Community-Based Interventions for Improving Perinatal and Neonatal Health Outcomes in Developing Countries: A Review of the Evidence

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ABSTRACT. *Background.* **Infant and under-5 childhood mortality rates in developing countries have declined significantly in the past 2 to 3 decades. However, 2 critical indicators, maternal and newborn mortality, have hardly changed. World leaders at the United Nations Millennium Summit in September 2000 agreed on a critical goal to reduce deaths of children <5 years by two thirds, but this may be unattainable without halving newborn deaths, which now comprise 40% of all under-5 deaths. Greater emphasis on wide-scale implementation of proven, cost-effective measures is required to save women's and newborns' lives. Approximately 99% of neonatal deaths take place in developing countries, mostly in homes and communities. A comprehensive review of the evidence base for impact of interventions on neonatal health and survival in developing-country communities has not been reported.**

Objective. **This review of community-based antenatal, intrapartum, and postnatal intervention trials in developing countries aimed to identify (1) key behaviors and interventions for which the weight of evidence is sufficient to recommend their inclusion in community-based neonatal care programs and (2) key gaps in knowledge and priority areas for future research and program learning.**

Methods. **Available published and unpublished data on the impact of community-based strategies and interventions on perinatal and neonatal health status outcomes were reviewed. Evidence was summarized systematically and categorized into 4 levels of evidence based on study size, location, design, and reported impact, particularly on perinatal or neonatal mortality. The evidence was placed in the context of biological plausibility of the intervention; evidence from relevant developed-country studies; health care program experience in implementation; and recommendations from the World Health Organization and other leading agencies.**

Results. **A paucity of community-based data was found from developing-country studies on health status impact for many interventions currently being considered for inclusion in neonatal health programs. However, review of the evidence and consideration of the broader context of knowledge, experience, and recommendations regarding these interventions enabled us to categorize them according to the strength of the evidence base and confidence regarding their inclusion now in programs. This article identifies a package of priority interventions to include in programs and formulates research priorities for advancing the state of the art in neonatal health care.**

Conclusions. **This review emphasizes some new findings while recommending an integrated approach to safe motherhood and newborn health. The results of this study provide a foundation for policies and programs related to maternal and newborn health and emphasizes the importance of health systems research and evaluation of interventions. The review offers compelling support for using research to identify the most effective measures to save newborn lives. It also may facilitate dialogue with policy makers about the importance of investing in neonatal health.** *Pediatrics* **2005;115:519–617.**

ABBREVIATIONS. ARI, acute respiratory infection; CCS, case-control study; CHW, community health worker; CI, confidence interval; CKMC, community-based application of kangaroo mother care; CQ, chloroquine; DBRCT, double-blind, randomized, controlled trial; DBRPCT, double-blind, randomized, placebo-controlled trial; EFA, essential fatty acid; EPI, Expanded Programme on Immunization; FHW, family health worker; Hb, hemoglobin; HBeAg, hepatitis B virus "e" antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDN, hemorrhagic disease of the newborn; IM, intramuscular; IMR, infant mortality rate; IPT, intermittent presumptive treatment; ITN, insecticide-treated bed net; IUGR, intrauterine growth restriction; IV, intravenous; IVH, intraventricular hemorrhage; KMC, kangaroo mother care; LBW, low birth weight; NIB, untreated bed net; NIH, National Institutes of Health; NMR, neonatal mortality rate; NTD, neural tube defect; OR, odds ratio; PCS, prospective cohort study; PMR, perinatal mortality rate; PROG, proguanil; PPROM, preterm premature rupture of membranes; PROM, premature rupture of membranes; QT, quasi-experimental trial; RCS, retrospective cohort study; RCT, randomized, controlled trial; RDA, recommended dietary allowance; RPCT, randomized, placebo-controlled trial; RPR, rapid plasma reagin; RR, relative risk; SEARCH, Society for Education, Action and Research in Community Health; SGA, small for gestational age; SP, sulfadoxine-pyrimethamine; STD, sexually transmitted disease; TBA, traditional birth attendant; TEWL, transepidermal water loss; TT, tetanus toxoid; UNICEF, United Nations Children's Fund; UTI, urinary tract infection; VLBW, very low birth weight; WHO, World Health Organization; WIC, Women, Infants, and Children Supplemental Nutrition Program; VHW, village health worker.

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EXECUTIVE SUMMARY

Background

Although there has been considerable improvement in child health globally, it is increasingly evident that important gaps and disparities remain. In particular, it is apparent that a disproportionate burden of infant and under-5 childhood mortality relates to deaths within the neonatal period, which frequently occur within the first few days after birth. Moreover, the vast majority of perinatal and neonatal deaths occur in conditions of socioeconomic deprivation in developing countries. As the health of the newborn infant is inexorably tied to the health of the mother, strategies to improve the health and care of women in low-resource communities and countries are also expected to improve both pregnancy and neonatal health outcomes. However, although it is true that poverty, illiteracy, poor status and care of women, as well as dysfunctional health systems are critical underlying factors that adversely affect maternal and child health in many developing countries, these factors are relatively difficult to change in the short term. Moreover, in sub-Saharan Africa, the devastating epidemic of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) threatens to reverse many of the gains achieved during decades of child health programming. This review does not attempt to evaluate the benefits of investing in social development, reducing inequity, and promoting economic growth among impoverished populations of developing countries. Although these are important long-term goals, pragmatic reality in most developing countries dictates the need for wide-scale implementation now of evidence-based, cost-effective health programs and interventions to improve child health outcomes. Moreover, achievement of Millennium Development Goal 4 to reduce under-5 mortality by two thirds by the year 2015 is critically dependent on a substantial reduction in neonatal mortality over the next decade.

The objectives of this review of community-based antenatal, intrapartum and postnatal intervention trials in developing countries were to (1) identify key behaviors and interventions for which the weight of evidence is sufficient to recommend their inclusion in community-based neonatal care programs and (2) identify key gaps in knowledge and priority areas for future research and program learning.

Methods

Current practice of summarizing evidence for the impact of interventions through meta-analyses of randomized, controlled trials (RCTs), although of high scientific validity, has more limited relevance when applied to research in developing countries, because most studies meeting the rigorous criteria for inclusion in such analyses were conducted in developed-country settings. In addition, the evidence base made up of interventions deriving from effectiveness trials in health system settings is scanty. In this review, we evaluated the available evidence in the global literature for the benefits and impact of various community-based interventions during the antenatal, intrapartum, and postnatal periods on perinatal and neonatal health status outcomes. The selection of interventions was based on biological plausibility and inclusion as a component in programs of maternal and/or perinatal health care. We did not, however, review the evidence for impact of skilled birth attendants, because this is the subject of other reviews.[1–4] The scientific evidence available from individual interventions or combinations thereof was reviewed, and information from programs and effectiveness trials that used packages of interventions was specifically solicited and analyzed. Although our principal focus was to seek information from community-based RCTs, we extended the evaluation to include studies with a variety of other, less rigorous designs. A few studies with a quasi-experimental trial (QT) design were included, especially if they represented information from developing countries and pertained to an intervention with little other evidence base. Community was defined as extending from the household to the peripheral health facility level; in general, studies at secondary or tertiary referral-level health facilities were excluded. However, where evidence for key interventions from community-based settings was sparse or not available, information was included from facility-based settings in developing countries and occasionally from the developed world. The evidence from developed-country studies, however, was used primarily to provide perspective and context for conclusions drawn from developing-country data. Evidence from the Cochrane database of RCTs and the World Health Organization (WHO) Reproductive Health Library was also considered, and studies from developing countries that were included in the Cochrane Reference Library were specifically evaluated. We also complemented the review of the scientific evidence based on intervention trials in developing countries with an assessment of public health programs and interventions currently in place; recommendations from the WHO and other expert institutions and individuals; and biological plausibility and evidence from developed-country studies.

Sources for potentially eligible studies included journal articles, book chapters, technical reports, conference proceedings, and theses. The search for community-based evidence encompassed all available electronic health and social science reference libraries (including indexed and nonindexed journals), and manual reviews of Safe Motherhood and Child Survival books and technical reports. Additional details were solicited directly from most agencies and institutions involved in community-based care in developing countries, especially Reproductive Health, Safe Motherhood, or Child Survival programs. Most leading global public health researchers in the field of perinatal and maternal care were also individually approached for information and unpublished material. It is important to underscore that, although we specifically sought evidence from RCTs, we were cognizant of the danger of relying on RCTs as the sole source of evidence for interventions,[5] especially in terms of consistency[6] and external validity.[7] This

TABLE 1. Numbers of Community-Based Trials of Interventions to Improve Perinatal/Neonatal Health in Developing Countries

Intervention	Number of Developing-Country Studies Reviewed In-Depth	Number of Community-Based Studies Reporting Primary Perinatal/Neonatal Health Status Outcomes*	Number of Community-Based RCTs Reporting Primary Perinatal/Neonatal Health Status Outcomes*	Number of Community-Based Studies Reporting Secondary Perinatal/Neonatal Health Status Outcomes†	Number of Community-Based RCTs Reporting Secondary Perinatal/Neonatal Health Status Outcomes†	Number of Health System Interventions or Effectiveness Trials
Maternal schooling/health education	0	0	0	0	0	0
Antenatal care package(s)	3	1	1	2	2	1
Protein supplementation	0	0	0	0	0	0
Balanced protein-energy supplementation	12	3	2	9	5	0
Antenatal iron supplementation	5	1	1	4	3	0
Periconceptional folate supplementation	1	0	0	0	0	0
Antenatal folate supplementation	1	0	0	1	0	1
Antenatal iodine supplementation	3	2	1	2	0	1
Antenatal vitamin A supplementation	6 (1)	1	1	1	1	0
Antenatal zinc supplementation	6	0	0	4	4	0
Multiple micronutrient supplementation	5 (3)	2	2	4	3	0
Malaria chemoprophylaxis or IPT	16	6	5	14	11	2
Malaria prevention using ITNs	4	2	2	4	4	1
Deworming	4 (1)	2	0	2	0	0
Syphilis screening and treatment	5	1	0	2	0	0
Antibiotics for UTIs and sexually transmitted diseases (STDs)	2	1	1	1	1	0
Antibiotics for asymptomatic bacteriuria	0	0	0	0	0	0
Antibiotics for bacterial vaginosis	1	0	0	0	0	0
Antibiotics for preterm labor	3	0	0	1	1	0
Antibiotics for PPROM	4	0	0	0	0	0
TT immunization	8	5‡	3‡	0	0	1‡
Clean delivery practices	5 (3)‡	5 (3)§	2 (2)§	0	0	1
Maternal pneumococcal immunization	1	0	0	0	0	0
Promotion of smoking cessation in pregnancy‖	0	0	0	0	0	0
Maternal care packages	2	1	1	0	0	0
Maternal vaginal and newborn skin antisepsis	2	0	0	0	0	0
Newborn resuscitation	13	8	1	2	0	0
Delayed umbilical cord clamping	1	0	0	0	0	0
Umbilical cord antisepsis	4	4§	3§	0	0	0
Prevention and management of neonatal hypothermia	4	0	0	3	1	0
Prevention and management of hypoglycemia	2	0	0	0	0	0
Breastfeeding	13	3	0	3	3	0
Prevention of ophthalmia neonatorum	2	0	0	0	0	0
Vitamin K prophylaxis	0	0	0	0	0	0
Hepatitis B vaccination	7	0	0	7	0	0
Neonatal vitamin A supplementation	3	2	2	0	0	0
KMC	9	1	0	0	0	0
Topical emollient therapy	2	0	0	0	0	0
Hyperbilirubinemia screening	5	0	0	0	0	0
TBA/CHW training	14 (7)	12 (7)	4 (1)	3	0	0
Pneumonia case management	4	2	1	2	0	1
Neonatal care packages	10 (4)	8 (4)	4 (2)	2	1	0
Care in peripheral health facilities	9	3	0	0	0	1
Cost-effectiveness studies	6 (2)	4 (2)	2 (2)	1	0	0
Totals	186	64	31	74	40	10

* Primary perinatal/neonatal outcomes included in this count were stillbirth rate, PMR, and NMR.
† Secondary perinatal/neonatal outcomes included in this count were preterm births, LBW and VLBW births, birth length, head/chest circumference, SGA/large-for-gestational-age births, neonatal weight gain, diarrheal infections, respiratory infections, congenital syphilis, ophthalmia neonatorum, NTDs, HIV infection, sepsis/infections, anemia, impetigo, HBV carrier rate, fetal/neonatal malaria, hypothermia, hypoglycemia, and breastfeeding rates.
‡ The numbers of studies in parentheses are repeated in earlier tables and are not considered in the totals.
§ Tetanus infection rate was used as a proxy outcome for tetanus-attributable neonatal case fatality.
‖ Eight smoking-cessation studies were reviewed but not counted in the study total because they were all from developed countries.

is especially true for those interventions that must be nested within health systems.[8]

The principal reviewers independently evaluated the data, and a common reporting matrix was used in summarizing the findings. Studies were evaluated for size, setting, quality, and design, ie, either efficacy or effectiveness trials.[9] The final categorization and assessment of evidence for impact of the interventions was made by mutual agreement and consensus. Emphasis was placed on assessment of impact on perinatal or neonatal primary health status outcomes. However, for some interventions for which data on primary health status outcomes were lacking, other indicators were considered.

The evidence from various interventions was categorized as follows:

1. No evidence of benefit: These interventions had been evaluated and found to have no demonstrable benefit either singly or in combination with other measures. In some cases, there was evidence of an adverse effect of the intervention. Therefore, these interventions were not recommended for inclusion in neonatal health care strategies.
2. Uncertain evidence of benefit: This category included interventions for which there was some evidence of benefit, but contradictory evidence or issues such as study design, location, or size precluded any firm conclusions. These interventions merited additional evaluation or research in developing-country community settings using well-designed protocols.
3. Some evidence of benefit: These interventions had some positive impact on perinatal and/or neonatal outcomes, but the evidence remained preliminary or the location of studies was not representative of the developing world at large. Furthermore, the trial designs were mostly efficacy studies, and therefore their effectiveness, if any, in large-scale programmatic interventions remained to be assessed. Inclusion of interventions in this category in neonatal health programs was considered optional, but a recommendation was made to evaluate the benefits whenever these interventions were implemented.
4. Clear evidence of benefit: This category of interventions was of incontrovertible benefit to mothers and/or newborn infants, and thus it was recommended that they be included in community-based intervention programs for maternal and neonatal care.

This report principally presents the initial analysis of the data based on quality and availability of the evidence. We do not report the projections of the impact of these interventions, either singly or combined as packages, on the global or regional burden of neonatal mortality. A preliminary exercise of this nature on a limited number of maternal and neonatal interventions was conducted by the Bellagio Child Survival Study Group,[10] and a comprehensive analysis is forthcoming in the *Lancet* Neonatal Survival Series in March 2005.

Results

We found a paucity of data from community-based settings in developing countries and a remarkable lack of large-scale effectiveness trials of a number of key interventions, especially in relevant health system settings. A total of 186 studies from developing countries were identified for in-depth review, of which only 64 were community-based studies reporting primary perinatal/neonatal health status outcomes such as stillbirths and perinatal and/or neonatal mortality, and 74 were community-based studies reporting secondary perinatal/neonatal health outcomes such as low birth weight (LBW) and/or anthropometrics, preterm birth, breastfeeding rates, and morbidities (Table 1). Of these studies reporting health outcomes, there were very few RCTs: 31 community-based RCTs reported primary neonatal health outcomes, and 40 reported secondary neonatal health outcomes. Only 10 studies were interventions conducted in health system settings, or effectiveness trials. Most interventions had been tested on relatively small numbers of individuals. There was also wide variation in the quality, size, location, design, and publication source of studies. This variability was considered while summarizing the information, although we refrain from direct comment on the quality of the evidence in individual studies, Table 2 (summarizing the strength of the evidence) represents a categorical ranking of interventions based on review of individual studies. In addition, however, as noted above, the evidence was placed in the context of biological plausibility and knowledge from developed countries, experience with the intervention in the context of health programs, and recommendations from the WHO and other leading maternal and child health agencies.

Discussion

Appropriate perinatal and neonatal care in any given circumstance in developing countries requires an integrated and holistic program of interventions at various levels. Interventions must not only include health-related measures that have a direct bearing on perinatal and/or neonatal outcomes but several other ancillary measures of equal importance. These measures include poverty alleviation; improved opportunities for female education; and improvement of women's social status, including empowerment and improvement of women's decision-making ability. Family size and short interpregnancy intervals are also critical factors in perinatal health.[11–13]

Implications for Programs

This review of evidence from developing-country community-based trials for impact of antenatal, intrapartum, and postnatal interventions on perinatal and neonatal outcomes highlights the paucity of available information, particularly from RCTs. Cost-effectiveness data were found to be almost entirely unavailable. The relative paucity of evidence for impact of interventions on neonatal mortality was also apparent in the recent analysis of the Bellagio Child Survival Study Group,[10] which nevertheless in-

TABLE 2. Summary of Impact of Antenatal, Intrapartum, and Postnatal Interventions on Perinatal and Neonatal Health Status Outcomes

Intervention	Evidence of No or Negative Impact (Leave out of Programs)	Uncertain Evidence (Need for Additional Research Before Including in Programs)	Some Evidence (May Include in Programs, but Additional Evaluation Is Warranted)	Clear Evidence (Merits Inclusion in Programs)
Antenatal interventions				
Maternal schooling/health education			X	
Antenatal care package(s)*			X	
Nutrition-related interventions				
Protein supplementation	X			
Balanced protein-energy supplementation			X	
Iron supplementation		X†		
Periconceptional folate supplementation			X	
Antenatal folate supplementation		X		
Iodine supplementation			X	
Antenatal vitamin A supplementation		X		
Zinc supplementation		X		
Multiple micronutrient supplementation		X		
Infection-related interventions				
Malaria				
Malaria chemoprophylaxis or IPT			X‡	
ITNs			X	
Deworming			X	
UTIs and reproductive tract infections				
Syphilis screening and treatment				X§
Antibiotics for asymptomatic bacteriuria			X	
Antibiotics for bacterial vaginosis		X		
Antibiotics for preterm labor	X			
Antibiotics for PPROM			X‖	
Tetanus				
TT immunization				X
Clean delivery practices				X
Maternal pneumococcal immunization		X¶		
Others				
Promotion of smoking cessation in pregnancy		X		
Maternal care packages			X	
Intrapartum interventions				
Maternal vaginal and newborn skin antisepsis			X	
Postnatal interventions				
Newborn resuscitation			X	
Delayed umbilical cord clamping		X¶		
Umbilical cord antisepsis		X		
Hypothermia prevention and management			X	
Hypoglycemia prevention and management			X	
Breastfeeding				X
Prevention of ophthalmia neonatorum			X¶	
Vitamin K prophylaxis		X		
Hepatitis B vaccination			X¶	
Neonatal vitamin A supplementation		X		
KMC			X	
Topical emollient therapy			X	
Hyperbilirubinemia screening		X¶		
TBA/CHW training			X	
Pneumonia case management				X
Neonatal care packages			X	
Care in peripheral health facilities			X	

* Priority interventions include TT immunization, iron-folate supplementation, detection and treatment of pre-eclampsia, and, where appropriate, detection and management of syphilis and malaria.
† Inclusion in programs may be warranted despite lack of evidence, which is due in part to ethical constraints in conducting RCTs of iron supplementation.
‡ Inclusion is indicated in endemic areas for reduction of maternal anemia and parasitemia and to improve birth weight; impact on mortality needs additional assessment.
§ Benefits of diagnosis and treatment are clear, but additional research is needed on cost-effective means of providing accessible and quality diagnosis and treatment at the community level.
‖ Appropriate at referral-level health facilities.
¶ Assessment based on health indicators other than neonatal health status outcomes.

