitus); monitor labor using a partograph; provide surgical procedures such as assisted delivery, removal of placenta, repair of perineal tears, manual vacuum aspiration; and manage other indirect complications associated with high rates of fetal mortality, including the need to resuscitate an asphyxiated baby.

Behavioral change: Characterized as proceeding through four stages—precontemplation, contemplation, action, and maintenance of a behavior—usually toward a healthy behavior.

Bilirubin: A breakdown product of heme that normally circulates in plasma as a complex with albumin. It is taken up by the liver cells and conjugated to form bilirubin diglucuronide, which is excreted in bile.

Birth asphyxia: Birth asphyxia is characterized by absent or depressed breathing at birth.

Birth defect: Any structural or functional abnormality determined by factors operating largely before conception or during gestation.

Birth prevalence: The number of individuals who have an attribute or disease at the time of birth divided by the population at risk of having the attribute or disease at the time of birth.

Birth weight: The first weight of the baby after birth. The mean birth weight is 3.2 kg.

Capacity building: Increasing the ability of a local institution to provide high-quality services appropriate to the local setting, which involves performance assessment and targeted strategies to improve staff competency, logistics, and other determinants of quality of care.

Case report and case series: This report or series of reports describe an intervention provided to an individual or a small group and the outcome or outcomes experienced by a by the subject(s).

Cerclage: A stitch that encircles and holds the incompetent cervix uteri.

Cesarean delivery: Abdominal delivery of the baby by laparotomy and section of uterus.

Clean delivery: A clean delivery is one that is attended by health staff in a medical institution or by a trained birth attendant at home observing principles of cleanliness (clean hands, clean surfaces, clean cutting of the cord).

Comprehensive emergency obstetric care: The ability of a health institution to perform all the basic obstetric care functions, as well as the ability to perform surgery under general anesthesia, remove retained placental pieces, and provide blood replacement. It is recommended that there should be one comprehensive obstetric care facility per 500,000 people.

Comprehensive essential obstetrical care facility: The facility should, in addition to providing basic obstetric care services, provide for surgical obstetrics including anesthesia (e.g. cesarean delivery, removal of ectopic pregnancy, laparotomy, repairs of cervical or high vaginal tears), and blood transfusion.

Confounder: A characteristic of the study population which is associated with both the risk factor and the outcome.

Controlled and uncontrolled observational studies: In a controlled study the researcher observes groups of persons who are exposed or are not exposed to the intervention of interest and compares the occurrence of one or more outcomes in these two groups. An uncontrolled study includes population-based survey, hospital-based studies, demonstration projects, and program reports.

Cost-effectiveness analysis: A systematic methodology for the comparison of the overall costs and health benefits of public health interventions.

Disability adjusted life years (DALY): An indicator that combines losses from premature death (the difference between the actual age at death and life expectancy in a low mortality population) and loss of healthy life resulting from disability.

Developing countries: See Appendix B.

Eclampsia: Convulsions and coma occurring in pregnant or puerperal women, which are associated with pre-eclampsia. (See hypertensive disorders of pregnancy.)

Effective treatment: The effect of a treatment as observed in the controlled circumstances of a clinical trial.

Efficacious treatment: The effect of a treatment that can be expected in real clinical practice.

Emergency obstetric care: The basic intervention capacity needed to appropriately manage obstetrical complications. This includes surgical obstetrics, cesarean sections, treatment of laceration, laparotomy; anesthesia; medical treatment of shock, eclampsia, and anemia; blood replacement; manual procedures; and assisted delivery.

Emergency preparedness: An approach to promote early recognition of complications for mother and baby at any time during pregnancy, delivery, or after delivery and to maximize the likelihood of timely referral and management. This involves preparedness in the community and in the formal health care system.

Encephalocele: A protrusion of the brain and its covering membranes through the skull.

Epidemiology: The study of the distribution and determinants of health-related states and events in populations and the application of this study to control health problems.

Essential newborn care: Basic preventive care for all newborns, especially warmth, cleanliness, breastfeeding, cord and eye care, and immunizations.

Essential obstetric and neonatal care: A set of minimal health care elements which should be made available to all pregnant women and that includes both preventive and curative health measures. Essential obstetric care includes both life-saving and emergency measures (e.g., cesarean section, manual removal of the placenta) as well as nonemergency measures (e.g., partograph, maternity waiting homes, intravenous oxytocics). It must have the basic intervention capacity to promote fertility regulation, prepregnancy care including nutrition, postabortion care, refocused antenatal care, essential obstetric care, essential newborn care, and postpartum care.