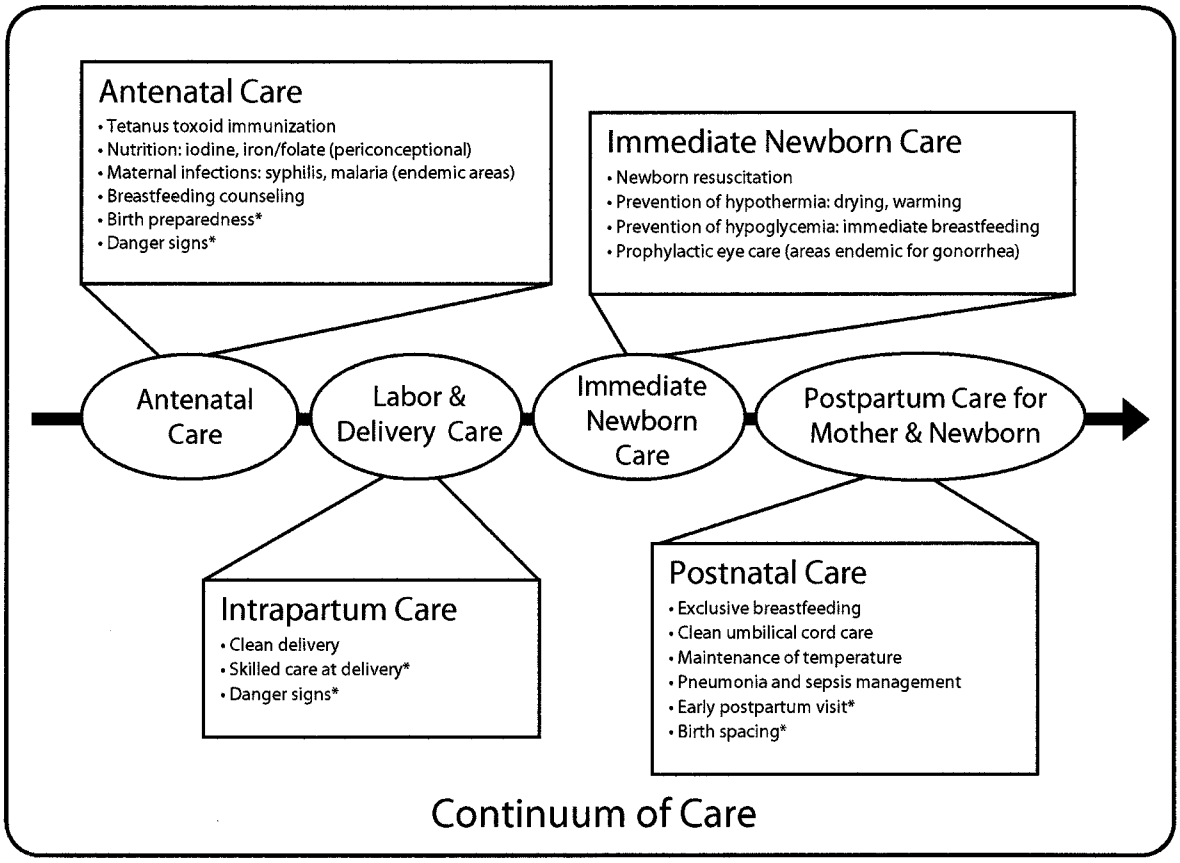

Fig 1. Summary of priority antepartum, intrapartum, and postnatal interventions for inclusion in programs of maternal and neonatal health care, based on assessment of available evidence for impact on perinatal and neonatal health status. * indicates essential elements of the Saving Newborn Lives conceptual framework for advancing newborn health and survival, which either were not reviewed in this report or for which evidence is lacking (see "Methods").

cluded several neonatal interventions because of their proven impact on infant and child survival. Not withstanding the above exercise, to broaden the relevance of the conclusions that can be drawn from the available data, we attempted to place the evidence in the context of biological plausibility, data from studies in developed countries, programmatic experience, and recommendations by the WHO and other leading child health agencies. In so doing, it is clear that the evidence for benefit of a number of interventions (Table 2) warrants their broad programmatic implementation (Fig 1). Interestingly, this group of evidence-based interventions closely resembles those advocated by the WHO[14–16] and also identified recently through a strategic planning process at the international level and in multiple countries, led by the Saving Newborn Lives Initiative of Save the Children/USA.[17] Thus, there seems to be broad convergence of expert opinion and the evidence base regarding priority interventions to advance perinatal and neonatal health and survival at the community level. Considering past experience of child health programs in implementation of various interventions and current recommendations of the WHO and leading child health agencies, a few additional interventions (marked with an asterisk) have been added to Fig 1 despite the lack of rigorous, prospective scientific evidence for their impact. These interventions include birth preparedness; recognition of and appropriate response to danger signs in the antenatal period; skilled health care at delivery (evidence reviewed elsewhere); recognition of and response to intrapartum danger signs; and early postnatal visitation for provision of anticipatory guidance and recognition/management of maternal and newborn illness. Many of these interventions have been included in comprehensive packages of maternal and newborn interventions but have not been evaluated per se for their specific contribution to the total impact of the package of care. Such evaluations must now be regarded as a priority, especially in health system settings.

Effective interventions span maternal and neonatal care, as anticipated when one considers that pregnancy-related causes, delivery-related causes, and infections each account for approximately one third of neonatal deaths.[18] This need for a continuum of care serves to illustrate the importance of integrating maternal and neonatal care while avoiding vertical programs for either the mother or the newborn. Moreover, although we emphasize impact on perinatal and neonatal outcomes (summarized in Tables 4–42), this review has further illustrated the principle that interventions in the antenatal and intrapartum periods frequently benefit both mother and newborn simultaneously.[19] Moreover, a coordinated approach to postpartum care for mother and newborn would similarly benefit both. Thus, one would

anticipate that an approach to maternal and neonatal health integrated within Safe Motherhood and Child Survival programs would not only foster continuity of care across the life cycle but also enhance the cost-effectiveness of packages of interventions.

Research Gaps

Although a number of interventions have been shown to reduce perinatal and/or neonatal mortality, there are fundamental gaps in our knowledge of how to most effectively improve perinatal and neonatal outcomes in developing-country communities. We know that implementation of comprehensive neonatal care programs can substantially reduce perinatal and/or neonatal mortality, but there is an urgent need to adapt and evaluate culturally and regionally appropriate packages of interventions in a variety of settings. Among these gaps in our knowledge is the critical issue of the determinants of family and community practices and their influence on newborn care and care-seeking behaviors. Better documentation of how behavior-change interventions are implemented and evaluation of these methods is needed to develop better tools for building individual, household, and community capacity for appropriate self-care and care seeking. In the context of the many parts of the developing world in which gender inequity and female feticide are major issues, this need for effective behavior-change approaches extends to newborn care and outcomes.

Pivotal questions regarding implementation of neonatal health care programs that demand additional operational research include: Which cadre of health workers in various settings can most effectively deliver the needed services for newborns at the community level, and how can they be linked effectively with referral facilities to provide care for maternal and neonatal illness? How will these workers be trained and supervised in a sustainable manner at scale, and what are the most effective methods for preservice and in-service training? What will be the scope of their service delivery (eg, with regard to client age, breadth of services, and geographic reach)? Is a team of skilled birth attendants and newborn care providers needed at the community level to provide simultaneous care for the mother and newborn during the critical intrapartum period?

The Save the Children/USA conceptual framework for newborn care at the community level[17] calls for provision of both preventive and curative care, particularly for birth asphyxia and infections. However, in many settings, provision of curative care for these major causes of neonatal mortality is beyond the capacity of current health care systems. Thus, critical unanswered questions are: Can effective implementation of a behavior-change communications package at the domiciliary level, without active identification and management of newborn illness, improve neonatal outcomes? What is the added benefit and cost-effectiveness of active identification and management of neonatal illness, particularly serious bacterial infections and intrapartum hypoxia/birth asphyxia? What are the most feasible and effective ways to deliver life-saving newborn resuscitation and antibiotic therapy in the community? How can barriers to care seeking for newborn illness be overcome most effectively so that home-based care and care seeking can be effectively linked with referral-level care at facilities? What is the impact and cost-effectiveness of postnatal visitation for promotion of healthful behaviors and recognition of neonatal illness? Can the same worker address the postnatal needs of both mothers and newborns? What is the optimal timing and number of routine visits with a health care provider?

Skilled care during delivery is universally recognized as a major long-term priority for improving the care of mothers and newborns, and plans for advancing health system capabilities for providing this care are paramount. Based on a consideration of the fact that most births and neonatal deaths occur at home during the early neonatal period, due to birth asphyxia and/or infections, and among LBW infants, the following emerge as major research gaps:

1. Understanding and improving household and community practices and their determinants: Local formative research is needed to better understand local beliefs and practices and the reasons behind them so that effective behavior-change strategies can be developed and evaluated.[23] This must be followed by appropriate research to develop intervention strategies to improve care-seeking behaviors at the household and community levels.
2. Improving health systems' capacity for providing essential preventive and special curative neonatal health care: As noted above, some of the most challenging questions in neonatal health care relate to how to most effectively deliver services to newborns in an integrated way within existing programs for maternal and child health.[20–22] Although difficult, determining the answers to these questions requires that many packages and combinations of interventions be tested through effectiveness trials in health system settings.
3. Preventing and improving recognition and management of birth asphyxia: Identification of sustainable interventions for management of intrapartum hypoxia/birth asphyxia is urgently needed at the community level.[24] Solutions must allow for immediate response at the time of delivery in a cost-effective manner and necessarily will require integration with skilled health care for mothers at delivery[16] and links with referral facilities.
4. Preventing and improving recognition and management of infections: There is an urgent need to identify how the burden and severity of maternal infections relate to perinatal outcomes. These infections may range from subclinical intrauterine infection and bacterial vaginosis to overt genital tract infections that may lead to preterm labor. The true burden of bacterial neonatal infections in community settings is also unclear, because many clinical bacterial infections may represent viral infections. Narrowing this information gap is vital; to devise optimal antibiotic treatment strate-

gies for neonatal infections,[25] we need to know the agents of life-threatening infections in the community and their antibiotic susceptibility patterns.[26] There is additional need for validated algorithms for accurate and rapid identification of infected neonates by community health workers (CHWs) and caregivers. We also must advance antibiotic-treatment strategies for serious infections, which may include simplified antibiotic-delivery systems and/or regimens. The potential development and evaluation of simplified oral treatment regimens that include oral administration will be a major advance for public health programs.

5. Preventing and improving care for LBW infants: Given that the majority of newborns who die in many developing countries are LBW, improved strategies for both prevention of and care for LBW infants are urgently needed. These strategies include interventions to reduce preterm births and the incidence of intrauterine growth restriction (IUGR) or combinations thereof. Prevention may be achieved by improved maternal nutrition and detection and treatment of maternal infections. Improved postnatal care of LBW infants may be achieved in part by behavior-change communications, topical emollient therapy, breastfeeding promotion, and widespread implementation of culturally adapted methods for skin-to-skin care (or variations thereof) with the mother and (when indicated) other household members. The development, validation, and availability of low-cost technology for the care of LBW infants in primary and secondary health care facilities is an important adjunct to community-based management strategies.
6. Improving information on the magnitude and causes of neonatal mortality: Lack of accurate global, regional, and country-specific data on the magnitude and causes of perinatal and neonatal morbidity and mortality currently is limiting advocacy and program planning in newborn health. Strengthening of information systems, including birth and death registration, and dissemination of information at local levels about causes of newborn morbidity and mortality (and their determinants), are needed to guide resource allocation and program and research priorities. Moreover, as programs incorporate newborn care, their impact must be monitored and accurate data fed back to those involved in health policy and program decision-making to enable them to use scarce resources more effectively. Integral to documenting and monitoring newborn health status is the need for improved verbal autopsy instruments to enable more accurate determination of causes of perinatal and neonatal deaths in the community and to assess the contribution of sociocultural and logistic factors. Perinatal audit may also be a powerful tool for identifying avoidable factors in deaths and mobilizing change in communities to improve maternal and neonatal health care.
7. Cost-effectiveness analyses: Assessment of cost-effectiveness must be incorporated into neonatal health research to guide selection of interventions and stimulate investment in neonatal health.
8. Development of indicators and simple management tools for assessing and monitoring health system performance for perinatal and newborn care at the national level: An important impediment to wider implementation of neonatal health programming is lack of inclusion of perinatal and neonatal health indicators among global indicators for measuring progress in child survival (eg, Millennium Development goals). Moreover, programs too often fail to monitor adequately and demonstrate the effectiveness of their programs. Tools for rapidly assessing the situation, prioritizing program activities, and accurately monitoring and documenting program effectiveness are urgently needed.

A major factor currently limiting our ability to identify effective interventions is the wide variation in study designs and indicators for assessing impact and the almost complete absence of cost-effectiveness data. In 2001, a group of neonatal health researchers met to discuss a common agenda and methodologies for neonatal health research in developing-country communities.[27] Our review further highlights the need, as recommended at that time, for dialogue among researchers, policy makers, program managers, and donors in the selection of research priorities, use of common (and, whenever possible, rigorous) study designs, and for sharing of data-collection instruments and research results.

Conclusions

A paucity of community-based data are available from developing countries on health status impact of many interventions that are currently considered for inclusion in health programs for newborns. However, a review of the evidence and consideration of the broader context of knowledge, experience, and recommendations regarding these interventions enabled us to categorize the interventions according to the strength of the evidence base and confidence that the intervention could be implemented widely and would improve perinatal and/or neonatal survival. As a result, a package of priority interventions for inclusion in programs was identified, and research priorities for advancing the state-of-the-art in neonatal health care were formulated. Thus, this review can serve as a guide for development of evidence-based maternal and newborn health care programming at the community level and for selection of research to advance community-based neonatal care. It also may facilitate dialogue with policy makers about the importance of investing in newborn health.

Clearly, there is ample evidence for benefit of several interventions, and, in many cases, operational questions of how to implement the intervention(s) in an affordable and acceptable manner at scale were of overriding concern. Thus, although there is great need for continued research on the cost-effectiveness of a number of interventions, it must not hamper implementation now of many interventions of known impact at wider scale. However, it is impor-

tant that these intervention packages be structured as integrated maternal and newborn care strategies that can be implemented in appropriate health system settings. Close communication between program managers as they gain experience with intervention implementation, the researchers who can provide answers to operational questions, and the donors who fund the work will be critical to advancing maternal and neonatal health care at the community level.

INTRODUCTION AND BACKGROUND

Infant and under-5 childhood mortality rates in developing countries have declined significantly in the past 2 to 3 decades, whereas neonatal mortality rates (NMRs) have remained relatively static.[18,20,24,28] Neonatal mortality, amounting to an estimated 4 million deaths worldwide each year, now comprises nearly two thirds and two fifths of infant and under-5 childhood mortality, respectively, in developing countries,[29] and 98% of global neonatal mortality occurs in developing countries.[30] An equal number of deaths are thought to occur during the last trimester of pregnancy, although data precisely quantifying the burden of stillbirths are lacking. Unfortunately, most of the countries with high rates of perinatal and neonatal deaths also have the lowest rates of vital registration of births and deaths.[31,32] Moreover, the likelihood of missing live births is highest for very low birth weight (VLBW) infants,[33] and rates of LBW are highest in developing countries, especially Asia.[18] In addition, neonatal health indicators are seldom included in Safe Motherhood or Child Survival program evaluations, nor are they among the outcomes of interest of global agencies and initiatives. Thus, current estimates of perinatal and neonatal mortality, although startlingly high, may nevertheless underestimate the true burden.

It is now recognized that reducing perinatal and neonatal mortality is of paramount importance for additional gains in child survival to be realized.[20,26,32,34,35] Moreover, because the majority of perinatal and neonatal deaths in developing countries occur in the home, there is an urgent need to identify solutions at the community level.[18,20,22,26] To achieve Millennium Development Goal 4 of halving child mortality by the year 2015, major advances in neonatal survival must be achieved through widescale implementation of cost-effective interventions in the community.[22]

There is little debate that perinatal and neonatal mortality are profoundly affected by proximal factors that influence maternal health such as socioeconomic deprivation, gender bias, illiteracy, and high fertility rates, and redress of these factors is critical to improving maternal and neonatal health in developing countries.[4,36] However, these elements are relatively resistant to change in the short term.[37–42] Moreover, as a consequence of such systematic neglect, a sense of fatalism and inevitability of adverse fetal and neonatal outcomes sets in and further impedes care seeking.[22,43,44] This in itself is a major barrier to improvement in perinatal and neonatal outcomes. The concept that all people possess equal rights to health, education, and social services is a key factor in creating demand for better allocation of health care resources for women and newborns. This must be coupled with greater participation of individuals and communities in planning and meeting their own health care needs, particularly women within traditional societies through empowering them to participate in decision-making processes.

Because the health of the mother and newborn are intimately entwined, they must be considered together when planning strategies to improve perinatal and neonatal outcomes. It is important to highlight that the peak period of vulnerability for both the mother and newborn is around pregnancy and childbirth. Thus, interventions must largely focus on addressing joint outcomes. There is evidence, however, that this has not been widely adopted, that Safe Motherhood interventions have not adequately addressed the newborn period, and that newborn interventions rarely focus on integration with existing maternal care programs and services.

To redress the burden of perinatal and neonatal mortality, several factors are required: (1) political commitment to newborn health at the global, regional, national, and local levels; (2) increased focus on the newborn within existing Safe Motherhood and Child Survival programs; (3) efficient allocation of resources; (4) effective implementation of cost-effective interventions; and (5) clear documentation of impact.[18] To aid in garnering political and programmatic will and action to improve perinatal and neonatal health care and status, the magnitude of the problem and evidence for effectiveness of interventions to prevent and manage adverse outcomes must be documented clearly. A recent analysis of the neonatal burden of disease in south Asia and sub-Saharan Africa, in which approximately three fourths of neonatal deaths occur, highlighted the dearth of information available on neonatal outcomes in developing countries, particularly at the community level.[28] Similarly, a recent meeting of neonatal health researchers highlighted the need for a review of available evidence for impact of interventions on perinatal and neonatal health and survival.[27]

Neonatal health experts agree that improving neonatal health and survival in developing countries depends in large measure on more effectively implementing what has already been shown to work.[18,26,34,35] Moreover, a number of health interventions for the mother and her newborn have been proposed by the WHO and others as global priorities for programmatic implementation.[14,18,26,34,35,45,46] Although many advances in obstetric and neonatal care are costly and require technologies that are unavailable in resource-poor countries, a substantial proportion of perinatal and neonatal morbidity and mortality in developing countries could be prevented through appropriate adaptations and applications of inexpensive, relatively simple methods to improve antenatal, obstetric, and neonatal care. The fact remains that improvements in care are often limited more by lack of adequate knowledge and its appropriate application than by technologic barriers. In other cases, however, additional research is needed

to devise, adapt, and evaluate sustainable solutions, particularly at the community level. Although reviews of the impact of certain antepartum, intrapartum, and postnatal interventions have been conducted, evidence for proven benefit, or lack thereof, of the many interventions that one might include in a neonatal health program at the community level has never been systematically evaluated and summarized. Major evidence gaps include lack of objective data on the methodologies of introducing interventions within health system settings and evaluating hard outcomes through effectiveness-trial designs. The limitations of the strictly randomized-trial design have been recognized in health systems research and interventions.[8]

This review of community-based antenatal, intrapartum, and postnatal intervention trials in developing countries was undertaken to (1) identify key behaviors and interventions for which the weight of evidence is sufficient to recommend their inclusion in community-based neonatal care programs and (2) identify key gaps in knowledge and priority areas for future research and program learning. We did not focus on long-term solutions of established and indisputable value in improving maternal and perinatal outcomes, such as poverty reduction, gender equity, fertility regulation and control, and improved health system performance. Rather, the focus of this review was on specific targeted interventions that may impact perinatal and neonatal health status outcomes, primarily perinatal and neonatal mortality.

METHODOLOGY USED FOR LITERATURE SEARCH AND REVIEW

This review aimed to consider all available published and unpublished data on the impact of community-based strategies and interventions on perinatal and neonatal health status outcomes. The community was defined as extending from the household to peripheral health facilities.

The search methodology included review of the following sources of information:

1. All available electronic reference libraries of indexed medical journals and analytical reviews
2. Electronic reference libraries of nonindexed medical journals
3. Nonindexed journals not available in electronic libraries
4. Pertinent books, monographs, and theses
5. Project documents and reports

Electronic Reference Sources

The following principal sources of electronic reference libraries were searched to access the available data on community-based intervention studies: Cochrane Reference Libraries, the WHO Reproductive Health Libraries, Medline, PubMed, ExtraMed, Embase, and Popline. Several search strategies were employed using key words, combinations, and medical subject headings (MeSH) words including "community-based care," "community care," "newborn or neonatal care," "perinatal care," "interventions," "intervention strategies," "perinatal or newborn care programs," "newborn survival," "perinatal outcomes," and "neonatal outcomes," among others.

Manual Literature Search

A detailed examination of cross-references and bibliographies of available data and publications was performed to identify additional sources of information. In particular, this search extended to reviewing the gray literature in nonindexed and nonelectronic sources. The bibliographies of 37 recently published textbooks or books with sections pertaining to community-based maternal and/or newborn care were also searched manually. Requests for information were sent to major development and aid agencies including the World Bank, United Nations Children's Fund (UNICEF), WHO, Department for International Development, United Nations Development Programme, United States Agency for International Development, MotherCare, JHPIEGO, the Wellcome Trust, LINKAGES, John Snow Inc, National Institute of Child Health and Human Development, National Institutes of Health (NIH) Institute of Medicine, CARE, Save the Children/USA, and several other nongovernmental organizations. In particular, requests for information were made to regionally active development agencies and research councils. In addition, personal requests for information on community-based perinatal and neonatal interventions were made to leading public health scientists in the field.

For in-depth review, we selected 186 studies from developing countries that directly related to the research question of health status impact of community-based perinatal and neonatal health care. These studies were analyzed in detail and summarized in the tables according to a standardized, prearranged evaluation format as to their location, size, design, nature of intervention, and outcome. The information was categorized according to whether the target group consisted of mothers, newborn infants, or both.

The following categorization of interventions was made:

Maternal Interventions

1. Maternal schooling/health education
2. Antenatal care packages
3. Protein supplementation
4. Balanced protein-energy supplementation
5. Iron supplementation
6. Folate supplementation
7. Iodine supplementation
8. Antenatal vitamin A supplementation
9. Zinc supplementation
10. Multiple micronutrient supplementation
11. Malaria chemoprophylaxis or intermittent presumptive treatment (IPT)
12. Malaria protection using insecticide-treated bed nets (ITNs)
13. Deworming
14. Syphilis screening and treatment
15. Antibiotics for asymptomatic bacteriuria
16. Antibiotics for bacterial vaginosis

17. Antibiotics for preterm labor
18. Antibiotics for preterm premature rupture of membranes (PPROM)
19. Tetanus toxoid (TT) immunization and clean delivery
20. Maternal pneumococcal immunization
21. Promotion of smoking cessation during pregnancy

Composite Interventions

In addition to the specific community-based interventions noted above, some studies evaluated packages of maternal interventions in community settings:

22. Maternal care packages

Intrapartum Interventions

1. Maternal vaginal and newborn skin antisepsis

Postnatal Interventions

1. Newborn resuscitation
2. Delayed umbilical cord clamping
3. Umbilical cord antisepsis
4. Hypothermia prevention and management
5. Hypoglycemia prevention and management
6. Breastfeeding
7. Prevention and treatment of ophthalmia neonatorum
8. Vitamin K prophylaxis
9. Hepatitis B vaccination
10. Neonatal vitamin A supplementation
11. Kangaroo mother care (KMC)
12. Topical emollient therapy
13. Hyperbilirubinemia screening
14. Traditional birth attendant (TBA)/CHW training
15. Pneumonia case management

Composite Interventions

Apart from community interventions focusing on the aforementioned specific areas, some studies evaluated packages of postnatal interventions or the functioning of hospitals in the community and interventions performed within them, including use of alternative methods of care to compensate for meager resources and facilities:

16. Neonatal care packages
17. Care in peripheral health facilities

Exclusions

Some interventions were excluded from this review because other investigators were evaluating the evidence base for their impact. Interventions excluded included the following:

1. Roles of skilled birth attendants
2. Family planning and birth spacing
3. Safe Motherhood strategies such as prevention and treatment for pre-eclampsia, pregnancy-induced hypertension, and antepartum hemorrhage; newer strategies for prevention of preterm labor (eg, magnesium, calcium, fish oil); emergency obstetric care; emergency transport services; communications strategies; community waiting homes; and use of fetal partograph
4. HIV prevention and mother-to-child transmission reduction strategies
5. Maternal tuberculosis treatment

Synthesis of Evidence

The principal reviewers independently evaluated all the data, and a common reporting matrix was used in summarizing the findings. Emphasis was placed on assessment of impact on perinatal or neonatal primary health status outcomes. For some interventions, however, for which data on primary health status outcomes were lacking, other indicators were considered.

The final categorization of the interventions was done by mutual agreement and consensus as follows:

1. No evidence of benefit: These interventions had been evaluated and found to have no demonstrable benefit either singly or in combination with other measures. In some cases, there was evidence of an adverse effect of the intervention. Therefore, these interventions were not recommended for inclusion in any neonatal health care strategy.
2. Uncertain evidence of benefit: This category included interventions for which there was some evidence of benefit, but contradictory evidence or issues such as study design, quality, location or size precluded any firm conclusions. These interventions merited additional evaluation or research using well-designed protocols and designs.
3. Some evidence of benefit: These interventions had some positive impact on perinatal or neonatal outcomes, but the evidence remained preliminary or the location of the studies was not representative of the developing world at large. Furthermore, the trial designs were mostly efficacy studies; therefore, their effectiveness, if any, in large-scale programmatic interventions remained to be assessed. Their inclusion in intervention programs was considered optional, but a recommendation was made to include an evaluation of benefits whenever they were included.
4. Clear evidence of benefit: This category of interventions was of incontrovertible benefit to mothers and/or newborn infants, and thus it was recommended that they be included in community-based intervention programs for maternal and perinatal care.

When categorizing the evidence for impact of interventions, we considered a variety of factors including the study size, location, and rigor of design; consistency and magnitude of impact reported, particularly on perinatal or neonatal mortality; biological plausibility of the intervention; evidence from relevant developed-country studies; experience with implementing the intervention in health care programs; and recommendations from the WHO and other leading agencies in maternal and child health. Thus, the evidence was put into a broader context to reach a composite assessment that was agreed on by the principal investigators (Z.A.B. and G.L.D.).

TABLE 3. Association of Maternal Education With RR of Neonatal Death (52)

RRs	Years of Schooling			
	0	1–3	4–6	≥7
Neonatal mortality				
Unadjusted	1.00	0.87	0.76	0.57
Adjusted for socioeconomic factors	1.00	0.98	0.90	0.86
Postneonatal mortality				
Unadjusted	1.00	0.82	0.73	0.45
Adjusted for socioeconomic factors	1.00	0.98	0.90	0.78

REVIEW AND ANALYSIS OF AVAILABLE DATA

Antenatal Interventions

Maternal Schooling/Health Education

BACKGROUND. The relationship between maternal antenatal education and perinatal and neonatal outcomes is well established. Caldwell and McDonald[47] demonstrated the close relationship between maternal education level (ie, schooling) and infant mortality from observations in Nigeria. Since then, this association has been borne out through a number of reviews.[40,48–51] Victora et al,[39] in a review of cause-specific infant mortality rates (IMRs) in Pelotas, Brazil, found a significant inverse relationship between maternal schooling and deaths from perinatal conditions, particularly infectious diseases. The association between increased maternal education and decreased infant mortality, particularly in reducing postneonatal deaths, was further strengthened by a review of 34 cross-sectional World Fertility Surveys between 1974 and 1980,[52] although the association was weakened when the data were corrected for socioeconomic status[53,54] (Table 3). The association between maternal education and neonatal survival was also corroborated by analysis of data from 11 Demographic and Health Surveys; in this review, the association held even after correction for socioeconomic status.[38,55] More recently, the importance of maternal education in reducing birth weight–specific perinatal mortality in Nigeria was further stressed by Harrison,[42] and the association between educational level of the maternal grandmother and utilization of health services for prenatal care and delivery by a skilled attendant was also demonstrated.[56]

There are surprisingly few intervention studies on the specific impact of maternal health education on perinatal and newborn outcomes. Kramer[57] evaluated the evidence, including that from an intervention trial in Greece,[58] of the potential benefit of maternal nutritional advice during pregnancy on several outcomes. Although an increase in energy and protein intake during pregnancy was notable, the overall impact on maternal, perinatal, and neonatal outcomes was unclear.

Reasons for improved survival of neonates born to more highly educated mothers is not clear, but the association is only partly explained by the economic advantages and access to health care afforded by education. Potential links between maternal education and reduced perinatal and neonatal mortality also include appropriate birth spacing and health-seeking behavior, particularly for prenatal care. There is strong evidence supporting the importance of community- and hospital-based maternal education and support programs on breastfeeding practices[59–62]; these programs are reviewed below (see "Breastfeeding").

COMMUNITY-BASED EVIDENCE. Although there are data available from developed countries on maternal educational strategies specifically aimed to improve perinatal and neonatal outcomes,[63–65] there are few systematic studies that have prospectively evaluated their impact,[57] particularly from developing countries. Woods and Theron[66,67] in South Africa demonstrated a significant improvement in cognitive knowledge of midwives who participated in an extended perinatal education program; however, impact on perinatal outcomes was not reported. In contrast, providing postnatal maternal education in Nepal through a limited didactic educational interaction met with little success in improving knowledge and practices, except for family-planning practices.[68] Although the impact of the didactic form of education was not found to be effective, the authors of the latter study subsequently concluded that community participation was a key to the success of educational strategies. These intervention strategies include the development of intervention strategies by community members themselves, based on their understanding of barriers to care seeking for newborn care.[69,70]

CONCLUSIONS. Maternal educational level is clearly associated with improved perinatal and neonatal survival. Thus, building the capacity of mothers through basic education is a key long-term strategy to improve perinatal and neonatal health in developing-country communities. More work is needed, however, to develop and test shorter-term maternal educational strategies targeted toward improving pregnancy outcomes in developing countries, particularly at the community level. The exact nature and content of the educational package, roles of different cadres of health workers, and ways to convey the messages at the community level most effectively may best be developed and evaluated considering the principles of appropriate and participatory community-based research.[71]

Antenatal Care Packages

BACKGROUND. Antenatal care is well regarded as 1 of the 4 main pillars of Safe Motherhood by the WHO.[14] Although the beneficial effects of antenatal care for maternal health and outcomes are well recognized and the practice is well established, there have been few systematic studies of the impact of "standardized" antenatal care programs on perinatal and neonatal outcomes.[72,73] No intervention studies are available that directly compared groups of women who received antenatal care and those who did not, thus limiting conclusions regarding the extent to which antenatal care improves perinatal/neonatal outcomes.

The benefits of antenatal care for maternal and newborn outcomes, including assessment of the most effective components, were addressed in sys-

TABLE 4. Components of Antenatal Care

Condition/Intervention	Test/Treatment	Expected Impact on Maternal and Newborn Outcomes
Prevention of anemia	Routine supplementation with iron and folate during pregnancy	Prevents or reduces fall in maternal Hb
	Malaria chemoprophylaxis	Reduces percentage of women who become anemic
Treatment of iron-deficiency anemia	Oral iron and folate	Can raise maternal Hb by 0.4–0.7 g/dL per wk
Detection and investigation of hypertensive disease of pregnancy	Measurement of blood pressure with sphygmomanometer using fifth Korotkoff sound	Detects maternal hypertension and allows selection of cases at higher risk of maternal and perinatal morbidity
	Analysis of clean catch urine	Detects maternal proteinuria, indicative of pre-eclampsia in the presence of hypertension
Treatment of severe pre-eclampsia	Transfer to first referral level for expert care	Control of maternal disease; reduces maternal case fatality
Screening for infection	Serological screening and treatment for syphilis	Detects asymptomatic maternal disease; coupled with effective treatment, contact tracing, and follow-up, reduces fetal loss and maternal and infant morbidity
	Microbiological screening for gonorrhea	Detects asymptomatic maternal disease; coupled with effective treatment, contact tracing, and follow-up, reduces fetal loss and maternal and infant morbidity
	Screening for bacteriuria with quantitative culture of urine	Detects asymptomatic disease; coupled with effective treatment, prevents pyelonephritis and preterm delivery/LBW
Prevention of infection	Tetanus immunization in pregnant and/or child-bearing–age women	Prevents maternal and neonatal tetanus

tematic analyses by Bergsjo and Villar[72,74] and Carroli et al.[75] Some of the major interventions introduced during antenatal care and their impact on pregnancy outcomes are detailed in Table 4. TT immunization, iron-folate supplementation, detection and management of pre-eclampsia, screening and treatment for bacteriuria, and where appropriate, screening and treatment for syphilis and malaria are priority activities. Although some studies have indicated that antenatal care alone may be insufficient for the identification of pregnant women at risk of obstetric complications and emergencies,[76–78] there is observational evidence from a variety of geographic settings that lack of antenatal care is associated with increased risk for late fetal death.[79,80] Although the evidence is somewhat mixed, the overall consensus is that quality antenatal care provided by a trained attendant within a functional health system reduces the risk of maternal mortality and adverse pregnancy outcomes.[81]

Although there is some evidence that antenatal care works, there is little consensus on critical related issues such as the minimum number of visits and the most cost-effective components of antenatal care. In an evaluation of antenatal care models in the United States, McDuffie et al[82] found comparable pregnancy outcomes among women who had attended a modified program of 2.7 fewer visits, on average, compared with the traditional program of 7 antenatal visits. To further evaluate whether a reduced system of 4 antenatal care visits was as effective as a program with more frequent visits, the WHO organized a multicenter trial involving urban centers in Saudi Arabia, Argentina, Cuba, and Thailand (Table 5).[83,84] No impact was observed in this large trial on either preterm birth or IUGR.[84] Women who received information about breastfeeding antenatally were more likely to initiate breastfeeding after birth. Those assigned to the reduced-visit model had similar maternal (ie, morbidity index, urinary tract infection [UTI], and anemia rates) and neonatal (ie, perinatal mortality rate [PMR], NMR, LBW rate) outcomes as those who were given standard antenatal care, although women who had >4 antenatal visits were more likely to feed their infants colostrum. The participants of the trials were generally satisfied with the quality of care in the new, modified system of antenatal care.[85]

A recent systematic review of randomized trials also 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.[75] This systematic review of pooled data on alternative models of reduced numbers of antenatal care visits showed similar odds of multiple health outcomes compared with the standard care model, including pre-eclampsia (odds ratio [OR]: 0.91; 95% confidence interval [CI]: 0.66–1.26), UTIs (OR: 0.93; CI: 0.79–1.1), maternal mortality (OR: 0.91; CI: 0.55–1.51), incidence of LBW (OR: 1.04; CI: 0.93–1.17), and overall perinatal mortality (OR: 1.06; CI: 0.82–1.36).

TABLE 5. Antenatal Care Packages

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Villar et al[84]	Multicenter trial in Saudi Arabia, Argentina, Cuba, and Thailand; urban centers; RCT	Women (n = 24 678) received either standard antenatal care (n = 11 958) or a new model involving fewer visits incorporating scientifically evaluated and objective-oriented activities (n = 12 568); the others were given the care appropriate to any detected condition or risk factor.	The maternal morbidity index (83) reached a threshold value in 14.5% of women for the new model and 16.5% for the standard model; there were no significant differences in UTI or maternal anemia rates between the 2 groups.	The PMR (2% vs 1.7%), NMR (0.4% each), and LBW rates (7.2% vs 6.7%) were similar in both models.
Munjanja et al[713]	Zimbabwe; rural setting; RCT	Study clinics had fewer visits but more objectively structured visits and fewer procedures (n = 15 994 women recruited: 9394 under the intervention program and 6138 under the standard program).	There were 6 maternal deaths in study clinics versus 5 in control clinics.	There were 12% fewer premature births in the study clinics (OR: 0.86; CI: 0.78–0.96); no effect was seen on LBW (OR: 0.96; CI: 0.85–1.08) or PMR (OR: 1.2; CI: 0.92–1.6; P = .18).
Srinivasan et al[714]	India; rural setting; RCT	Women were randomized to receive 1 of 3 packages: (1) high-risk package, in which trained midwives identified high-risk pregnancies and intervened accordingly; (2) Tamil Nadu package, which included trained midwives but not high-risk pregnancy identification; and (3) a control group that received a basic package of government-approved care (n = 1145 pregnant women in the study area; 380 were in the high-risk pregnancy group, 320 were in the Tamil Nadu group, and 445 were in the control group).	Higher rates of TT immunization were seen in the high-risk package and Tamil Nadu groups (98% and 95%, respectively) than in the control group (72%). Similarly, higher rates of iron-folate usage were observed in the high-risk package and Tamil Nadu groups (75% and 79%, respectively) than in the control group (13%); the proportion of women with maternal Hb <8 g/dL at 34 wk was 16.6% in the Tamil Nadu series but only 5.5% in the high-risk package series.	The proportion of preventable neonatal morbidity was lower in the high-risk package series than in the Tamil Nadu series by 11% (CI: −0.8–22.8; P = .06).

CONCLUSIONS. The benefits and importance of antenatal care in improving maternal health and pregnancy outcomes are widely accepted, yet little direct evidence of impact exists from intervention trials. An antenatal care package that consists of fewer but qualitatively better and more goal-oriented visits is recognized to be more cost-effective than the "conventional" antenatal care packages promoted previously, which involved more frequent visits. However, this evaluation was also not undertaken as an effectiveness trial in health system settings. It is also important to point out that there are no studies evaluating different community-based models of antenatal care using primary heath care workers and CHWs.

The exact margin of improvement in neonatal mortality after antenatal care is unclear, and we could not cite a specific figure based on objective evidence and controlled trials. Moreover, a controlled trial to determine the level of effect would now be unethical. The exact contents of such a package would need to be based on evidence of the efficacy of each individual component of the package plus the cost-effectiveness and relative ease of implementation by primary care workers. Based on the available evidence elaborated in this review, the antenatal care package should contain, at a minimum, TT immunization, iron-folate supplementation, and promotion of clean delivery and exclusive breastfeeding. Based on health system capacity, the package should also include supplementation with iodine and screening and treatment for bacteriuria, preeclampsia, and syphilis.

Nutrition Interventions in Pregnancy

Maternal malnutrition is widespread in developing countries and is an underlying factor in fetal malnutrition and LBW as well as other adverse pregnancy outcomes such as premature births, abruptio placentae, and stillbirths.[86,87] A large proportion (16%) of births in developing countries are LBW, which is a major underlying risk factor for morbidity and mortality in the perinatal and neonatal periods and later in infancy.[86,88] Poor maternal nutritional status is associated with adverse birth outcomes,[11,89] but the association with fetal mortality is less clear. Given the recognized association between maternal malnutrition and LBW, there has been considerable interest in nutritional interventions that may improve birth weight as well as other adverse pregnancy outcomes.[87] With the emerging evidence of the long-term implications of fetal malnutrition, nutrition transition, and adverse metabolic outcomes such as diabetes,[90] it becomes even more imperative to improve maternal and fetal nutrition in developing countries. Two recent reviews evaluated the impact of nutrition interventions on prematurity[91] and pregnancy outcomes[92] and underscored the fact that few studies have addressed this problem in community settings in developing countries.

Evidence for impact of nutritional interventions on maternal, perinatal, and neonatal outcomes has been reviewed extensively, largely within the Cochrane collaboration using meta-analyses of RCTs. Available data have also been reviewed recently as part of an evaluation of the evidence base for Safe Motherhood strategies[93] and a review of the efficacy and effectiveness of nutrition interventions.[94] Our evaluation of the evidence was drawn largely from these sources, especially the individual community-based studies in developing countries within the Cochrane reviews. In addition, we evaluated recent studies that have not yet been included in the Cochrane reviews and others with a quasi-experimental design that were not considered as part of the meta-analyses.

Protein Supplementation

BACKGROUND. Benefits of unbalanced protein supplementation in pregnancy were largely refuted recently in a meta-analysis of available evidence.[95] Such interventions have been tried historically in a variety of malnourished and at-risk populations including poor communities in developed countries.[96,97] In 3 studies among Asian women in the United Kingdom and Chile, where the usual maternal energy intake was isocalorically replaced with 10% to 11% protein,[98–100] there was no effect on pregnancy outcomes, although there was a trend toward reduced birth weight. Even higher levels of protein supplementation (>25% of energy) in relatively well-nourished populations failed to show any benefit on pregnancy outcomes and birth weight.[101,102] Thus, protein supplementation alone is no longer viewed as a viable intervention during pregnancy.[103]

CONCLUSIONS. Based on a large body of evidence, pure or high levels of dietary protein supplementation cannot be recommended as an antenatal intervention, nor is additional research warranted on this intervention.

Balanced Protein-Energy Supplementation

BACKGROUND. Balanced protein-energy supplements, by definition, provide <25% of their total energy content in the form of protein. A systematic review done by the Cochrane collaboration on the effect of antenatal maternal balanced protein-energy supplementation[95] concluded that this intervention significantly improved fetal growth and reduced the risk of fetal and neonatal death. The findings of this review, however, were largely influenced by 1 large trial undertaken in The Gambia that indicated a significant reduction in perinatal mortality.[104] However, this efficacy study also included micronutrient supplementation in addition to balanced protein-energy intake. Excluding this single study drastically altered the conclusions of this meta-analysis, leaving no demonstrable impact.

COMMUNITY-BASED EVIDENCE. A review of the literature identified 19 studies, 12 of which were undertaken in community settings and discussed pregnancy outcomes, thus fulfilling our criteria for selection. The details of these studies are given in Table 6. These trials were largely conducted in developing countries and inner-city populations in industrialized countries. Inconsistent results may have been related to the variability in the background rates of maternal malnutrition in the different study

TABLE 6. Antenatal Balanced Protein-Energy Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Ceesay et al[104]	The Gambia; rural setting; RCT	Treatment group consisted of pregnant women who received high–protein energy biscuits; the control group consisted of women who did not receive the supplement (247 normal singleton live births among 1460 women; treatment group: 1010 live births; control group: 1037 live births).		Incidence of stillbirths decreased by 53% in the intervention group (OR: 0.47; CI: 0.23–0.99; $P < .05$); a 46% decrease was recorded in the number of deaths occurring in the first week of life (OR: 0.54; CI: 0.35–0.85; $P < .01$), but there was no effect on mortality rates after 7 d of life ($P > .2$); there was a significant increase in birth weight of infants born to mothers in the intervention group (mean increase: 136 g; $P < .001$); a 39% decrease was seen in LBW rates among the infants of the intervention group ($P < .001$).
Kusin et al[109]	East Java, Indonesia; rural setting; QT	Pregnant women ($n = 542$) were assigned to low- and high-energy supplementation groups.		For women who consumed the supplements for >45 d, there was a significant difference in birth weight (463 g) between the 2 groups; a difference of 421 g ($P = .017$) was seen in infant weight at 12 mo of age.
Kardjati et al[116]	East Java, Indonesia; rural setting; double-blind, randomized, controlled trial (DBRCT)	Pregnant women ($n = 741$) in 3 villages were assigned to a high-energy ($n = 272$) or low-energy ($n = 265$) group; there were 204 noncompliers excluded from these groups; among these, 6 additional groups were formed according to the number of energy packets consumed during the trial.	No difference in weight gain was seen among the women of the 2 groups compared with noncompliers.	There was no significant effect of the supplementation on birth weight and LBW rates when compared to the baseline period during which no supplementation was provided.
Villar and Rivera[111]	Guatemala; rural setting; QT	169 mothers and their offspring were enrolled during 2 consecutive pregnancies and the interim lactation period; 2 types of supplements (*atole,* a high-protein and high-calorie gruel, and *fresco*, a no-protein/low-calorie cold liquid drink) were offered to pregnant and/or lactating women.		There was an impact of the supplement on birth weight, with a linear trend for increased ($P < .05$) birth weight from the highest (*atole*) to the lowest (*fresco*) supplemented groups.
Tontisirin et al[110]	Thailand; rural setting; RCT	Women ($n = 43$) in their third trimester were divided into 3 groups: groups 1 and 2 (14 in each group) received 2 different levels of supplementation, whereas group 3 ($n = 15$) acted as controls; group 2 had the highest protein and calorie content in their supplement.		There was a significant increase in birth weight of infants born to women in group 1 (3089 ± 308 g; $P < .025$) and group 2 (3104 ± 259 g; $P < .025$) compared to the group 3 controls (2853 ± 247.9 g); the placental weights also were significantly higher in the 2 supplemented groups (630 ± 669 and 616 ± 68 g in groups 1 and 2, respectively; $P = .005$) that were supplemented compared to the control group (563 ± 509 g).
Girija et al[117]	India; urban hospital setting; RCT	Pregnant women ($n = 20$) were recruited for the study: 1 group ($n = 10$) was supplemented in the last trimester with sesame cakes, *jaggery* (raw sugar), and oil; women in the control group ($n = 10$) were not given the supplement.	There was no difference in weight gain of women in the supplement compared with the control group; women in the supplemented group, however, had a significantly greater increase in Hb levels.	There was no significant difference in birth weight and length at birth of infants born to the 2 groups of women.