Evidence-based medicine/health care: In evidence-based health care, the policies and practices used for prevention are based on principles that have been proven through appropriate scientific methods. As well as proving the clinical effectiveness of a procedure, this involves evidence of use and provider satisfaction and demonstrations of the feasibility and cost-effectiveness of the procedure in different settings.

Feticide: Intentional destruction of a human fetus.

Gestational age: The number of completed weeks since the last menstrual period of the mother. This can be assessed by obstetric ultrasound or clinical assessment.

Incidence: The number of new cases of a disease or condition in a particular population in a specified time interval.

Hospital: A health facility performing all essential obstetric functions. Also described as first referral level, or a district or subdistrict hospital.

Hyperbilirubinemia: An excess of bilirubin in the blood.

Hyptertensive disorders of pregnancy: A diagnosis of hypertension in a pregnant woman is made when the blood pressure is 140/90 mm Hg or greater, or there has been an increase of 30 mm Hg systolic or a 15 mm Hg diastolic rise over baseline values on at least two occasions, 6 or more hours apart. Pregnancy-induced hypertension (which occurs without a previous history of hypertension) is differentiated from preexisting hypertension.

Infant mortality rate (IMR): Number of deaths among infants under one year of age per 1,000 live births.

Infanticide: The intentional killing of an infant.

Intrapartum fetal deaths: Fresh stillbirths that occur during labor.

Intrauterine growth restriction (IUGR): A baby less than 10 percent of the expected weight for gestational age and gender, born after ≥37 weeks gestation. Formerly interuterine growth *retardation*, this term is used synonymously with small for gestational age (SGA), (although not all SGA infants are affected by IUGR; some are simply at the lower tail of the "normal" fetal growth distribution).

Kangaroo care: A neonate wearing only a diaper is placed between the mother's breasts and both are covered. The uninterrupted body heat through skin to skin can maintain the newborn's body temperature and facilitate early breastfeeding.

Kernicterus: A condition with severe neural symptoms, associated with high levels of bilirubin in the blood.

Late fetal deaths: Fetal deaths that occur between 22 or 28 weeks (varies with organizations and countries) of gestation and birth. Synonymous with stillbirth.

Lay providers: Delivery by unskilled persons such as traditional birth attendants, relatives, or on one's own, is a norm in many developing countries.

Live birth: A baby born with any signs of life, independent of weight or gestation.

Low-birth-weight (LBW): Birth weight less than 2,500 grams.

Management: A process by which one plans, implements, and evaluates an organized response to a health problem.

Maternal mortality: A maternal death is the death of a woman while pregnant or within 42 days of termination of the pregnancy, irrespective of the duration and the site of pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

Maternal mortality rate (MMR): The maternal mortality rate is the number of maternal deaths per 1,000 women of reproductive age.

Maternal mortality ratio: The maternal mortality ratio is the number of maternal deaths per 100,000 live births.

Meta-analysis: Meta-analysis is the statistical method used to integrate results from more than one study to produce a summary estimate of the treatment effect across studies (typical relative risk).

Midwife: A midwife has successfully completed the prescribed course of studies in midwifery and has acquired the requisite qualifications to be registered and/or legally licensed to practice midwifery. She must be able to give the necessary supervision, care, and advice to women during pregnancy, labor, and the postpartum period; to conduct deliveries on her own responsibility; and to care for the mother and infant. This care includes preventive measures, the detection of abnormal conditions in mother and child, the procurement of medical assistance and the execution of emergency measures in the absence of medical help. She provides health counseling and education for women, families, and the community on preparation for parenthood, health risks during pregnancy, family planning, and child care. She may practice in hospitals, clinics, health units, or homes.

Miscarriage: Spontaneous early fetal loss.

Morbidity: Any departure from a state of physiological or psychological well-being.

Neonatal death: A death of a liveborn infant during the period between birth and 28 completed days after birth. Early neonatal deaths occur during the first 7 days of life, and late neonatal deaths occur after the seventh day but before 28 completed days of life.

Neonatal mortality rate (NMR): Number of deaths among live births during the first 28 completed days of life per 1,000 live births.

Neonatal period: The first 28 days of life. Divided into early neonatal period (first 7 days) and late neonatal period (days 8-28).

Newborn/neonate: Baby from birth until 28 completed days of life (the neonatal period).

Obstructed labor: A labor in which progress is arrested by mechanical factors. Delivery often requires cesarean section.