TABLE 6. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Prentice et al[112]	The Gambia; rural setting; QT	Pregnant women who were, on average, in their 16th wk of gestation were supplemented with peanut-based biscuits and a vitamin-fortified tea drink (n = 652 nonsupplemented women and 577 supplemented women).		Infants born to the supplemented mothers were significantly heavier (101 g) than those born to nonsupplemented mothers ($P < .05$); this beneficial effect of supplementation was seen only in the wet season, not during the dry season; a 67.5% decrease was observed in the proportion of LBW infants in the supplemented group over the year ($P < .01$); this effect was greater in the wet season, during which there was a decrease of 83.3% in the proportion of LBW infants ($P < .01$); supplementation also seemed to contribute to increased head circumference in infants.
McDonald et al[108]	Taiwan; rural setting; DBRCT	Women (n = 212) were distributed randomly to groups A (n = 107) and B (n = 105); pregnant women in group A were given high-protein and -calorie liquid supplements, and the supplement was provided to group B was low in calories and had no protein; the trial started after the birth of the "first study infant," and the women were supplemented until onset of lactation of the "second study infant."		There was no difference in the incidence of fetal deaths among the "first" and "second" study infants of the 2 groups; a mean increase in birth weight of 161.4 g was observed in the second study infants in group A ($P < .05$); LBW rates decreased to 2.8% for the second infant in group A (statistically insignificant), whereas it remained the same for group B at 6.8%; there was no effect of the supplements on prematurity rates.
Kielmann et al[118]	India; rural setting; RCT	3 groups of villages were randomized into nutrition care (NUT), nutrition care plus medical care (NUT + MC), or medical care (MC); a fourth group (emergency care only) served as the control group; nutrition care was comprised of nutrition education, surveillance, and food supplementation (1675 J and 11 g of protein per day, fortified with iron and folate) through special feeding centers; medical care included immunization, health education, early diagnosis, and treatment through frequent surveillance, provided singly and combined as needed; monitoring from birth to age 36 mo was done through longitudinal anthropometry, morbidity, and vital statistics.		There was a 41.3% decrease in PMR in the nutrition group compared to the control group; this decrease was higher among the 3 intervention groups (MED, NUT, and MED + NUT groups) compared to controls; the decrease in NMR was highest in the nutrition intervention group (41%) compared to the control group.
Mora et al[245*]	Colombia; urban setting; QT	Women (n = 456) in their third trimester and from a family having at least 50% of children malnourished were given dry milk, bread, and vegetable oil for the whole family.	Antenatal weight gain significantly increased (mean increase: 140 g/wk; $P = .05$) among supplemented women who gave birth to male infants.	Birth weight was significantly greater (95 g; $P < .05$) among male infants born to supplemented compared to nonsupplemented women; there was no significant effect of the supplement on LBW rates.
Mora et al[105*]	Colombia; urban setting; RCT	456 pregnant women were recruited for the study; women in the supplemented group (n = 226) were given a total of 230 g of dry skim milk, enriched bread, vegetable oil, and vitamin mineral supplement during the third trimester; controls (n = 230) were not supplemented.		There was a 46% decrease in the NMR and a 25% reduction in the PMR. A 75% decrease was detected in the stillbirth rate among the infants of women in the supplemented group (on pooled sample of stillbirths and neonatal deaths, χ^2 (1 df) = 4.1; $P < .05$).

TABLE 6. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Lechtig et al[115]	Guatemala; rural setting; QT	Chronically malnourished women of 2 villages ($n = 405$) received *atole* (a high-protein/-calorie gruel), whereas women of 2 villages were given *fresco* (a low-calorie/no-protein cool drink).		There was a significant correlation between caloric supplementation during pregnancy and birth weight ($P = .01$); the rate of LBW births was approximately half in the high-calorie/protein-supplemented mothers compared to the low-calorie/protein-supplemented mothers ($P < .05$).
Qureshi et al[114]	India; rural setting; RCT	3 groups of women ($n = 126$) were formed and followed from 20 wk gestation to birth; women in group 1 ($n = 37$) received an iron + folate supplement, and group 2 ($n = 39$) received a dietary supplement high in protein and calories, as well as the iron + folate supplement; group 3 ($n = 50$) received none of the above and served as the control group.	Women in group 2 gained an average of 1 kg more during pregnancy than those in group 1.	Infants born to women in group 1 were 0.27 kg heavier than the infants born to women in the control group; the infants born to women in group 2 were 0.81 kg heavier than those in the control group.

* Data are from the same trial.

settings and the relative size of the individual studies. Of the trials included in this review, only 4 reported preterm birth rates.[97,101,105–107] Supplementation was not associated with an increase in mean gestational age (mean difference: −0.1 week; CI: −0.2 to +0.1 week) or a significant reduction in preterm birth (OR: 0.83; CI: 0.65–1.06). Supplementation generally resulted in increased birth weight and/or a reduction in the LBW rate.[104,105,108–115] Overall, however, balanced energy-protein supplementation seems to have only a modest effect on mean birth weight (weighted mean difference: 25 g; CI: −4 to +55 g) but a more substantial effect on reducing IUGR (OR: 0.68; CI: 0.57–0.80). No evidence was found that these effects were greater in undernourished than in well-nourished women. However, the magnitude of the birth weight increase was substantially larger (136 g) in the Gambian study,[104] in which the supplement provided an additional 3780 kJ per day, as compared with an 840- to 1050-kJ-per-day increase in most of the other trials. Although a trend toward increased weight gain of the supplemented mothers was observed in 2 studies, the differences were nonsignificant.[105,114] Moreover, other studies showed no impact on maternal weight gain.[116,117] In the few studies that examined effects on the stillbirth[104,105] and perinatal mortality[104,105,118] rates, reductions were seen. The largest of these studies[104] was undertaken in The Gambia, where, in an RCT, chronically undernourished pregnant women were provided a higher-energy supplement (3780 kJ), largely toward the last trimester, with little micronutrient content. Results from this Gambian study[104] reported significant reductions in rates of stillbirths (53% reduction), early neonatal deaths (46% reduction), and LBW (39% reduction).

In contrast to findings noted above regarding unbalanced protein supplementation alone in pregnancy,[95] the impressive reduction in rates of stillbirths and perinatal mortality from this large trial provided strong evidence of the potential benefit of balanced protein-energy supplementation during pregnancy.

CONCLUSIONS. Although Kramer[95] did not find a differential effect of balanced protein-energy supplements according to the degree of maternal malnutrition, the weight of evidence is strong in favor of improving perinatal mortality and birth weight through balanced protein-energy supplementation of malnourished pregnant women. Most of the evidence, however, comes from strict efficacy trials conducted under intense supervision, and the overall results are largely driven by a single trial from The Gambia. No effectiveness trials have been undertaken to evaluate the benefit of balanced-energy protein supplementation at the community level nor of using home-available diets to provide these supplements. We believe that balanced protein-energy supplementation merits additional field evaluation in diverse geographic locations and may be cautiously included in intervention programs in malnourished populations. However, if such a program is instituted, data must be collected to evaluate the program's benefit and cost-effectiveness. Ideally, the benefit of improved protein-energy intake in pregnancy may be achieved through dietary diversification strategies as well as targeted supplementation in at-risk populations, although the cost may be substantial.

Iron Supplementation

BACKGROUND. Global estimates by the WHO indicate that 55% of all pregnant women living in developing countries and 18% of those in developed countries are anemic (hemoglobin [Hb] concentration <11 g/dL).[119] It is also recognized that anemia underlies some 8% to 15% of maternal deaths in developing countries.[120–122] Although the exact contribution of maternal anemia to maternal mortality

may be unclear,[123,124] it is also widely recognized as a major determinant of maternal morbidity in developing countries. The majority of such cases of anemia are related to iron deficiency, although malaria and hookworm infestation, as well as protein and other micronutrient deficiencies, may play a role also.[121]

Iron-deficiency anemia is highly prevalent in developing countries, affecting an estimated 2 billion people, including one fourth of the world's women and children.[125,126] Thus, there has been much interest in interventions geared toward improving iron intake and status during pregnancy. Despite the evidence that gastrointestinal iron absorption increases during pregnancy, it is highly unlikely that sufficient amounts can be absorbed from the diet during this period to compensate for the increased requirement of the body. Thus, supplementation with iron generally is required, especially where diets may be deficient in iron and body stores of iron may be inadequate to meet requirements.[127]

Although it is widely accepted that iron-deficiency anemia poses an increased risk of complications in pregnancy and of maternal and perinatal mortality,[128] there is surprisingly little evidence to support this relationship. An association has been suggested by some epidemiologic studies,[129–131] but other studies, in fact, have failed to demonstrate a relationship between iron-deficiency anemia and adverse pregnancy outcomes.[132,133] Most of the evidence in the literature has been largely derived from retrospective studies and has not been controlled for ancillary factors such as overall nutrition, underlying health, and health service delivery.[123] Several reviewers[123,134–138] believe that anemia, which itself can be due to a variety of factors, is just one of a multitude of determinants of maternal and perinatal mortality and that there is no conclusive evidence of a link between maternal anemia and LBW or maternal or perinatal mortality. Moreover, there is little documentation that health status can be improved by treating anemia alone. There are no iron-supplementation trials with maternal mortality as a measured outcome, and all intervention trials that used perinatal mortality as the outcome involved nonanemic women,[139] were poorly designed,[140,141] or were too small to be conclusive about iron effects.[142] However, despite the fragmentary nature of the data on the association between maternal anemia and mortality, one can infer that there is a steep rise in maternal mortality with increasing severity of anemia, especially Hb levels <5 g/dL.[143] Nevertheless, the association may not be causal.[128] There also seems to be a U-shaped relationship between maternal anemia and birth weight, because both low and high maternal Hb values are associated with an increased risk of LBW.[135,144,145] Again, although no causal evidence has been established overall to support or refute the relationship between iron-deficiency anemia and LBW, the evidence from developing countries, in which iron-deficiency anemia is common, shows that maternal iron deficiency is positively associated with LBW and poor obstetric outcome.[136] There is also evidence suggesting that a relationship exists between maternal anemia in early pregnancy and increased risk of preterm birth.[146–149]

Meta-analyses of iron-supplementation trials, conducted under the auspices of the Cochrane collaboration,[150–152] concluded that although iron supplementation significantly reduced the prevalence of low Hb concentration (<105 g/L), it had no detectable effect on any other substantive measures of maternal or perinatal outcomes. Although iron reduces maternal anemia, there is no evidence that iron supplements administered alone or with folate have any effect on birth weight or fetal survival in developed countries. There are insufficient data from developing countries to draw conclusions; the few RCTs are inconclusive because of small sample size, problems with compliance, and large losses to follow-up. Small trials in The Gambia, Nigeria, and India showed no significant effects on birth weight,[140,153–155] although 1 large trial in Niger showed a significant increase in birth length and Apgar scores and a reduction in PMR.[156]

There are several other reports of iron therapy in pregnancy from developing countries that are relatively less stringent in their inclusion and exclusion criteria.[157–163] However, most of these studies were based in health facilities within developing countries and varied considerably in design. The overall effects of iron therapy in these studies were largely mixed and did not suggest a particular effect. A review of 9 RCTs of iron supplementation from health facilities in developing countries showed that the increment in Hb level for given amounts of supplementation was not greatest among those with the lowest Hb levels, suggesting that factors other than iron deficiency alone were operative.[164]

COMMUNITY-BASED EVIDENCE. Few community-based iron-supplementation trials have resulted in improvement in either iron stores or measures of maternal and perinatal health.[164–166] Among iron-supplementation trials conducted to date, 5 were in developing countries: 1 in a periurban setting and the other 4 in rural settings (Table 7). All 5 studies demonstrated a convincing effect of iron supplementation on reducing rates of maternal anemia.[141,154–156,167,168]

Several studies have evaluated the benefit of combining iron with other micronutrients in an effort to address multiple deficiencies. In a randomized, placebo-controlled trial (RPCT) in Indonesia, Suharno et al[168] found a synergistic effect of vitamin A and iron supplementation in reducing rates of maternal anemia, with two thirds of the response attributable to vitamin A. Another study in India[141] demonstrated a reduction in LBW rates and an increase in birth weight of infants born to women who were supplemented with both iron and folate. Increased birth weight, however, was seen only in offspring of women who began supplementation from 16 to 20 weeks' gestation but not in those supplemented after week 20 of gestation. Christian et al[169] indicated that both iron-folate supplements and multiple micronutrients reduced the prevalence of LBW comparably among pregnant women in rural Nepal (16% vs

TABLE 7. Antenatal Iron Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Preziosi et al[156]	Niger; periurban setting; DBRCT	Women (n = 197) were given 100 mg/d elemental iron (n = 99) or placebo (n = 98).	Supplementation had a significant effect in decreasing the prevalence of anemia (a 6% decrease in anemia prevalence was observed at delivery compared to 6 mo of gestation).	Of 8 fetal or neonatal deaths, 7 were in the placebo group, and 1 was in the iron group; Apgar scores were significantly better in the supplemented group than the controls; the supplement also was associated with increased birth length of infants but not birth weight ($P < .05$).
Menendez et al[154]	The Gambia; rural setting; DBRCT	Multigravida women (n = 550) were given 60 mg/d elemental iron (n = 273) or placebo (n = 277); all women received 5 mg of folic acid weekly.	Supplementation increased Hb level by 0.5 g/dL ($P < .01$) and improved plasma iron level by 2.7 μmol/L ($P = .001$) in the pregnant women.	Supplementation was not found to have any significant influence on birth weight and prevalence of LBW except in women who had taken the supplement for >80 d; this subgroup of women delivered significantly heavier babies (mean difference: 9.2 g; P = .04) compared to the controls.
Atukorala et al[167]	Sri Lanka; rural setting; prospective cohort study (PCS)	Pregnant women (n = 195) were given a fortified food supplement (*thriposha*), iron supplements (60 mg/d), and 0.25 mg of folate.	Iron supplementation improved maternal Hb parameters irrespective of how many tablets were taken ($P < .01$); supplementation for >17 wk was more effective than <17 wk.	No effect of the supplementation on birth weight was noted.
Agarwal et al[141]	India; rural setting; RCT	Pregnant women between 16 and 24 wk of gestation (n = 418) were selected from 6 subcenters of a rural block of Varanasi district; women from 3 subcenters who chose to participate in the study group (n = 137) received 60 mg of elemental iron combined with 500 μg of folic acid daily for 100 d; women from another 3 subcenters who were unsupplemented served as controls (n = 123).	Compared to baseline, iron-folate supplementation increased Hb level (mean difference: 1.8 g/dL; $P < .001$) as well as serum ferritin level (mean difference: 20.57 g/dL; $P < .001$) in the pregnant women.	Supplemented women delivered significantly heavier babies compared to controls (2.88 ± 0.41 vs 2.59 ± 0.34 kg; $P < .001$); there was a 46% decrease in LBW rates in the supplemented group compared to controls; the percentage of LBW babies was 20.4% in the study group compared to 37.9% in the control group ($P < .05$); the mean birth weight of infants born to women given supplements starting between 16 and 19 wk of gestation was greater than the mean birth weight of infants born to women supplemented after the 20th week of gestation (2.95 ± 0.31 vs 2.86 ± 0.43 kg).
Suharno et al[168]	West Java, Indonesia; rural setting; double-blind, randomized, placebo-controlled trial (DBRPCT)	Women (n = 251) with Hb levels between 80 and 109 g/L were randomized to 1 of 4 groups receiving vitamin A and placebo iron (n = 63), iron and placebo vitamin A (n = 63), iron and vitamin A (n = 63), or both placebos (n = 62) for 8 wk.	Maximum Hb was achieved in women receiving both vitamin A and iron (12.78 g/L; CI: 10.86–14.70); one third of the response was attributable to vitamin A, and two thirds of the response was attributable to iron; the proportion of women who became nonanemic was 35% in the vitamin A-supplemented group, 68% in the iron-supplemented group, 97% in the group receiving vitamin A plus iron, and 16% in the placebo group.	

14%). A different study[167] found a synergistic effect of antihelminthics with iron supplementation. However, this particular study also indicated that women who were supplemented for <17 weeks did not show any benefits, and there was no overall effect of supplementation on birth weight. One study[154] showed an increase in birth weight but only in the offspring of women who had taken the iron supplement for a period of ≥80 days.

It must be pointed out also that there is evidence that administration of parenteral iron to iron-deficient women during pregnancy in malaria-endemic areas may be associated with an increase in the incidence of malarial infections and clinical episodes of disease.[170,171] Thus, care must be exercised in administering iron supplements alone (without chemoprophylaxis) in malaria-endemic areas.

CONCLUSIONS. Oral iron supplementation may improve maternal anemia, but there is no clear effect of iron supplementation on maternal and perinatal or neonatal outcomes. However, the evidence for impact of iron supplementation on health outcomes is inconclusive, primarily due to a paucity of adequately designed and robust trials of iron supplementation in developing countries rather than a demonstrated lack of effect.[123,136] In any case, it seems that initiation of therapy early in gestation is important.

Pending the results of well-designed trials that might more definitely delineate the role and mode of iron supplementation in deficient populations, and given the apparent importance of anemia, especially severe anemia, as a risk factor for maternal mortality and morbidity,[128] it would seem prudent (pending additional research, including meta-analyses) to continue with iron supplementation, concomitant with folate administration (see "Folate Supplementation"), during pregnancy and in at-risk populations of women of reproductive age. In malaria-endemic areas, routine iron supplementation during pregnancy must be accompanied by malaria chemoprophylaxis (see "Malaria Chemoprophylaxis or Intermittent Therapy"). Current WHO/UNICEF guidelines recommend universal iron-folate prophylactic supplementation of young children and pregnant women in areas where anemia is highly prevalent.[172]

Folate Supplementation

BACKGROUND. Folate is critical for DNA synthesis, and folate deficiency is associated with dysfunction in rapidly dividing cells. Observational studies have suggested that lower maternal serum folate levels are associated with LBW and prematurity.[173,174] A large US study suggests an association between higher maternal serum folate at 30 weeks' gestation and lower risk of IUGR, higher birth weight, and higher Apgar scores,[175] although these results have not been corroborated by data from South America.[176,177]

There is a large body of literature, mainly from developed countries, reporting observational studies and RCTs of folic acid in pregnancy. These have been reviewed by Ramakrishnan et al,[145] de Onis et al,[86] and Mahomed.[151,152] Some observational studies[178] have shown positive associations between maternal folate status and birth weight, but the evidence is inconsistent. Twenty-one trials of folate supplementation were included in the Cochrane review,[151] which concluded that, despite a significant reduction in maternal anemia, there was only a small and nonsignificant effect on the incidence of LBW (OR: 0.73; CI: 0.47–1.13). de Onis et al[86] included 4 folate trials in their review of nutritional interventions to prevent IUGR and found a significant reduction in LBW, but they commented on the poor quality of much of the data. Although 2 studies from India[179] and South Africa[180] showed significant increases in birth weight of offspring of malnourished women, this result has not been confirmed in subsequent studies.

Folate deficiency in early pregnancy is an important factor underlying the occurrence of neural tube defects (NTDs) such as spina bifida, encephalocele, and anencephaly. Worldwide, NTDs (particularly the 2 major types, anencephaly and spina bifida) and encephalocele are estimated to affect ≥300 000 infants each year.[181,182] A trial of periconceptional folate supplementation (400 μg of folic acid per day before and during the first 28 days after conception), conducted by the Medical Research Council[183] in 33 centers among developed countries, showed a reduction of NTDs by 50% to 70%. Similar data were reported by Berry et al.[184] Universal folic acid fortification of flour at 240 μg/100 g in consumed food products has been shown to significantly reduce NTD-affected conceptions and births.[185] Currently, the benefits of periconceptional folate supplementation in terms of reducing the incidence of NTDs are well established, and this intervention should be made universally available.

Although there is little evidence of widespread folate deficiency, folic acid is commonly administered along with iron supplements during pregnancy. The benefit of periconceptional folate administration has been convincingly demonstrated in a large cohort (n = 23 491) in the United States.[186] Prevalence ratio estimates of NTDs among women who took multivitamins containing folic acid during the first 6 weeks of pregnancy were 0.27 and 0.29, respectively, depending on whether they had a family history of an NTD.

Two meta-analyses undertaken by the Cochrane collaboration evaluated the impact of folate supplementation during either pregnancy[151] or the periconceptional period.[187] In the former review of 21 studies, folate supplementation during pregnancy was associated with a reduction in the proportion of women with low Hb levels in late pregnancy (OR: 0.61; CI: 0.52–0.71). Apart from the small, nonsignificant reduction in the incidence of LBW noted above (OR: 0.73; CI: 0.47–1.13), folate supplementation seemed to have no measurable effect on any other substantive measure of pregnancy outcome such as pregnancy-induced hypertension, placental abruption, or preterm delivery. Although folate administration significantly improved maternal Hb levels and folate status, there was insufficient evidence to evaluate whether folate supplementation during

pregnancy had any effect, either beneficial or harmful, on clinical outcomes for mother and infant.

The second meta-analysis of periconceptional folate supplementation trials[187] principally included 4 trials with 6425 women and concluded that periconceptional folate supplementation significantly reduced the incidence of NTDs (OR: 0.28; CI: 0.15–0.53). Of the 4 trials, 3 also evaluated different multivitamin combinations, including various micronutrients. Multivitamins or micronutrients alone were not associated with prevention of NTDs and did not produce any additive benefits when given with folate. There was no effect on rates of miscarriage (OR: 1.12; CI: 0.98–1.29) or stillbirth (OR: 0.78; CI: 0.34–1.78). There was some evidence that folate supplements increase the risk of multiple births (OR: 1.40; CI: 0.93–2.11); although not statistically significant, this was a consistent finding in 3 studies. None of these studies reported birth weight as an outcome. A trial of periconceptional and first trimester folic acid and multivitamins conducted by the Indian Council of Medical Research showed no effect on abortions or stillbirths and a nonsignificant effect on LBW (12.5% [folic acid] vs 15.6% [placebo]).[188]

We identified an additional 10 studies in developed countries that also evaluated the potential benefits of periconceptional folate administration; only 1 of these studies[189] presented data on neonatal outcomes other than congenital malformations. This large study from Denmark[189] showed a decrease in preterm, small-for-gestational-age (SGA), and LBW rates in neonates born to mothers who were supplemented with folate. Women who benefited were those supplemented with folate in the periconceptional period, compared with women who either were not supplemented or were supplemented during some other time of pregnancy. There was no difference in the effect of a 1-mg daily dose compared with a 2.5-mg daily dose of folate. Other studies revealed a significant reduction in the incidence of primary and recurrent cases of NTDs among neonates born to mothers supplemented with folate.[190,191] Furthermore, these studies showed a decrease in the incidence of other congenital malformations (eg, limb defects, cardiovascular problems, urinary tract anomalies, orofacial abnormalities).[191–195]

Given the recent interest in the prevalence of maternal hyperhomocysteinemia among folate and B_{12}-deficient populations and the potential relationship with adverse pregnancy outcomes,[196,197] there is renewed emphasis on ensuring adequate maternal folate and B_{12} status during pregnancy. The serum concentrations of these nutrients have been shown to correlate with maternal pre-eclampsia,[198] perinatal outcomes,[199] and newborn measurements.[200]

COMMUNITY-BASED EVIDENCE. Two studies from developing countries provide evidence for efficacy of folate supplementation (Table 8). In South Africa, there was a significant decrease in the incidence of LBW births among native African women supplemented with folic acid during pregnancy.[180] In China, a large-scale intervention with optional folic acid supplementation given to women premaritally revealed a significant reduction in the incidence of NTDs in infants born to women who had received the folic acid supplements.[184]

CONCLUSIONS. Based on the demonstrated impact of folic acid supplements given along with iron in improving Hb levels in iron-deficient populations, folate merits inclusion in antenatal supplementation programs in developing countries. Overall, the evidence also strongly supports the use of periconceptional folate supplementation to reduce NTDs, although the impact of folate supplementation on other pregnancy outcomes such as LBW and preterm births is not clear.

Several other aspects of folate use in pregnancy remain unanswered, such as the optimal dosage, the role of genetic polymorphisms at a population level, and the considerable logistic difficulties in providing folic acid to susceptible women periconceptionally.[201] Our review of the evidence on folate supplementation suggests that this intervention is important in areas of maternal malnutrition and endemic micronutrient deficiencies, and it already is used

TABLE 8. Antenatal Folate Supplementation

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Berry et al[184]	China; population-based trial; QT	247 831 pregnant women were studied (31 960 from the northern provinces having high rates of NTDs and 215 871 from the southern region of China with lower rates of NTDs); of the 31 960 women in the northern region, 18 591 women used folic acid, whereas 13 369 did not; in the southern region, 111 551 used folic acid, whereas 104 320 did not.	Among the women who did not take any folic acid, the rates of NTDs among offspring were 6.5 of 1000 pregnancies of at least 20 wk of gestation in the northern region and 0.8 of 1000 pregnancies of at least 20 wk of gestation in the southern region; among the fetuses or infants of the women who used any folic acid, the respective rates were 1.3 of 1000 (79% reduction; OR: 0.21; CI: 0.13–0.32) and 0.7 of 1000 (16% reduction; OR: 0.84; CI: 0.61–1.14) pregnancies of at least 20 wk gestation.
Baumslag et al[180]	South Africa; tertiary hospital; RCT	Women (n = 354) were randomized to 1 of 2 groups; group 1 received 200 mg of iron daily, group 2 received 5 mg of folic acid daily + iron, and group 3 received 50 μg of vitamin B_{12} + iron and folate.	19 babies born to native African women in group 1 had a birth weight <2270 g, compared with only 4 such babies among native African women in group 2.

routinely in maternal health programs. Better targeting of this intervention, by ensuring that young women receive folic acid along with iron, may reduce rates of NTDs and other congenital malformations and improve pregnancy outcomes.

Iodine Supplementation

BACKGROUND. Iodine-dependent thyroid hormones play a critical role in brain cell proliferation, synapse formation and microtubular assembly. The beneficial effect of iodine supplementation on endemic cretinism and goiter has been well established, and deficiency disorders are now understood to manifest across a spectrum ranging from subclinical iodine deficiency to overt hypothyroidism and goiter. The global importance of endemic iodine deficiency in many developing countries is well recognized.[202] It is typically associated with mountainous areas but may pose a problem anywhere that iodine is leached from the soil by heavy rainfall or flooding. It is estimated that approximately ≥1 billion people live in high-risk areas, particularly China, India, Eastern Europe, and parts of Africa. Clinical effects of iodine deficiency are particularly serious during pregnancy, and can result in miscarriages, early infant death, LBW, and cognitive deficiencies.

Three trials involving 1551 women were included in the Cochrane review of data on the impact of maternal iodine supplementation on pregnancy outcomes, including cretinism and mortality of offspring.[203] In these trials,[204–207] which were conducted in areas of endemic iodine deficiency, the use of injectable iodized oil resulted in a significant reduction in mortality in infancy and childhood (OR: 0.71; CI: 0.56–0.90) and reduced risk of endemic cretinism by the age of 4 years (OR: 0.27; CI: 0.12–0.60). The trial from Zaire further revealed that administration of iodized-oil injections was effective in reducing infant mortality and improving neurologic outcome even when given in midpregnancy.[207–209]

COMMUNITY-BASED EVIDENCE. Apart from the data from Zaire and Papua New Guinea, our search identified 1 additional community-based trial of iodine supplementation (Table 9). In rural China, administration of iodine in drinking water resulted in a significant (65%) reduction in neonatal mortality (see ref 715). However, no data on neurologic development or cognitive function were available from this intervention trial.

CONCLUSIONS. Although limited data on the impact of iodine supplementation on pregnancy outcomes are available from developing-country communities, the potential benefits (ie, reduced neonatal mortality and neurologic deficits) are substantial. Moreover, these findings are in accord with a vast body of literature from developed countries that also establishes the crucial role of iodine in cognitive development. The evidence indicates the enormous potential of public health approaches to this problem, especially in countries with endemic iodine deficiency. Therefore, administration of adequate amounts of iodine during pregnancy to expectant mothers should be an important component of health care interventions during pregnancy. Although universal salt iodization is a well-established intervention to control endemic iodine deficiency, there is still a need to develop innovative means of providing iodine supplements to deficient populations.

Antenatal Vitamin A Supplementation

BACKGROUND. Although there is conclusive evidence for reduction of childhood mortality after vitamin A supplementation,[210] the corresponding evidence for impact of vitamin A supplementation in pregnancy on outcomes in the perinatal/neonatal period is less well established. In Nepalese women, night blindness in the third trimester was associated with a significantly increased risk of anemia, infections, and pre-eclampsia as well as maternal mortality.[211] Similarly, maternal night blindness was associated with increased risk of mortality in early infancy.[212] Although there is evidence of an association between serum vitamin A or carotenoids and birth weight,[213,214] it has not been found consistently.[173,175,215–217]

COMMUNITY-BASED EVIDENCE. Five trials performed in rural settings in developing countries provided information on vitamin A supplementation relevant to this review (Table 10). None of the trials reported birth weight as an outcome. In an RPCT in Indonesia in which women were supplemented with vitamin A, iron, or both, Suharno et al[168] found that women given both supplements had maximal Hb increases and one third of this response was attributable to vitamin A supplementation, suggesting that vitamin A may help reduce rates of maternal anemia and subsequent adverse birth outcomes.

In Nepal, a recent series of double-blind, cluster-randomized trials examined the impact of low-dose vitamin A or β-carotene supplementation on a number of associated maternal and neonatal health outcomes. Daily supplementation of married women ($n = 44\,646$) with vitamin A or β-carotene provided preconceptionally, during pregnancy, and during lactation resulted in a highly significant (44%) reduction in maternal mortality and reduced the maternal mortality ratio by 40%.[218] There was no impact, however, on perinatal or neonatal mortality, nor was there any impact on rates of fetal loss (miscarriage, stillbirth, loss due to maternal death), preterm births, or early infant survival.[219] However, the risk of early infant mortality was reduced among night-blind women supplemented with vitamin A.[212] These trials in Nepal showed no broadly observed effect of vitamin A supplementation on neonatal mortality or mortality in the first 6 months,[219] although subanalysis suggests that there may have been a trend toward an effect.[212]

Some of the most important data on the potential benefits of high-dose antenatal vitamin A supplementation are from studies in HIV-infected women. Trials among HIV-positive mothers in Tanzania[220] and South Africa[221,222] showed no effect of vitamin A alone on fetal growth or fetal loss. In an RCT, HIV-positive pregnant women supplemented with 5000 units of vitamin A and 30 mg of β-carotene during the third trimester and 200 000 units of vitamin A at birth had a reduced incidence of preterm births of

TABLE 9. Antenatal Iodine Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
DeLong et al[715]	China; rural setting; RCT	Potassium iodate was added to the rivers that were the main source of water for the entire population of intervention villages; control villages used water from rivers without any potassium iodate.		Neonatal mortality was reduced by 65% in the population supplemented with iodine (OR: 0.35; CI: 0.18–0.68).
Pharoah et al[204,206]	New Guinea; population-based; QT	The entire population (16 000 individuals in 27 villages) was given injectable iodized oil (4 mL if >12 y of age); however, the follow-up cohort was considerably smaller.		Definite cretinism was reduced by 100% in the neonates born to the intervention group (0 of 274 in the intervention group vs 14 of 248 in the control group; χ^2 (3 *df*) = 33.87; $P < .001$); the 15-y cumulative survival of the children whose mothers received supplementary iodine was significantly greater than the survival of control children ($P = .002$).
Thilly et al[208]	Zaire; rural setting; PCS	Pregnant women ($n = 109$) around 28 wk of gestation attending antenatal clinics in a severely iodine deficient area in Zaire were allocated to either a treatment or control group; the treatment group received 1 iodized oil injection at the time of the first antenatal clinic visit, and the control group received an injection of iodine-free vitamins; there were 118 newborns born to these women during the intervention period.	Correlation between infant thyroid function and maternal thyroid function was noticed; treatment with iodized oil significantly improved mean thyroxine serum concentration (15.7 ± 0.7 vs 11.5 ± 0.7 μg/dL in untreated versus treated mothers; $P < .001$) and lowered mean thyroid-stimulating hormone (5.4 ± 0.5 vs 8.7 ± 1.2 μU/mL; $P < .001$).	Birth weight increased by a mean 101 g (−13.5 to 215.5 g); there was also a trend toward reduced infant mortality (RR: 0.66; CI: 0.44–1.03).

11%, compared with 17% among unsupplemented women.[222] In Malawi, administration of 10 000 units of vitamin A in HIV-positive women lowered the incidence of LBW compared with placebo-treated control women.[223,224]

CONCLUSIONS. Data on the impact of antenatal vitamin A supplementation are limited, and the biological plausibility of the intervention has been questioned.[88] The impact seems to be robust for maternal mortality, but evidence of benefit for perinatal or neonatal outcomes is lacking. There is an urgent need to undertake additional studies of antenatal vitamin A supplementation in areas of endemic or subclinical vitamin A deficiency. These trials must be designed with sufficient power to determine impact on maternal mortality, pregnancy outcomes, and mortality in infancy. Similarly, the strong evidence for efficacy of β-carotene in reducing maternal mortality suggests that other forms of supplementation also merit consideration. However, all such trials must be designed as effectiveness trials, with sufficient information regarding appropriate process indicators to inform programs.

Notwithstanding the above, the data on reduction of maternal mortality are compelling. Thus, it makes sense to ensure that pregnant women in areas of endemic subclinical vitamin A deficiency and night blindness receive at least the recommended dietary allowance (RDA) of vitamin A during pregnancy from both dietary sources and supplements.

Zinc Supplementation

BACKGROUND. Because zinc is a critical nutrient involved in immunocompetence, growth, and development, there has been much interest in its role in pregnancy. King[225] and Keen et al[226] reviewed the evidence for an association between zinc deficiency and adverse outcomes in pregnancy. They concluded that, although evidence for the critical nature of zinc in pregnancy is based largely on animal studies, there were data to suggest that zinc was indeed an important nutrient in human pregnancy. A review of 17 studies published from 1977 to 1994 also indicated an association between maternal indicators of zinc status and birth weight of offspring, although several others were inconclusive.[175] A further in-depth review of 10 zinc-supplementation trials conducted up to 1996 revealed that birth weight increased after zinc supplementation in 4 of the 10 trials.[145] However, the Cochrane review on maternal zinc supplementation[227] revealed no significant differences in maternal or neonatal outcomes after zinc supplementation, although there was a small effect of supplementation on reduction of preterm delivery rates. It

TABLE 10. Antenatal Vitamin A Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Christian et al*[212]	Nepal; rural setting; DBPRCT	See Katz et al[219] (below)		Compared to offspring of non–night-blind women, risk of infant mortality during the first 6 mo of life was increased the least among offspring of night-blind mothers supplemented with vitamin A (OR: 1.14; CI: 0.67–1.93), was intermediate for those whose night-blind mother had received β-carotene (OR: 1.50; CI: 0.97–2.33), and was highest for those born to placebo-control night-blind women (OR: 1.63; CI: 1.09–2.38).
Katz et al*[219]	Nepal; rural setting; RPCT	All married women of child-bearing age in each of the 9 study wards (n = 43 559) were assigned randomly to (1) a weekly dose of 7000 μg of retinol equivalent as retinyl palmitate (vitamin A), (2) 42 mg *all-trans* β-carotene (7000 μg of retinol equivalent), or (3) placebo (n = 15 832 women who contributed data; during the study period, 17 373 were pregnant, and there were 15 987 live-born infants).		There was no effect of either supplement (vitamin A or β-carotene) on fetal loss, neonatal mortality, or prevalence of preterm births.
Coutsoudis et al[222]	South Africa; urban hospital setting; DBRPCT	Pregnant HIV-infected women (n = 728) were randomized to receive either vitamin A (n = 368) or placebo (n = 360); the vitamin A treatment consisted of a daily dose of 5000 IU of retinyl palmitate and 30 mg of β-carotene during the third trimester of pregnancy and 200 000 IU of retinyl palmitate at delivery.	Women receiving the vitamin A supplement were less likely to have a preterm delivery (11.4% in the vitamin A group and 17.4% in the placebo group, P = .03).	HIV-infection results were available on 632 children who were included in the Kaplan-Meier transmission analysis. There was no difference in the risk of HIV infection by 3 mo of age between the vitamin A (20.3%; CI: 15.7–24.9) and placebo (22.3%; CI: 17.5–27.1) groups, nor were there differences in fetal mortality rate or IMR between the 2 groups; among the 80 preterm deliveries, those assigned to the vitamin A group were 50% less likely to be HIV infected (17.9%; CI: 3.5–32.2) than those assigned to the placebo group (33.8%; CI: 19.8–47.8).
West et al*[218]	Nepal; rural setting; DBRPCT	See Katz et al (above) (n = 44 646 married women, of whom 22 119 were pregnant).	Maternal mortality was reduced 44% (OR: 0.56; CI: 0.37–0.84; P < .005) among women supplemented with vitamin A or β-carotene compared to placebo.	
Fawzi et al[220]	Tanzania; urban setting; DBRCT	HIV-infected women (n = 1075) were randomized into 4 groups: group 1 (n = 269) received a daily dose of vitamin A, group 2 (n = 269) was given multivitamins excluding vitamin A, group 3 (n = 270) received multivitamins including vitamin A, and group 4 (the control group, n = 267) was given placebo.		Risk of LBW (<2500 g) was decreased by 44% (OR: 0.56; CI: 0.38–0.82; P = .003); risk of severe preterm birth (<34 wk) was reduced by 39% (OR: 0.61; CI: 0.38–0.96; P = .03), and risk of SGA was reduced by 43% (OR: 0.57; CI: 0.39–0.82; P = .002) in groups 2 and 3 (multivitamin-supplemented groups with and without vitamin A); vitamin A given alone had no effect on incidence of fetal deaths (OR: 0.89; CI: 0.58–1.36; P = .59), LBW (OR: 1.14; CI: 0.68–1.94; P = .62), VLBW, preterm births, or SGA births (OR: 0.83; CI: 0.58–1.18; P = .29).
Kumwenda et al[224]	Malawi; urban hospital setting; RCT	HIV-infected women (n = 697) were randomized to receive daily doses of iron and folate either alone (control group) or combined with vitamin A (3 mg of retinol equivalent), from 18 to 28 wk of gestation until delivery.		In the vitamin A and control groups, the mean birth weight was 2895 ± 31 and 2805 ± 32 g, respectively (P = .05), and the proportion of LBW infants was 14.0% and 21.1% (P = .03) in vitamin A-supplemented and control groups, respectively; the proportion of anemic infants at 6 wk postpartum was 23.4% and 40.6% in the 2 groups, respectively (P < .001).
Suharno et al[168]	See Table 7			

* Data are from the same trial

was concluded, however, that there was insufficient evidence to fully evaluate the effect of zinc supplementation during pregnancy. Moreover, it is important to point out that most of the studies in the Cochrane review were from developed countries with relatively few malnourished women, and there have been a number of more recent studies from developing countries that may shed more light on this subject (reviewed below). On the other hand, other reviewers[94,228] have also concluded that it is unlikely that zinc supplementation alone will influence birth weight or improve pregnancy outcomes in developing countries. Recent studies have focused also on combinations of zinc with other nutrients such as vitamin A. However, the results have been inconsistent. In 1 instance, although a positive impact of either zinc or vitamin A supplementation on maternal iron status during pregnancy was observed, the combination of the 2 failed to improve serum ferritin or Hb concentrations.[229]

COMMUNITY-BASED EVIDENCE. Our search identified 6 studies for additional review, only 1 of which took place in a rural setting (Table 11). The majority of the studies were undertaken in urban slums and were comprised of subjects who had low zinc intake and were considered to be at high risk of zinc deficiency during pregnancy.

The additional studies of zinc supplementation in pregnancy reviewed here also produced mixed results. Only 1 study from Chile[230] showed a decrease in prematurity rates in the supplemented group, along with a reduction in rate of LBW; the latter result was also seen in a study from the United States.[231] Overall, the majority of the studies failed to show a significant impact of zinc supplementation on birth weight, preterm delivery rate, and either neonatal or perinatal mortality. A study from the urban slums of Bangladesh,[232,233] however, showed a significant impact of zinc supplementation on rates of infectious disease morbidity (eg, diarrhea, dysentery, and impetigo) during the first 6 months of life among LBW infants born to zinc-supplemented mothers.

There are also ancillary studies that have evaluated the effect of zinc supplementation on maternal and infant outcomes that may be of value. Sazawal et al[234] showed a significant (68%) reduction in mortality during the first 9.5 months of life among SGA infants born to zinc-supplemented women in urban India. Thus, although it is unlikely that isolated zinc supplementation among malnourished women will impact LBW rates, it is possible that zinc supplementation may improve infectious disease morbidity and boost immunity beyond the neonatal period. Recent data on combined vitamin A and zinc supplementation of pregnant women in central Java indicate that this combination supplement may significantly reduce anemia and rates of puerperal sepsis,[229] highlighting the need to address multiple micronutrient deficiencies in at-risk populations. Moreover, data from Bangladesh showed that offspring of women supplemented with zinc from 4 months' gestation to delivery had lower scores on mental and psychomotor development indices at 13 months of age.[235,236] These findings suggest the need for caution in addressing micronutrient deficiencies in malnourished populations with single-nutrient solutions.

CONCLUSIONS. It is highly unlikely that isolated zinc deficiency exists in at-risk populations; significant iron deficiency, among other nutrient deficiencies, frequently coexists with subclinical zinc deficiency. Evidence for benefit of isolated zinc supplementation on pregnancy outcome is relatively weak, and at present we cannot recommend isolated zinc supplementation in pregnancy. However, all attempts should be made to replenish zinc stores or provide at least the RDA of zinc in malnourished populations. Whenever possible, this must be done through formulations that address other key micronutrient deficiencies that coexist with zinc deficiency, such as iron and vitamin A deficiencies, and implemented through multiple program pathways.[237]

Multiple-Micronutrient Supplementation

BACKGROUND. With the emerging evidence of multiple micronutrient deficiencies in pregnancy, especially in HIV-endemic areas,[238,239] there has been much interest recently in interventions employing multiple micronutrient supplements in pregnancy by using the standard UNICEF multiple-micronutrient supplements. Randomized trials of multiple micronutrient interventions in pregnancy are currently underway in a number of developing countries with malnourished populations, such as Nepal, Pakistan, Guinea Bissau, Bangladesh, and Indonesia.