Parity: Number of of full-term children previously born by a woman, excluding miscarriages and abortions in early pregnancy but including stillbirths.

Partograph: A written record charting the progress of labor and delivery and showing the key observations to monitor the women, the fetus, and labor progress.

Perinatal mortality rate (PMR): The perinatal mortality rate is the number of deaths of fetuses weighing at least 500 g (or, when birth weight is unavailable, after 22 completed weeks of gestation), plus the number of early neonatal deaths, per 1,000 total births (livebirths and stillbirths). Because of the different denominators in each component, this is not necessarily equal to the sum of the fetal death rate and the early neonatal mortality rate. There is considerable confusion regarding PMR as countries use definitions that vary in minimal gestation and numerical weight. WHO encourages countries to report (internationally) the PMR for babies over 1,000 g or 28 weeks of gestation.

Perinatal period: As defined by WHO, this period begins at 28 completed weeks of gestation (the time when birth weight has normally reached 1,000 grams), and ends seven completed days after birth. It includes: late fetal deaths (weight above 1kg = 28 weeks gestation) and early neonatal deaths (birth to 7 days). WHO prefers weight to gestation, as gestation is often unknown in developing countries. Many industrialized and some transitional countries use 22 weeks gestation as cutoff.

Postpartum care: Care from the delivery until the sixth completed week after delivery, including care both at home and in the formal health care system.

Postpartum hemorrhage (PPH): Excessive loss (usually of 500 milliliters or more) of blood from the genital tract within 24 hours of delivery. If uncontrolled, hemorrhage can quickly lead to shock and death, which generally occurs within 7 days of childbirth. Because of the difficulty of measuring blood loss, a more practical definition of PPH is any blood loss that causes a physiological change, such as low blood pressure, that threatens a woman's life.

Postterm birth: Baby born after 42 completed weeks of gestation.

Pre-eclampsia: A condition in pregnancy manifested by hypertension, edema, and/or proteinuria.

Premature rupture of membranes (at term or preterm): Rupture of the membranes before onset of labor.

Preterm birth delivery or prematurity: Live birth before 37 completed weeks of gestation.

Prevalence: The number of instances of a given disease or other condition in a particular population at a specified time.

Prolonged labor: Active labor with regular uterine contractions for more than 12 hours.

Prolonged pregnancy: A pregnancy beyond 42 weeks gestation.

Prolonged rupture of the membranes (regardless of labor status): Rupture of the membranes for more than 12 hours.

Puerperal sepsis: Infection of the genital tract occurring at any time between the onset of rupture of membranes or labor and the 42nd day postpartum in which, apart from fever, one or more of the following are present: pelvic pain, abnormal discharge (e.g. presence of pus), abnormal smell/foul odor of discharge, delay in the rate of reduction of size of uterus (<2 cm/day during first 8 days). These can occur as a result of unhygienic practices during delivery, excessive examinations, and increasing rates of STDs and AIDS. Serious puerperal infections are more likely after prolonged or obstructed labor.

Randomized controlled trials (RCT): Experiments in which investigators randomly allocate eligible people or health care units into groups to receive, or not to receive, the interventions(s) being compared. When sample size is adequate, randomization ensures baseline comparability of known and unknown prognostic variables. Outcomes are selected *a priori* in order to achieve unbiased assessment of the results.

Relative risk: The ratio of the risk of disease or death among those exposed to the risk compared to the risk among the unexposed; this usage is synonymous with risk ratio.

Safe delivery: A safe delivery is one where the birth attendant monitors progress to avoid prolonged labor and to detect obstructed labor that can lead to hemorrhage, infection, and shock in the mother and birth asphyxia and brain damage in the infant.

Sector-wide approaches to health: These address all components of health services, including maternal and neonatal health.

Sickle cell disease (SCD): Sickle cell disease results from the pairing of hemoglobin S (Hb S) with another abnormal hemoglobin; the most frequent and severe phenotypes are hemoglobin SS (Hb SS) and hemoglobin SC (Hb SC). The abnormal hemoglobins distort the shape of the red blood cells and damage and destroy them. Patients develop anemia and other serious complications.

Skilled birth attendant: A midwife, physician, or nurse who has completed nationally recognized professional training and is proficient in basic techniques for clean and safe delivery; recognition and management of prolonged labor, infection, and hemorrhage; and recognition and resuscitation of neonates who fail to initiate respiration at birth.