The 10-year observational Camden Study on the impact of multivitamin supplementation on pregnancy and perinatal outcomes was conducted in a poor US urban setting[240] and included 1430 pregnant women in various stages of pregnancy. Risk of LBW was reduced approximately twofold with supplement use during the first (OR: 0.63; CI: 0.39–1.0) and/or second (OR: 0.57; CI: 0.38–0.86) trimester. The use of prenatal supplements during the first and second trimester was also associated with an approximately twofold reduction in risk of preterm delivery (ORs: 0.53 and 0.71; CIs: 0.35–0.81 and 0.5–1.01; for first and second trimester use, respectively). Thus, it seemed that the decrease in rates of LBW or VLBW was not due to a decrease in rates of IUGR but rather to a decrease in the rates of preterm infants. In another large trial in the United States reported in 1989, use of multivitamins lacking in folic acid content had no impact on prevalence of NTDs.[186]

In contrast to the above-mentioned studies, which focused on micronutrient supplementation, there are a large number of studies that have used combinations of food and energy supplements and micronutrients. Most of these data are derived from programs and interventions in developed countries. The US government's Women, Infants, and Children Supplemental Nutrition Program (WIC) provides low-income mothers with vouchers for milk, eggs, cheese, fruit juice, cereals, legumes, and peanut butter.[241] Although this intervention has not been assessed prospectively in a randomized trial, it has been estimated retrospectively[242] that participation

TABLE 11. Antenatal Zinc Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Castillo-Duran et al[230]	Chile; urban slum; RCT	Pregnant adolescents <20 wk gestation (n = 804) were administered either zinc supplementation (S) at 20 mg/d (n = 401) or placebo (P) (n = 403) until delivery.		No effect of supplementation was seen on mean birth weight of the infants; however, the proportion of LBW births (<2500 g) in the S group was significantly lower than in the P group (6/249 vs 16/258, P = .036). The LBW rate and the preterm birth rate decreased by 66% and 51%, respectively, in the S group. Multiple regressions found a significant effect of maternal nutritional status (P = .011) and zinc supplementation (P = .05) on birth weight.
Dijkhuizen et al[716]	Indonesia; rural setting; RCT	Women between 10–20 wk gestation (n = 229) were assigned to 1 of the 4 groups. All groups received iron + folate. 1 received β-carotene (n = 42), 1 was given zinc at 30 mg/d (n = 42) and 1 was given all 4 supplements (n = 42). The control group received only iron + folate (n = 38).	Combination of prolonged labor and/or retained placenta, both indicative of uterine contractile dysfunction, was significantly higher in the zinc group compared to all other groups.	The male infants born to the women supplemented with β-carotene + zinc + iron + folate were significantly heavier (mean weight 3.4 ± 0.3 kg) than the infants in the zinc + iron + folate group (3.0 ± 0.6 kg, P < .05) or the infants in the zinc + iron + folate group (3.1 ± 0.4 kg).
Merialdi[717]	Peru; urban shantytown; RCT	Women receiving iron and folate (n = 242) were recruited between 10–16 wk pregnancy and randomized to receive either 25 mg zinc/d versus placebo.	In addition to birth weight, growth of fetal anatomical parameters was assessed by ultrasonography.	A positive effect of maternal zinc supplementation on fetal femur diaphysis growth was detected. No effect was seen on birth weight.
Osendarp et al*[233]	Bangladesh; urban slum; PCS	See below, Osendarp et al.		Infants of mothers taking zinc supplements had significantly fewer episodes of acute diarrhea (16% risk reduction, RR: 0.84; CI: 0.72–0.98; P = .037), dysentery (64% risk reduction; RR: 0.36; CI: 0.52–0.84; P = .019) and impetigo (47% risk reduction; RR: 0.53; CI: 0.34–0.82; P = .005). Impact was isolated to LBW infants.
Osendarp et al*[232]	Bangladesh; urban slum; RCT	Pregnant women at 12–16 wk gestation (n = 559) were given either 30 mg/d of zinc (n = 269) or placebo (n = 290) until delivery.	Supplementation had no effect on maternal pregnancy weight gain or mid upper arm circumference. There was no effect of the supplement on rates of pregnancy loss.	No significant effect of treatment was observed on birth weight, gestational age, length, and head or chest circumference. No differences were observed in the rate of LBW by supplement group (RR: 1.12; CI: 0.90–1.41).
Caulfield et al[718]	Peru; urban hospital setting; RCT	Pregnant women 10–24 wk gestation (n = 1295) were randomly assigned to receive either iron and folate alone or iron, folate plus 15 mg/d of zinc.		No significant additional effect of the zinc supplement was seen on birth weight, or LBW or preterm delivery rates.
Garg et al[719]	India; urban hospital setting; RCT	Women in the intervention group (n = 106) were given 45 mg/d of zinc supplement; controls (n = 62) received no supplements.		Maternal supplementation significantly increased birth weight of infants (P < .001); the degree of increase was directly related to the duration of supplementation. Infants born to mothers supplemented for 6–9 mo were significantly heavier (3.45 ± 0.04 kg) than those born following supplementation for 1–3 mo (2.98 ± 0.07 kg); the mean birth weight for controls was 2.65 kg. Gestational age of supplemented babies was significantly higher than controls when given for more than 3 mo (P < .01) and was related to duration of zinc supplementation (P < .05).

* Data from the same trial

in the WIC program was associated with reduced preterm delivery and fetal death and small but significant increases in mean birth weight (+22.7 g) and head circumference. Retrospective analyses of mothers with poor diets who had received supplemental milk, eggs, and oranges revealed a higher mean birth weight compared with siblings (+107 g).[243] These effects were relatively greater in thinner mothers. In a large Hungarian trial of micronutrient supplementation,[192] there was no impact on birth weight.

Data from developing countries are limited and relate to disparate programs of varying sizes. In some cases, the trial design does not allow for clear conclusions to be drawn regarding the contribution of multiple micronutrients to the impact of the intervention. Two large trials in Guatemala[115] and Taiwan[108] evaluated the benefit to pregnant women of increased energy intake as well as multiple mineral and vitamin supplements. The trial in Guatemala administered 2 supplements, 1 caloric and 1 protein-caloric, to malnourished pregnant women during pregnancy to examine effects of supplementation on birth weight. Both supplements were fortified with comparable amounts of micronutrients including vitamin C (4 mg), calcium (0.0–0.4 g), phosphorus (0.0–0.3 g), thiamine (1.1 mg), riboflavin (1.5 mg), vitamin A (18.5 mg), iron (~5 mg), and fluoride (0.2 mg). There was no difference in birth weight between the 2 intervention groups, but infants born to the subgroup of mothers who had consumed >83 750 J of either supplement during pregnancy had a correspondingly greater increment in birth weight. In contrast, the increment in birth weight was comparable in Taiwan, where the supplements were given to well-nourished women and were not significantly fortified with micronutrients.[108] Although the results from the Guatemala trial have been attributed to increased energy intake, there may also have been an effect of the micronutrients present in both supplements. However, because of the open study design, it is difficult to measure the attributable effects of micronutrient supplementation on birth weight in this trial.

A small trial in a poor rural population of Thailand studied the effect on birth weight of improving the mothers' dietary quality.[110] Mothers (n = 43) were randomized into 3 groups to receive either extra food (preprepared cooked food containing legumes, sesame, peanuts, and sugar; or rice, oil, peanuts, shrimp, and sugar) or no extra food. Newborn infants born to mothers who had received the food-based interventions were ~250 g heavier than infants born to controls. In the Narangwal Study from Indian Punjab,[244] villages were assigned to 1 of 4 groups, receiving (1) nutrition care, (2) health care, (3) both, or (4) neither. In nutrition villages, pregnant mothers received bulgar wheat porridge, sugar, milk powder, and oil. Although birth weight was not recorded, stillbirths were reduced by 40% compared with control villages.

COMMUNITY-BASED EVIDENCE. As indicated above, several community trials of multiple micronutrients are currently underway. Preliminary results from a community-based cluster-randomized trial of multiple micronutrient supplements in Pakistan suggest a significant impact on birth weight (Z.A.B., unpublished observations, 2004).

The major published data available on efficacy of multiple micronutrient supplementation in developing countries currently derive from a study in HIV-infected women in Tanzania[220] and another trial in The Gambia of high-energy biscuits that also contained extra micronutrients, calcium and iron[104] (see Tables 6 and 12). The results of the Gambian study have been presented already (see "Balanced Protein-Energy Supplementation"). In Tanzania, after micronutrient supplementation, the mean birth weight was higher among HIV-negative infants (+100 g; $P < .01$), and there were significant reductions in rates of LBW (−44%), preterm births before 34 weeks' gestation (−39%), and IUGR (10% vs 18%; $P = .002$). Moreover, use of multiple micronutrients and multivitamins resulted in significantly fewer fetal deaths (5.9% vs 9.6%; $P = .02$). Recent unpublished data from the same group indicate that multiple RDAs of multivitamins and micronutrients may be required in HIV-infected pregnant women (W. Fawzi, MD, DrPH, verbal communication, 2002).

In a trial in Chile,[100] mothers received either powdered milk or milk fortified with vitamins and minerals. Mean birth weight was higher in the fortification group (+73 g; $P < .05$), and the percentage of IUGR infants was lower (32% vs 44%; $P < .05$). In Bogotá, Colombia, birth weight was greater (+95 g) in urban slum families who were randomly allocated to receive extra food (milk, fortified bread, and vegetable oil).[245] Similarly, infants born to women in South Africa who received a supplement of maize porridge and skim milk fortified with vitamins A, B_1, B_2, and calcium were an average of 300 g heavier than infants born to unsupplemented women.[246] However, in Mexico, other studies of multiple-micronutrient supplementation during pregnancy have failed to demonstrate any benefit regarding increased birth weight[250] or maternal hematologic parameters.[251]

CONCLUSIONS. Although benefit from supplementing pregnant women with multiple vitamins and micronutrients seems plausible, particularly due to increased nutritional requirements during pregnancy and lactation,[94] there has been concern that multiple-micronutrient–supplement formulations designed for developed countries may be inappropriate for women in developing countries with significantly different staple diets.[247] It is thus very important that these studies be undertaken with full attention to potential adverse outcomes. Recent data from Nepal on the use of multiple micronutrients suggest that multiple micronutrients may confer no additional advantage over iron-folate supplements but rather may alter the distribution of birth weight, leading to higher PMR and NMR due to obstructed labor.[169,248,249] Current field trials of multiple micronutrient supplementation in pregnancy will provide useful data on efficacy, impact on LBW and other perinatal outcomes, and potential interactions of mi-

TABLE 12. Antenatal Multiple-Micronutrient Supplementation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Fawzi et al[220]	Tanzania; urban setting; DBRCT	Women (n = 1075) were randomized into 4 groups. Group 1 (n = 269) received a daily dose of vitamin A, group 2 (n = 269) was given multivitamins excluding vitamin A, group 3 (n = 270) received multivitamins including vitamin A, and group 4 (the control group, n = 267) was given placebo.	The multivitamin had a beneficial effect on Hb levels and CD4 cell counts.	A 40% decrease in fetal deaths was seen in groups 2 and 3, (multivitamin-supplemented groups) (RR: 0.61; CI: 0.39–0.94; P = .02). There was also a 43% decrease in the rate of SGA births in these groups (OR: 0.57; CI: 0.39–0.82; P = .002). Multivitamins significantly decreased the incidence of LBW by 44% (OR: 0.56; CI: 0.38–0.82; P = .003), and the risk of VLBW by 58%. Although the risk of extremely preterm births was reduced by 39% in group 2, the overall effect of multivitamins on preterm births was not significant.
Mora et al[245]	See Table 6			
Ceesay et al[104]	See Table 6			
Mardones-Santander et al[100]	Chile; urban setting; PCS	Pregnant women attending 9 prenatal clinics were given powdered milk, powdered milk with high milk-fat content, or multiple-micronutrient–fortified powdered milk. Nonconsumers of any supplement were controls.	Maternal iron status was significantly better in the fortified group than in the powdered-milk group or the control group.	Mean birth weight was higher (mean weight difference 73 g; $P < 0.05$) in the multiple-micronutrient–fortified group than in the group given powdered milk and even higher when compared to controls (mean weight difference 335 g; $P < 0.05$).
Ross et al[246]	South Africa; rural setting; RCT	Nutritionally deficient pregnant women >20 wk gestation (n = 171) were randomized to 1 of 4 groups receiving (1) a micronutrient-fortified high-bulk supplement (high in niacin and iron); (2) a micronutrient-fortified low-bulk supplement (high in vitamin A, calcium, thiamine, and riboflavin; (3) a zinc supplement; or (4) placebo.		Mean birth weight was 9.5% greater in the low-bulk fortified-supplement group compared with the high-bulk supplement group and 6.5% greater in the low-bulk fortified-supplement group than the placebo group. There was no effect on length of gestation.
Ramakrishnan et al[251]*	Mexico; rural setting; RCT	Pregnant women (n = 420) were randomized to receive iron-only supplements (Fe) or multiple-micronutrient supplements containing iron (MM) to assess the effect on maternal iron status.	Mean Hb (g/L) was lower for the MM group (104.2; 95% CI: 102.5, 106.0) compared to the Fe group (108.1; 95% CI: 106.4, 109.8) after adjusting for baseline serum ferritin.	
Ramakrishnan et al[250]*	Mexico; rural setting; RCT	Pregnant women (n = 873) were recruited before 13 wk gestation and received supplements 6 d/wk at home, as well as routine antenatal care, until delivery. Both supplements contained 60 mg of Fe, but the MM group also received 1–1.5 times the recommended dietary allowances of several micronutrients.		Mean birth weight and birth length did not significantly differ between the 2 groups.

* Data are from the same trial.

cronutrients. Pending these data, however, the widespread use of these multiple micronutrients cannot be recommended.

Infection Control and Prevention

Interventions in Malaria-Endemic Areas

Malaria continues to be a major health problem in endemic countries and a matter of concern within the global community. Globally, malaria affects almost 10% of the world's population, and of the nearly 500 million cases, 1 million may die annually.[252] In areas of high malarial transmission, chronic and repeated malaria infections greatly increase the risk of maternal anemia.[253–257] In areas of low malarial transmission, immunity is low, and malaria in pregnancy can rapidly progress to complications such as severe ane-

TABLE 13. Antenatal Malaria Chemoprophylaxis or IPT

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Wolfe et al[283]	Kenya; periurban setting; cost-effectiveness evaluation of treatment regimen	Using existing data from western Kenya (not an intervention study, no women enrolled), article compared 4 strategies of malaria prophylaxis using SP for effectiveness and cost-effectiveness, including 2-dose SP (1500 mg sulfadoxine, 75 mg pyrimethamine), monthly SP, HIV testing and an SP regimen, and a case management approach including SP.		The monthly SP regimen was the most effective strategy for reducing LBW associated with malaria. The 2-dose SP and monthly SP regimens would prevent 172 and 229 more LBW births out of a cohort of 10 000 pregnant women, respectively, compared with the case management approach. At HIV seroprevalence rates >10%, the monthly SP regimen is the most cost-effective strategy. At HIV seroprevalence rates < 10%, the 2-dose SP regimen would be the most cost-effective option.
Ndyomugyenyi et al[279]	Uganda; rural setting; DBRCT	Primigravidae in their first and second trimester (n = 860) were randomized to: group A (n = 284), oral 300 mg CQ base, placebo iron and placebo folate; group B (n = 282), placebo of all 3 interventions; group C (n = 294), weekly oral elemental iron 120 mg/d and folic acid 5 mg, placebo CQ.	The risk of being anemic at delivery was lower in group A (25.6%) and group C (24.7%) compared to group B (38.1%) (P = .01).	Women in group A had a significantly lower frequency of LBW (2%) than women in group B (9%) (P = .009). There was no significant difference in the frequency of LBW between groups B and C, or groups A and C.
Shulman et al[274]	Kenya; rural setting; DBRCT	Women presenting between 16–30 wk of gestation (n = 1264) were given 1, 2, or 3 doses of SP, depending on stage of pregnancy (n = 640). Another group (n = 624) was given placebo.	Lower rates of severe anemia (<8 g/dL) were seen in the intervention group, with an overall protective efficacy of 39% (P = .0001). A protective effect of intervention was also seen for malarial parasitemia (85%, P = .0001) and placental parasite infection (17%, P = .027).	Although the intervention decreased the stillbirth rate (22%), the results did not reach significance. There was no effect on premature birth rates. The intervention decreased NMR by 38%, but this result was not significant; similarly, the PMR decreased 32%, but this result was not significant.
Parise et al[280]	Kenya; periurban setting; RCT	2077 pregnant women were enrolled in the study. The Case Management (CM) group (n = 736) received medication only upon presentation with fever and parasitemia. The 2-dose group (n = 680) received SP at enrollment and again in the third trimester. The third group (n = 661) received SP monthly.	Compared to the CM group (27%), the 2-dose (12%) and monthly treatment groups (9%) had lower rates of placental malaria infection (P < .001). The monthly regimen was more effective in decreasing third trimester anemia rates and also in decreasing placental infection among HIV-positive women (P = .002).	No differences between groups were seen in rates of stillbirths, premature births, spontaneous abortions, or neonatal mortality. The stillbirth rate was 2.1% in the CM group, 2.6% in the 2-dose group, and 37% in the monthly group. The NMR was 1.2% in the CM group, 1.3% in the 2-dose group, and 0.3% in the monthly group. Birth weight was significantly increased in the 2-dose SP and the monthly SP groups (mean birth weight 3079 ± 585 g and 3198 ± 528 g, respectively) compared to the CM group (3183 ± 534 g).
Verhoeff et al[282]	Malawi; rural setting; QT	All pregnant women (n = 525) received SP (1500 mg sulfadoxine, 75 mg pyrimethamine) at the time of pregnancy registration and between weeks 28–34 of gestation; some received an additional dose if they developed malaria.		Those who received 2 or 3 doses delivered significantly heavier babies (mean difference 257 g, P < .01) than those who received only 1 dose. The incidence of LBW in primigravidae and multigravidae who had been given 2 doses was half that seen in subjects who had been given 1 dose (33.9% vs 13.5%, P = .009, and 13.9% vs 6.5%, P = .02, respectively).
Bouvier et al[281]	Malawi; rural setting; RCT	In the observational phase, women (n = 126) were given malaria chemoprophylaxis as CQ 300 mg/wk in a single dose along with iron. In the intervention phase the drug regimen was combined PROG 200 mg/d and CQ 300 mg/wk.	In the observational phase, hematocrit decreased during the rainy season, whereas in the intervention phase, hematocrit increased regardless of season.	An annual cycle of birth weight was observed in the observation phase, whereas no seasonal variation in birth weight was observed in the intervention phase.

TABLE 13. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Steketee et al[258]	Malawi; rural setting; RCT	1766 pregnant women were enrolled: group A received CQ 25 mg/kg divided over 2 d, followed by 300 mg weekly; group B received CQ 25 mg/kg divided over 2 d and repeated every 4 wk; group C received CQ 300 mg of base weekly; and group D received a single mefloquine (MQ) dose of 750 mg followed by 250 mg weekly.	The multivariance model suggested that improvement of birth weight among offspring of women using MQ was directly related to the drug's effect on clearance of placental infection.	MQ use was a significant protective factor for LBW (OR: 1.4; CI: 1.03–1.9; $P = .03$). In contrast, poorly effective malaria prevention (ie, CQ use) was significantly associated with IUGR-LBW (OR: 1.63; CI: 1.16–2.29). Proportion of LBW in MQ treated mothers was 12.5% vs 15.5% in those treated with CQ ($P = .05$).
Cot et al[284]	Cameroon; rural and periurban setting; RCT	266 pregnant women were enrolled. The CQ group ($n = 136$) received a 300 mg oral dose weekly until delivery. The controls ($n = 135$) were untreated.	CQ prophylaxis provided a 32% protective effect against malarial placental infection (OR: 0.68; CI: 0.46–0.99, $P = .043$).	Infants born to mothers who received CQ prophylaxis were significantly heavier (mean difference: 207.5 g; $P = .02$) than the infants born to untreated mothers. There was a 62% decrease in the LBW rate due to the intervention (OR: 0.38; CI: 0.16–0.89; $P = .017$).
Greenwood et al[276]	The Gambia; rural setting; RPCT	Data were collected from pregnant women ($n = 406$) during the course of 2 controlled trials of chemoprophylaxis with Maloprim (pyrimethamine 25 mg and dapsone 100 mg) administered every 2 wk after registration with a TBA ($n = 200$). The control group ($n = 206$) was untreated.	No difference was observed in maternal mortality (5/206 in the Maloprim group vs 4/200 among those receiving placebo).	Stillbirth rates among offspring of women who received chemoprophylaxis were about one-half that of offspring of women who received placebo (62/1000 vs 116/1000), although the difference was not statistically significant. PMR and NMR decreased by 33% and 14%, respectively, in the intervention group.
Menendez et al[155]	The Gambia; rural setting; DBRCT	Primigravid women ($n = 230$, enrolled over 3 y) were randomized to receive weekly either 1 tablet of Maloprim (pyrimethamine12.5 mg and dapsone 100 mg) or placebo.	Women in the intervention group had 86% less parasitemia compared to the placebo group ($P < .01$).	Women taking Maloprim gave birth to heavier babies (mean difference: 153 g; $P = .02$; $\chi^2_{1\ df} = 1.2$) than the placebo. There was no effect on the stillbirth rate.
Schultz et al[287]	Malawi; rural setting; RCT	357 pregnant women were recruited for the trial. The CQ/CQ group ($n = 104$) received an initial treatment dose of CQ (25 mg base/kg) followed by CQ (300 mg base) weekly. The SP/CQ group ($n = 117$) received an initial treatment dose of SP (1500 mg sulfadoxine, 75 mg pyrimethamine) followed by CQ (300 mg base) weekly until delivery. The SP/SP group ($n = 136$) received an initial treatment dose of SP with a second dose at the beginning of the third trimester.	The SP/SP regimen was the most effective and consistent in decreasing parasitemia in pregnant women by 83%. The SP/SP regimen was also the most effective in decreasing placental infection (32%, 26% and 9% in the CQ/CQ, SP/CQ SP/SP groups, respectively, $P = .006$).	There were no significant differences in birth weight, LBW or prematurity rates among the 3 regimens.
Mutabingwa et al[278]	Tanzania; rural setting; RCT	312 women were enrolled in the study and randomly assigned to 1 of 3 prophylaxis regimens were employed. The CQ group ($n = 107$) received CQ 300 mg once weekly, and the PROG group ($n = 116$) received PROG 200 mg daily. The CQ + PROG group ($n = 89$) received a combination of CQ and PROG in the above dosages.	The mean Hb of primigravidae was highest in the PROG group (10 ± 1.6 g/dL after 2 mo of beginning prophylaxis) and lowest in the CQ group (9.4 ± 1.6 g/dL).	Primigravidae in the CQ + PROG group delivered heavier infants (mean weight: 2.89 ± 0.52 kg) than primigravidae in the PROG group (2.79 ± 0.42 kg) or CQ group (2.71 ± 0.34), respectively. The CQ group had the highest frequency of LBW (21%) compared to 12% for the PROG group and 15% for the CQ + PROG group.

TABLE 13. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Nyirjesy et al[277]	Zaire; rural setting; PCS	Study compared pregnant females presenting for intrapartum management (n = 302) who took CQ prenatally versus those who did not take CQ.	CQ prophylaxis prevented maternal malaria (RR: 0.4; CI: 0.16–1.0).	CQ prophylaxis prevented fetal malaria (RR: 0.2; CI: 0.09–0.44), significantly decreased the risk of perinatal mortality by 62% (OR: 0.38; CI: 0.16–0.80) and reduced LBW by 61%.
Cot et al[720]	West Africa; urban setting; RCT	Women in the treatment group (n = 745) were given CQ 300 mg once weekly; controls (n = 719) were given no malarial prophylaxis.	The RR of placental infection in the treated group decreased with increasing duration of prophylaxis; women treated >12 wk had an RR of 0.14 (CI: 0.06–0.3; P = .00004).	There was no effect of treatment on birth weight and LBW rates.
Greenwood et al[275]	The Gambia; rural setting; RPCT	Once a woman reported to the TBA that she was pregnant, she was allocated to receive 1 tablet of Maloprim (pyrimethamine 25 mg and dapsone 100 mg) every 2 wk or placebo. 1208 pregnant women participated in the study, and 1049 received Maloprim from a TBA.	Level of parasitemia was lower, 19% vs 38%, in primigravidae and 8% vs 20% among multigravidae receiving chemoprophylaxis with Maloprim compared to placebo. The medication also was effective in increasing the mean hematocrit, from 26.6 to 30.1 g/dL (P < .05) in primigravid women.	Compared to women who did not report to the TBA and were not given medication or placebo, the women who received Maloprim had a 69% lower stillbirth rate. The reduction was less marked when the Maloprim group was compared to placebo (11% lower stillbirth rate). Early NMR was 25% and 32% for the Maloprim and placebo groups, respectively. Late NMR was 10% and 13% for the Maloprim and placebo groups, respectively. Women using Maloprim delivered heavier babies (mean difference in birth weight among treated primigravidae 159 g; CI: 8–310 g). There was a 72% reduction in the LBW rate among the offspring of Maloprim-treated women (P < .05).
van Eijk et al[286]	Kenya; rural hospital setting; PCS	Data on frequency of IPT using SP and birth outcomes (vital status, birth weight, gender, and presence of congenital abnormalities) were collected over a 12-mo period for 2302 consecutive deliveries in a provincial hospital in western Kenya.	IPT (>1 dose of SP) was associated with a reduction in placental malaria (OR: 0.56; CI: 0.39–0.95). There was a substantial reduction in parasitemia among most women who had received IPT; however, women who had received IPT but remained parasitemic had similar parasite density to women who had never received IPT.	IPT (>1 dose of SP) was associated with a reduction in LBW (OR: 0.65; CI: 0.45–0.95). 1 dose of IPT was associated with a mean increase in birth weight of 54 g (CI: 12–120 g; P = .11). ≥2 doses of IPT were associated with a mean increase in birth weight of 128 g (CI: 42–213 g; P = .004).

mia, cerebral malaria, and death.[258–262] Primigravidae also tend to have a much higher prevalence and density of parasitemia than both nonpregnant women and multigravidae.[256,263] Where malaria is endemic, women become more susceptible to infection during pregnancy, but this susceptibility decreases with successive pregnancies.[256,264] Given the propensity of parasitized red blood cells to sequester in the placenta, malaria is associated with maternal anemia, increased risk of preterm birth, LBW, and neonatal mortality.[265–268] The estimated population attributable risk of LBW among primigravidae with malaria is 10% to 40%.[269] Recent data also suggest that HIV infection may impair the ability to acquire pregnancy-specific immunity, thus increasing the likelihood of complications of malaria among HIV-positive multigravidae in endemic areas.[258–262,270]

Malaria Chemoprophylaxis or IPT

BACKGROUND. Although malaria chemoprophylaxis with chloroquine (CQ) has been the main strategy for management of malaria in endemic areas, there is uncertainty about its efficacy in comparison with IPT. A review of 15 trials by the Cochrane collaboration[271] revealed that women who were given regular, routine antimalarial drugs had less risk of developing severe anemia and had fewer episodes of fever antenatally than those who did not receive prophylactic therapy. Newborn infants of these women also had higher birth weight compared with those born to women who did not receive prophylaxis; this effect was principally seen among primigravidae. However, there was no overall benefit of antimalarial chemoprophylaxis on perinatal and neonatal mortality.

Several studies indicated that IPT can be given under directly observed therapy in antenatal clinic programs and achieve high program effectiveness.[272] Additional support for the effectiveness of IPT was given in a meta-analysis by Newman et al,[273] which found that the 7 most promising drug regimens for malaria prevention in terms of program effectiveness and efficacy, were all IPT as opposed to chemoprophylaxis because of their ease of delivery and lower cost. IPT with sulfadoxine-pyrimethamine (SP) in areas without SP-resistant strains was ranked highest in terms of effectiveness due to the low cost, wide availability, easy deliverability, and acceptability of SP.

COMMUNITY-BASED EVIDENCE. A variety of antenatal antimalarial chemotherapy drugs (eg, SP, CQ, proguanil [PROG], and Maloprim [pyrimethamine-dapsone]) given for prophylaxis have been evaluated in developing countries (Table 13). Decreases in rates of stillbirths and perinatal, neonatal, and/or infant mortality were observed in some instances,[274–277] but overall, the impact on these outcomes was not significant. The preterm birth rate also was not impacted. An increase in birth weight, however, was observed in nearly all studies[155,258–262,275,277–284]; thus, the evidence for a beneficial effect of chemoprophylaxis on birth weight in endemic areas is strong. Chemoprophylaxis also had a uniformly significant effect in reducing maternal anemia, parasitemia, and/or placental parasite load.

Studies comparing various drug regimens revealed that mefloquine was of particular benefit in clearance of parasitemia and in some neonatal health outcomes (eg, reduction in LBW rate) in areas with high rates of CQ resistance.[258–262,285] Another study by van Eijk[286] in Kenya found IPT (at least 1 dose of SP) during pregnancy was associated with a significant reduction in the LBW rate (OR: 0.65; CI: 0.45–0.95).

A growing body of research evaluates the cost-effectiveness of different drug prophylaxis/IPT regimens. In Malawi, Schultz et al[287] found that ≥2 doses of trimethroprim/sulfamethoxazole during pregnancy were equally effective as 1 dose. Another study evaluated the cost-effectiveness of 3 approaches to malaria chemoprophylaxis compared with case management of malarial disease in areas with variable HIV prevalence and high malaria endemicity.[283] In malaria-endemic areas with high HIV prevalence (>10%), administering 1 dose of SP prophylaxis per month was more cost-effective, whereas in malaria-endemic areas with low HIV prevalence (<10%), administering 2 doses of SP prophylaxis during pregnancy was more cost-effective. In any setting, the monthly and the 2-dose strategies were more cost-effective than the case management approach.

CONCLUSIONS. Malaria prophylaxis during pregnancy is an important intervention in community settings in malaria-endemic areas, because it serves to reduce maternal anemia and parasitemia and improve birth weight. In general, however, little improvement in survival of offspring (eg, stillbirths, PMRs, and NMRs) has been demonstrated, although most studies lacked sufficient power to evaluate mortality outcomes. Case management strategies alone are less effective than continuous or intermittent prophylaxis, and in areas with high rates of CQ resistance, alternative agents such as mefloquine are superior.

There is a real need to undertake concerted research in this area by means of large-scale effectiveness trials of various prophylaxis strategies for malaria, particularly IPT. Pending evidence to the contrary or for alternative strategies, the current policies of antimalarial prophylaxis in high-risk populations must continue.

Malaria Prevention Using ITNs

BACKGROUND. Consistent use of bed nets impregnated with permethrin, an insecticide, reduces the frequency of bites from infected mosquitoes and can consequently reduce rates of malarial infection and parasitemia. A meta-analysis of RCTs evaluating ITNs showed that when ITNs were compared with untreated nets or no nets at all, the efficacy for prevention of moderate to severe malarial infection was 17%, and child mortality was reduced 23%.[271] On average, 6 lives were saved annually for every 1000 children protected with ITNs. ITNs also reduced the incidence of mild malarial episodes by 48% and 34%

TABLE 14. Antenatal Malaria Prevention Using ITNs

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Shulman[290]	Kenya; rural setting; RCT	503 pregnant women and their households participated in the study. In the intervention households, nets measuring 190 × 180 × 150 cm were impregnated with permethrin to achieve a target dose of 0.5 g permethrin per m^2 of netting.	No significant effect of the impregnated net intervention was observed in maternal Hb levels or rates of anemia or placental infection.	No significant effect of the intervention was seen on stillbirth rate (RR: 0.67; CI: 0.19–2.32; $P = .51$). No significant effect on PMR or birth weight was seen.
D'Alessandro et al[272]	The Gambia; rural setting; RCT	651 primigravidae lived in study villages; 308 lived in intervention villages, which were provided with insecticide-treated bed nets (20% permethrin). 343 women lived in control villages without bed nets.	The prevalence of severe anemia was significantly lower (73% reduction) in villages with treated bed nets compared with control villages, but this effect was limited to the dry season.	No significant differences between the 2 village groups were seen for PMR or birth weight. The preterm birth rate was lower (72% reduction) in villages with treated bed nets during the rainy season (OR: 0.28; CI: 0.08–0.97; $P = 0.02$).
Dolan et al[291]	Thailand; rural setting; DBRCT	348 pregnant women were randomly assigned to 1 of 4 groups: 1) 111 women to the permethrin-impregnated (500 mg/m^2) bed net (PIB) group, 2) 112 women to the NIB group, 3) 30 women to the no bed net group, and 4) 88 women in the family-size nonimpregnated bed net (FNIB) (These 88 women were originally assigned to the no bed net group, but obtained family-size bed nets and were reclassified.)	Women who used their own FNIB or a PIB had fewer episodes of malaria than the combined NIB and no-net groups (PIB 33%, $P = .04$; FNIB group 32%, $P = .07$). Thus, the risk of at least 1 attack of malaria was 1.67 (CI: 1.07–2.61) times higher in the NIB and no-net group than in the pooled PIB and FNIB group ($P = .03$ allowing for parity). Use of PIBs was associated with a reduction in anemia in all camps and in women of all gravidae, independent of the effect on parasitemic malaria.	No significant effect of the nets was observed on IMR, birth weight or gestational age at birth.
ter Kuile et al[288]	Kenya; rural setting; RCT	All households in 40 of 79 villages were randomized to receive ITNs. Women were followed monthly through pregnancy to monitor health and birth outcomes.		No significant effect of the ITNs was found on preterm birth rates. LBW was lower among ITN users than controls (protective efficacy: 28%; CI: 2–47%). Adjusted mean birth weight was 77.6 g higher during first 4 pregnancies of women in ITN villages ($P = .0008$).

compared with no net and untreated bed net (NIB) controls, respectively.

There is some evidence that the widespread use of ITNs, particularly in high-transmission, malaria-endemic areas, may reduce rates of maternal anemia and placental infection, consequently reducing the risk of adverse birth outcomes such as stillbirth and LBW due to prematurity and IUGR.[288] There are also significant data showing that ITNs can reduce child morbidity and mortality, particularly in infants. In a high-transmission area of western Kenya, an RCT by Hawley et al[289] reported that ITNs reduced all-cause postneonatal mortality (deaths of infants between 1 and 11 months old) by 23%. However, no single research study has had sufficient size to observe a specific significant impact of ITNs on neonatal mortality; benefits of ITNs on neonatal mortality have been largely inferred from pregnancy outcome data.[290]

COMMUNITY-BASED EVIDENCE. Table 14 summarizes the major studies evaluating efficacy of ITN use among pregnant women in malaria-endemic areas. Overall, use of bed nets was effective,[272,291] although not uniformly so,[292] in reducing rates of maternal anemia. In Kenya, the incidence of severe maternal

anemia (Hb <8 g/dL) was slightly lower in the bed-net group (15% vs 20%), but the overall incidence of anemia was the same (92% in the bed-net group and 91% in the control group).[292]

The impact of ITNs on pregnancy outcomes was unclear, but overall, the results were not significant. The ITN intervention showed a trend toward reduced stillbirth rates and PMRs in Kenya,[292] whereas a study in The Gambia failed to show an impact on perinatal mortality.[272] This latter study, however, revealed a decrease in premature birth rate and a corresponding increase in birth weight, although only among primigravid women.[272] Another study in Thailand showed no impact of ITN use on gestational age at birth,[291] and overall, no study showed a significant impact on birth weight.[272,291,292] The impact of the intervention on IMR also was mixed.[291,293]

CONCLUSIONS. There is strong evidence for the efficacy of ITNs in reducing childhood mortality and morbidity from malaria. There is encouraging evidence for improved pregnancy outcomes and reduced perinatal or neonatal mortality from representative settings in developing countries. Some of the variability in data may be a result of the considerable heterogeneity in the treatment groups. Although the overall effect of this intervention shows promising trends, particularly in reducing rates of maternal anemia, the number of well-designed studies with the requisite power to assess outcomes of interest is limited. Cost-effectiveness studies and operations research are needed to help make this intervention more feasible at scale. Currently, we are able to recommend both chemoprophylaxis and PIB use in pregnancy in malaria-endemic areas, which, coupled with the recommendation for use in childhood, makes the case for family-centered approaches.[10]

Deworming

BACKGROUND. A conservative estimate by the WHO suggests that at any given time, nearly 44 million pregnant women globally may be infected with hookworms.[294] In endemic areas, hookworm infestation is known to be a major contributing factor in development of anemia in women of reproductive age.[295]

Although the current recommendation during pregnancy is to use a single-dose regimen of either mebendazole or albendazole for treating hookworm infestation,[296] in combination with iron-folate supplements, there have been almost no systematic studies of the impact of this intervention on pregnancy outcomes.

COMMUNITY-BASED EVIDENCE. Our review revealed little community-based information on the impact of maternal deworming. A recent intervention trial in rural India[297] used a combination strategy with iron supplementation, deworming, and nutrition education using specially developed information, education, and communication materials (Table 15). Significant decreases in the prevalence of maternal iron-deficiency anemia and increases in mean Hb levels were seen and were greater the earlier the intervention was introduced in pregnancy.

Despite the lack of community-based data, there were a few smaller studies on the impact of deworming in developing-country settings. In a nonrandomized study in Sri Lanka[167] women who received deworming along with iron folate as part of their antenatal care had better Hb and higher birth weight infants than women who did not. In Bangladesh, a randomized trial using a 2 × 2 factorial design tested the effects of iron and antihelminthic treatment on Hb and wormload in female tea-plantation workers.[298] The group receiving both iron supplements and antihelminthics had the largest increments in Hb concentration compared with the controls. Prevalence and intensity of *Ascaris*, *Trichuris trichiura*, and hookworm infestation declined in the 2 groups that received antihelminthic treatment.

The only studies of the impact of deworming on neonates undertaken in developing countries were in Nepal and Sri Lanka[299] (Table 15). This retrospective observational study in an urban hospital setting in Sri Lanka found that antihelminthic therapy (mebendazole) was associated with significantly lower stillbirth rates and PMRs (OR: 0.55; CI: 0.4–0.77). Taking medication was also associated with a decrease in the proportion of women delivering a VLBW infant (1.1% vs 2.3%). Women who took mebendazole during the first trimester, however, had a higher proportion of congenital malformations compared with the untreated women. In Nepal, another study found that 2 doses of albendazole during pregnancy was associated with a 46% decrease in neonatal mortality (RR: 0.54; CI: 0.37–0.78).[300]

CONCLUSIONS. These data suggest that deworming in areas of high endemicity may reduce rates of maternal anemia and lead to improved pregnancy outcomes (eg, stillbirth, PMR, and LBW rates). However, there is a need to formally evaluate the benefits and potential complications of antihelminthic therapy in community-based effectiveness trials in diverse programmatic settings and locations.

UTIs and Reproductive Tract Infections

Ascending bacterial infections of the genitourinary tract can be a significant underlying factor in many late fetal deaths[301] as well as spontaneous onset of preterm labor.[302] Although colonization of the lower genital tract by fecal flora can occur commonly without adverse consequences,[303,304] infection of the amniotic fluid, the interior of the placenta, and/or the fetus is associated with serious complications.[301] Chorioamnionitis or amniotic fluid infection has been identified as an important cause of fetal death in several studies from developing countries.[305–309] The following section will review the evidence of interventions pertaining to common genitourinary infections in pregnancy.

Syphilis Screening and Treatment

BACKGROUND. Although syphilis is widely recognized as an important cause of morbidity among the adult population, there are few reliable estimates of the exact contribution of syphilis to the burden of perinatal and neonatal mortality in developing countries. Congenital syphilis continues to

TABLE 15. Antenatal Deworming

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Abel et al[297]	India; rural setting; PCS	Iron supplementation and deworming were provided to all pregnant women in the intervention area (n = 458) from the fourth month of pregnancy. An intensive information, education, and communication effort was carried out that provided facts on anemia and diet modification to each pregnant woman, using a 1-to-1 approach in the community, and a group method in the mobile clinics. This was carried out for a period of 18 mo. Pregnant controls in a neighboring village (n = 387) received only the previously available standard of care.	A significant decrease in the prevalence of anemia was found, from 56% to 25% ($P < .001$), 73% to 49% ($P < .001$) and 69% to 57% ($P < .01$) among women treated from the first, second and third trimesters, respectively, in the intervention area. Significant ($P < .001$) increases of 0.85 g/dL in mean Hb level (CI: 0.79–0.91), 0.59 g/dL (CI: 0.57–0.61) and 0.36 g/dL (CI: 0.32–0.40) were also observed in treated women in the first, second and third trimesters, respectively.	
De Silva et al[299]	Sri Lanka; urban hospital setting; retrospective cohort study (RCS)	All women recruited (n = 7087) were questioned directly about their use of antihelminthics during that pregnancy. 5275 had taken mebendazole and 1737 had not taken antihelminthics and were in the control group.		The stillbirth, PMRs and VLBW rates were 45%, 45% (P = .004) and 53% (P = .003) lower, respectively, among the women who took mebendazole during pregnancy.
Atukorala et al[167]	See Table 7			
Christian et al[300]	Nepal; rural setting; PCS	Pregnant women received 1 of 5 groups of multinutrient supplements, some of which contained albendazole doses. Women who received albendazole during the second trimester were compared to women who did not receive albendazole.		NMR of infants born to women treated with albendazole compared to those born to controls declined by 46% (RR: 0.54; CI: 0.37–0.78).

be a major public health problem in developing countries.[310]

Untreated syphilis was found to cause fetal death in ~22% of pregnancies among infected African mothers; the risks for antepartum and intrapartum stillbirths among infected women were 18-fold and 8-fold higher, respectively.[311] In Malawi, a longitudinal population-based study revealed a population-attributable risk for syphilis of 26% among all fetal deaths and 38% for antepartum fetal deaths.[312] Syphilis was the attributed cause of 10% of 315 late fetal deaths in a case-control study (CCS) in Port Moresby, Papua New Guinea.[79] Syphilis is particularly common in Africa, with prevalence estimates around 10%.[313–315] Syphilis is also recognized as a major contributor to perinatal and infant mortality in the African region.[311,315–317] In Ethiopia, ~6% of perinatal mortality was due to syphilis.[318] In Zambia, almost 9% of infants seen at the University Teaching Hospital were found to have congenital syphilis,[319] and in the Central Hospital of Maputo, Mozambique, ~1% of neonates had congenital syphilis.[320] The reported seroprevalence of syphilis among women attending antenatal clinics in African, Asian, and Latin American countries ranges from 4% to 19%.[321–324] Some reports also indicate that the incidence of congenital syphilis may be increasing in many developing countries; to illustrate, a 10-fold increase in congenital syphilis was reported in the Brazilian Federal District from 1980 (0.17 cases per 100 000 inhabitants) to 1984 (1.7 per 1000).[325] Early diagnosis and treatment sharply reduce the risk of fetal death due to syphilis.[326]

The potential benefits of large-scale population-based intervention strategies for the prevention, detection, and treatment of congenital syphilis is strengthened by the experience in developed countries. To illustrate, the prevalence of congenital syphilis was reduced by as much as 70% by a large screening and intervention program in Milwaukee.[327]

TABLE 16. Antenatal Syphilis Screening and Treatment

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Patel et al[330]	South Africa; urban hospital setting; QT	5 nurses were trained by a laboratory technician to perform and read the RPR card test. The result of on-site RPR testing (n = 513 women) was compared with RPR test results reported by the laboratory.	Sensitivity for the onsite test was 50%, specificity was 91%, positive predictive value was 33% and negative predictive value was 95%.	
Osman et al[329]	Mozambique; urban hospital setting; QT	Before the intervention, nurses referred patients (n = 918) to an STD doctor. The intervention trained the nurses to be autonomous in diagnosis and treatment of syphilis with benzathine penicillin.		Perinatal mortality was significantly higher in the control group (P = .03; 98.7% of the neonates were alive on the seventh day of life in the intervention group, vs 95.8% in the control group).
Temmerman et al[332]	Kenya; urban hospital setting; CCS	Of the 22 466 neonates born to women giving birth in the hospital, 12 414 were tested for syphilis. Cases were defined as mothers whose babies were stillborn or LBW.	Syphilis treatment during pregnancy reduced the rate of adverse outcome significantly from 26% to 15%.	Women who were seropositive and untreated were 4 times more likely to have adverse pregnancy outcomes, including a stillbirth (OR: 3.34, $P < .03$) or LBW baby (OR: 4.01, $P < .0001$).
Hira et al[328]	Zambia; periurban setting; QT	Staff was trained in methods of health education, clinical evaluation, on-site RPR serological testing for syphilis and on-site treatment. Number of patients was 3005. Prior to the intervention, the study center had 491 patients and the control center had 434. Post-intervention, the study center had 806 patients and the control center had 1274.		Adverse pregnancy outcomes (abortion, stillbirth, preterm birth, LBW and congenital syphilis) were evaluated as a combined entity. Adverse outcomes were significantly lower in the study area (28%) compared to the control area (72%) ($P < .001$).
Guinness et al[316]	Swaziland; rural setting; QT	Nurses performed the RPR test for 283 deliveries and the women who were positive were treated in this community-based screening and treatment protocol.		Screening averted 35% of congenital syphilis but missed the remaining 65%.