Small for gestational age (SGA) (also called "small-for-dates"): Lower than 10 percent on a birth-weight-for-gestational-age, sex-specific, single/twins growth reference curve.

Spina bifida: Incomplete closure of the spine through which the cord and meninges may or may not protrude.

Stillbirth: The death of a fetus weighing at least 500 g (or when birth weight is unavailable, after 22 completed weeks of gestation, or with a crown-heel length of 25 cm or more) before the complete expulsion or extraction from its mother. Synonymous with late fetal death.

Surveillance: The systematic collection and analysis of data in order to make management decisions.

Term birth: Baby born between 37 and 42 completed weeks of gestation.

Total births: All births, live and stillborn (late fetal deaths).

Traditional birth attendants: Lay persons who assist women in many rural settings during labor and delivery. They have minimal formal education, minimal or no medical training, minimal or no medical oversight, and generally a low caseload.

Unsafe abortion: Unsafe abortion is termination of an unwanted pregnancy by persons lacking the necessary skills or in an environment lacking minimal medical standards, or both. An abortion can be considered as unsafe when it is performed under circumstances in which there are risks of morbidity and mortality over and above those inherent in the procedure when performed under optimal conditions—that is, under conditions of asepsis and with appropriate skills and equipment.

Very early neonatal period: First 24 hours of a newborn's life.

Very low birth weight (VLBW): Less than 1,500 grams.

Vital registration: Identifying and recording every live birth and every death of a pregnant woman, late fetal death (22 or 28 weeks, depending on the jurisdiction), infant death (neonatal or postneonatal), and maternal death.

Acronyms

3TC	lamivudine
ACTG	AIDS Clinical Trials Group
AFP	Alpha-feto protein
AIDS	Acquired immunodeficiency syndrome
ANC	Antenatal care
APFD	Antepartum fetal death
ARI	Acute respiratory infection
ART	Antiretroviral therapy
AZT	zidovudine
BCG	Bacillus Calmette-Guerin vaccine (to prevent tuberculosis)
BEOC	Basic essential obstetric care
BMI	Body mass index
CARE	Cooperative for Relief and Assistance Everywhere
CDC	Centers for Disease Control
CEOC	Comprehensive essential obstetric care
CFR	Case fatality rate
CI	Confidence interval
CM	Congenital malformations
CMV	Cytomegalovirus
CNS	Central nervous system
CPD	Cephalic-pelvic disproportion
CRS	Congenital rubella syndrome
DALY	Disability adjusted life years
DHS	Demographic health surveys

ECLAMC	Estudio Colaborativo Latino Americano de Malformaciones Congénitas (Latin American Collaborative Study of Congenital Malformations)
ECV	External cephalic version
EmOC	Emergency obstetric care
EOC	Essential obstetric care
GDP	Gross Domestic Product
GNP	Gross National Product
Hg	Hemoglobin
HiB	Hemophilus influenza Type B
HIV	Human immunodeficiency virus
ICBDMS	International Clearing House for Birth Defects Monitoring Systems
ICD	International Classification of Diseases
IDD	Iodine-deficiency disorders
IDDM	Insulin-dependent diabetes mellitus
IMCI	Integrated management of childhood illnesses
IMMAT	Deaths due to immaturity
IMMPACT	Initiative for maternal mortality programme assessment
IMPAC	Integrated management of pregnancy and childbirth
IMR	Infant mortality rate
INCLEN	International Clinical Epidemiology Network
IOM	Institute of Medicine of the U.S. National Academies
IPFD	Intrapartum fetal deaths
IU	International units
IUGR	Intrauterine growth restriction *(formerly retardation)*
IV	Intravenous
LBW	Low birth weight (less than 2.5 kilograms)
MCH	Maternal and child health
MMR	Maternal mortality rate
NGO	Nongovernmental organization
NIH	National Institutes of Health of the United States
NMR	Neonatal mortality rate
NTD	Neural tube defects
NVP	Nevirapine
PHC	Primary health care
PIH	Pregnancy-induced hypertension
PMR	Perinatal mortality rate
PPH	Postpartum hemorrhage
PTB	Preterm birth
RCT	Randomized, controlled trials
RTI	Reproductive tract infections
SGA	Small for gestational age

STD	Sexually transmitted disease
STI	Sexually transmitted infection
TB	Tuberculosis
TBA	Traditional birth attendant
UNFPA	United Nations Fund for Population Activities
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VHW	Village health worker
VLB	Very low-birth-weight (less than 1,500 grams)
WHO	World Health Organization

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