COMMUNITY-BASED EVIDENCE. We identified 5 intervention trials in developing countries that addressed the issue of antenatal screening and treatment of syphilis and evaluated the impact on pregnancy outcomes (Table 16). Of these, only one[316] was rural-based, and one was in a periurban/suburban setting[328,329]; the rest were urban hospital-based studies. We included these hospital-based studies in the current review because they were conducted in developing countries and represented typical catchment populations.

The data reviewed suggested that serologic and clinical testing for syphilis did not have sufficient sensitivity for case detection, especially when conducted by paramedical or nursing staff.[316,330] One study reported sensitivity of 50% and specificity of 91% for on-site rapid plasma reagin (RPR) testing done by nurses.[330] Universal screening, preferably on site, is the appropriate option,[331] because it ensures immediate treatment. High-risk patients, however, should be rescreened in the third trimester.

The studies reviewed demonstrated a significant reduction in the incidence of congenital syphilis among cases identified and treated antenatally.[316,328,329] Stillbirths and perinatal mortality[328,329,332] were reduced in offspring of mothers diagnosed and subsequently treated for syphilis during pregnancy. An observational study also demonstrated that women who were diagnosed and treated for syphilis during pregnancy had lower risk (OR: 0.25; $P < .0001$) of giving birth to an LBW infant.[332] Screening for and treatment of syphilis is thus a cost-effective means of reducing fetal deaths.[332]

CONCLUSIONS. Case identification and treatment of maternal syphilis have significant benefits in improving perinatal and neonatal outcomes, particularly in endemic areas such as sub-Saharan Africa. There are major challenges, however, in implementing diagnostic testing and treatment in programs while assuring quality and access. Additional operational research is needed on how to make accurate testing and effective treatment feasible and available at scale.

Antibiotics for Asymptomatic Bacteriuria

BACKGROUND. Although treatment for symptomatic UTIs in pregnancy is standard-of-care in developed countries, and the role of specific antimicrobial

therapy in pregnancy is well established,[333] there are no community-based studies of treatment for asymptomatic bacteriuria during pregnancy and its impact on pregnancy outcomes. Most available data are from facility-based cases and from developed countries. In a meta-analysis of the available evidence on benefits of antimicrobial therapy for asymptomatic bacteriuria in pregnancy, mostly from developed countries but also including poor populations, Smaill[334] convincingly established a reduction in rates of pyelonephritis (OR: 0.25; CI: 0.19–0.32) and a pooled relative risk (RR) of 0.64 (CI: 0.50–0.82) for the composite outcome of preterm delivery or LBW based on 10 controlled clinical trials.

COMMUNITY-BASED EVIDENCE. No studies were identified that reported data from developing-country community settings on the impact of antimicrobial therapy on asymptomatic bacteriuria in pregnancy. There is considerable evidence, however, that bacteriuria and occult UTIs are widespread in developing countries.[335–337]

CONCLUSIONS. Although there are no valid studies of screening and treatment strategies for maternal asymptomatic bacteriuria from community-based settings in developing countries, there is little reason to doubt the association of occult and overt UTIs in developing countries with increased risk of preterm/LBW births and neonatal infections, given the strength of the relationship in developed countries.[338,339] Moreover, although the choice of antibiotics may vary, there is little reason to suggest that the findings of the main Cochrane review[334] would not be applicable in diverse settings.[340] Given the available evidence and biological plausibility, all clinically symptomatic UTIs must be appropriately treated, and attempts must be made to collect evidence from representative developing-country settings regarding the importance of treating asymptomatic bacteriuria. However, the logistics, technical requirements, and frequency of screening necessary for diagnosis of asymptomatic bacteriuria in developing-country settings are formidable barriers to wide-scale implementation of this intervention. Thus, pending additional evidence as to the feasibility and cost-effectiveness of this strategy, and require additional operational and cost-effectiveness research.

Antibiotics for Bacterial Vaginosis

BACKGROUND. Although reliable estimates of the global burden of bacterial vaginosis are unavailable, the disorder is known to affect a large proportion of women in developed countries (~16%) and is associated with adverse pregnancy outcomes including increased risk of preterm (~40%) or LBW birth and premature rupture of membranes (PROM).[326,341–344] Some studies have found high rates of bacterial vaginosis in developing countries,[345] but data are lacking on the attributable risk of bacterial vaginosis for LBW.

Despite strong epidemiologic evidence of an association between bacterial vaginosis and preterm birth, randomized trials of topical clindamycin, as well as systemic antibiotic treatments using any of a variety of agents (eg, erythromycin, amoxicillin, or metronidazole), have not shown clear evidence of benefit.[302] This may be explained partly by heterogeneity in the patient populations studied. In the only published trial among low-risk (ie, no history of prior preterm birth) asymptomatic women, screening and treatment with oral clindamycin resulted in nearly a 50% reduction in the rate of preterm birth or PROM.[346] It has been suggested, however, that data showing benefit from a prospective double-blind, placebo-controlled trial are needed before such an approach is undertaken routinely in low-risk pregnant women.[347]

Antibiotic treatment of bacterial vaginosis among high-risk pregnant women in developed countries who previously had a preterm delivery has significantly reduced the risk of subsequent preterm birth.[348–351] Although Duff et al[348] used oral amoxicillin for therapy, Hauth et al[350] used a combination of metronidazole and erythromycin for 7 days, and others[349,351] used a short course of metronidazole alone. However, in a recent large trial from the NIH Maternal-Fetal Medicine Network,[352] a 2-dose regimen of oral metronidazole had no effect on rates of fetal and neonatal deaths, LBW, or VLBW. Moreover, a slightly increased risk of preterm birth was found for women with a prior history of preterm birth. Another recent publication from the same NIH network also reported an increased risk of preterm birth after treatment of women with asymptomatic trichomoniasis with metronidazole.[353] Similarly, a combined intravenous (IV)-oral regimen of ampicillin/amoxicillin plus erythromycin had no impact on fetal or infant death rates.[354] In the latter trial, however, treatment resulted in reduced incidence of neonatal necrotizing enterocolitis, intraventricular hemorrhage (IVH), respiratory distress, and early-onset sepsis. A single trial of treatment for reproductive tract infection due to chlamydia failed to reduce the risk of preterm birth.[355] In a recent review of the impact of treatments for bacterial vaginosis, Joesoef et al[347] concluded that women with symptomatic disease, whether pregnant or not, should be treated with metronidazole (500 mg, twice daily, for 7 days), clindamycin vaginal cream (2%, once daily as a nocturnal intravaginal application, for 7 days), or metronidazole vaginal gel (0.75%, twice daily, for 4 days), because these regimens have produced equivalent cure rates. For pregnant women with high risk of an adverse pregnancy outcome (ie, those with a prior preterm birth) but asymptomatic disease, intravaginal clindamycin is not recommended, because it has failed to reduce rates of preterm births. If screening of high-risk women is undertaken, it is best performed early in the second trimester, and treatment doses should be limited to 250 mg of metronidazole orally 3 times daily for 4 days to minimize any potential teratogenic effects of treatment.

COMMUNITY-BASED EVIDENCE. Diagnostic methods for bacterial vaginosis in developing-country settings have not been standardized, and relatively few studies have explored the impact of potential interventions to screen and treat bacterial vaginosis on

TABLE 17. Antibiotics for UTIs and STDs

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Wawer et al[345]	Uganda; rural setting; RCT	Intervention clusters(n = 12 733, of whom 6609 were HIV-negative) were given broad-spectrum treatment for STDs that consisted of azithromycin (1000 mg single dose), cefixime (400 mg single dose) and metronidazole (2 g single dose). The control group (n = 6124) was untreated.	Prevalence rates of STDs other than bacterial vaginosis at the postnatal visit were significantly lower in the intervention group than the control group.	There was a 17% reduction in early neonatal death and a 23% reduction in the risk of preterm delivery in the intervention group.
Gichangi et al[357]	Kenya; urban hospital setting; DBRCT	Pregnant women (n = 320) were randomized into an intervention group (n = 160) and placebo (n = 160). The intervention group received a single oral dose of 2 g cefetamet-pivoxil; the control group received placebo.	In the intervention group there were 65% fewer *Neisseria gonorrheae* cervical infections (P = .04).	The intervention had no effect on the rate of stillbirth. However, infants born to mothers in the intervention group were heavier (mean difference 155 g) than those in the placebo group (P = .04). The intervention reduced LBW by 44% (18.7% vs 32.8%) but had no effect on gestational age (P = .01).
Joesoef et al[344]	Indonesia; multicenter trial, urban hospital setting; RCT	Women seeking prenatal care at 14–26 wk of gestational age and who had bacterial vaginosis (n = 681) were given either 2% clindamycin vaginal cream (n = 340) or a placebo cream (n = 341).	2 weeks after the completion of the treatment, 88.5% of the women were cured.	The rate of preterm delivery (<37 wk) was 15% for clindamycin patients and 13.5% for placebo patients (OR: 1.1; CI: 0.7–1.7). The rate of LBW was 9% for clindamycin patients and 6.8% for placebo patients (OR: 1.3; CI: 0.8–2.4).

pregnancy outcomes (Table 17). A double-blind, randomized, placebo-controlled trial at 7 maternity clinics in Indonesia reported an 85.5% cure rate among women with bacterial vaginosis treated with 2% clindamycin vaginal cream, but rates of preterm delivery or LBW were not affected.[344] It was suggested that systemic treatment may be needed to eradicate upper reproductive tract disease and to reduce preterm births. Treatment of women in South Africa in early preterm labor for 4 days with metronidazole and ampicillin (agents effective against, but not specifically targeted toward, bacterial vaginosis in this trial) increased pregnancy duration, but preterm birth rates were not reported, and no reduction was observed in either neonatal deaths or length of hospital stay.[356]

Broad-spectrum treatment for reproductive tract infections in rural Uganda with single doses of azithromycin, cefixime, and metronidazole resulted in a significant decrease in preterm birth rates (−23%) and early NMRs (−17%).[345] In Kenya, a single oral dose of cefetamet-pivoxil given to women at 28–32 weeks of pregnancy with a prior history of stillbirth or an LBW infant resulted in significant reductions in the LBW rate (probably due largely to preterm birth) and postnatal endometritis and an increased birth weight.[357] No effect was observed on stillbirths or preterm birth rates. Large losses to follow-up, however, suggest the need for cautious interpretation of these results. 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 (OR: 0.72; CI: 0.56–1.05) and early neonatal death (OR: 0.83; CI: 0.71–0.97).[358] Each of these treatment regimens broadly decreased rates of maternal reproductive tract infections including bacterial vaginosis.

CONCLUSIONS. Available data suggest that antibiotic therapy effective for treatment of bacterial vaginosis may be beneficial in decreasing rates of LBW and, possibly, prematurity and neonatal mortality.[345] Treatments that are effective against bacterial vaginosis may also decrease rates of other reproductive tract infections such as those due to chlamydia and gonorrhea. However, results have been mixed, with some studies showing increased risk for preterm births. Moreover, there are still major problems with operationalizing these interventions into programs, because simple, affordable diagnostic methods and additional large-scale effectiveness studies of simple treatment regimens, particularly in asymptomatic pregnant women, are needed. It is also unclear if the prevention of preterm births between 34 and 37 weeks' gestation will substantially improve perinatal and newborn survival in public health programs.[359] These interventions merit additional exploration be-

fore their inclusion in routine antenatal care strategies.

Antibiotics for Preterm Labor

BACKGROUND. A major proportion of the burden of global perinatal mortality relates to preterm births. The WHO estimates that prematurity is responsible for nearly one fourth of neonatal deaths.[29] Of ~13 million annual preterm births globally,[360] one third may be related to spontaneous preterm delivery,[361] and in 30% to 40% of preterm births, labor may follow spontaneous rupture of membranes.[362]

Several studies have identified an association of subclinical chorioamnionitis (ie, intact membranes) with spontaneous preterm labor.[363–365] Pathogens were identified from the amniotic fluid in 10% to 15% of cases presenting with preterm labor.[366] A meta-analysis by the Cochrane collaboration of available RCTs of antibiotic therapy in preterm labor with intact membranes[367] identified that antibiotic treatment in this situation prolonged pregnancy (weighted mean difference: 5.4 days; CI: 0.9–9.8 days). There was no effect on reduction of preterm births or on respiratory distress syndrome or neonatal sepsis, but a significant reduction in neonatal necrotizing enterocolitis (OR: 0.33; CI: 0.13–0.88) was noted. The meta-analysis also revealed, however, an increase in mortality related to preterm birth or its sequelae (OR: 2.43; CI: 0.92–6.43) and an increase in perinatal mortality in the group receiving antibiotics (OR: 3.36; CI: 1.21–9.32). With regard to maternal effects, antibiotic treatment significantly reduced maternal infection (chorioamnionitis/endometritis) (OR: 0.68; CI: 0.48–0.98). Still, overall evidence for the benefit of antibiotic therapy in preterm labor with intact membranes is lacking.

This large meta-analysis has been supplemented by the large multicenter ORACLE II trial in several developed countries, including almost 6300 pregnant women randomized into 1 of 4 groups to receive (1) erythromycin, (2) amoxicillin/clavulanic acid, (3) both, or (4) placebo.[368] The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. There was no evidence that any of the antibiotic regimens improved maternal or neonatal outcomes; length of pregnancy, length of maternal hospital stay, mode of delivery, birth weight, proportion of infants admitted to intensive care or ventilated, proportion of infants with a positive blood culture, or composite neonatal outcome were not different among the treatment groups.

COMMUNITY-BASED EVIDENCE. Most of the trials of antibiotic therapy for preterm labor have been conducted in developed countries; none have been reported from community settings. Table 18 illustrates the 2 studies of antibiotic therapy for preterm labor in developing-country settings.[356,369] The overall conclusions from these studies were consistent with the results of the Cochrane meta-analysis[367] and the ORACLE II study.[368]

CONCLUSIONS. No clear overall benefit for routine antibiotic therapy for preterm labor with intact membranes has been demonstrated in trials in urban settings in developed or developing countries. Thus, this intervention cannot be recommended routinely. Evidence indicates that antibiotic administration in preterm labor should be considered only when there are clear indications of associated infection, or, as indicated in the next section, in the presence of other risk factors.

Antibiotics for PPROM

BACKGROUND. The most common antecedent of preterm labor is PPROM.[362] The culture positivity rate of amniotic fluid for microbial organisms in such cases ranges from 32% to 35%.[366] The mechanisms underlying PPROM may include local subclinical infection and inflammation leading to weakening of the amniotic membranes.[370]

A Cochrane meta-analysis of the benefits of antibiotic therapy in cases of PPROM concluded that maternal antibiotic therapy in this situation is effective in prolonging pregnancy and reducing maternal and neonatal infection-related morbidities.[371] A subsequent large (n = 4826) multicenter RCT (ORACLE I)[372] in urban centers in multiple developed and developing countries (eg, Argentina, Brazil, Lithuania, Malaysia, South Africa, Sri Lanka) corroborated the findings of the meta-analysis and suggested that administration of erythromycin to women with PPROM was associated with significant health benefits for the newborn. Fewer infants (P = .08) tended to have the primary composite outcome (ie, death, chronic lung disease, or major abnormality on cerebral ultrasonography) in the erythromycin group (151 of 1190 [12.7%]) than in the placebo group (186 of 1225 [15.2%]). Among the 2260 singletons in this comparison, significantly fewer had the composite primary outcome in the erythromycin group (125 of 1111 [11.2%] vs 166 of 1149 [14.4%]; P = .02). Use of erythromycin was also associated with prolongation of pregnancy beyond 48 hours of presentation (P = .004), reduction in neonatal treatment with surfactant (P = .05), reduced requirement for supplemental oxygen (P = .02), and fewer positive blood cultures (P = .02). An important additional finding among singletons was a lower rate of neonatal cranial ultrasonographic abnormalities at discharge (P = .04) and a probable reduction in childhood disability. Although co-amoxiclav only and co-amoxiclav plus erythromycin were associated with prolongation of pregnancy, they were also associated with a significantly higher rate of neonatal necrotizing enterocolitis (4-fold higher with co-amoxiclav alone versus placebo, 2.5-fold higher with any co-amoxiclav than with none).

COMMUNITY-BASED EVIDENCE. The findings of 3 other studies[373–375] conducted in developing countries largely corroborated findings from studies in developed countries, although data are very limited (Table 19). No trials of antibiotic therapy for PPROM, however, have been conducted solely in community settings in developing countries.

CONCLUSIONS. Although there are few systematic studies of antibiotic therapy for PPROM in developing countries and none in community settings, the

TABLE 18. Antibiotics for Preterm Labor

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Oyarzun et al[369]	Chile; urban hospital setting; DBRPCT	Women in labor between 22–36 wk gestation (n = 173) were given either amoxicillin and erythromycin for 6–7 d, plus tocolytic therapy (n = 83) or placebo (n = 90).	No significant differences between the groups were found for maternal outcomes, including duration of randomization-to-delivery interval and frequency of clinical chorioamnionitis and endometritis. Rate of cesarean section was significantly higher in the placebo group (28% vs 12%).	No significant differences in neonatal outcomes were detected between the groups, including preterm birth rate, neonatal death, respiratory distress syndrome, proven sepsis, and birth weight. Suspected sepsis was significantly more frequent in the placebo group (6/90 vs 0/78).
Norman et al[356]	South Africa; multicenter trial, urban slum setting; RCT	The study recruited 81 pregnant women. The study group (n = 43) received ampicillin and metronidazole for 5 d. The control group (n = 38) received no antibiotics. In all women, contractions were suppressed with hexoprenaline and indomethacin for 24 hours, and betamethasone was given for fetal lung maturity.	In those receiving ampicillin and metronidazole, pregnancy was significantly prolonged (median 15 d vs 2.5 d, P = .04) with significantly more women still pregnant after 7 d (63% vs 37%, P = .03, OR: 0.34; CI: 0.13–0.94).	Significantly fewer infants in the treatment group developed necrotizing enterocolitis than in the control group (0 vs 5, P = .02).
Kenyon et al[368] (ORACLE II trial)	Multicountry, multicenter trial; urban hospital setting; RPCT	6241 women in suspected or confirmed preterm labor (<37 wk gestation) were randomized to receive 1 of 4 possible treatments: 1) co-amoxiclav (325 mg) plus erythromycin (250 mg); 2) co-amoxiclav plus erythromycin placebo; 3) erythromycin plus co-amoxiclav placebo; or 4) co-amoxiclav placebo plus erythromycin placebo and followed for pregnancy outcomes.	Antibiotic use did not prolong pregnancy, as most women did not deliver within 48 h (89.9%) or 7 d (84.6%).	The only significant difference between the antibiotic and placebo groups was that the rate of oxygen dependence at 36 wk post-conception was higher with erythromycin use than with no erythromycin (P = .04). Importantly, the other measure of chronic lung disease (oxygen dependence at >28 d of age) did not show this difference. There were no significant differences between the babies with respect to birth weight or need for intensive or special care. Co-amoxiclav was associated with a (non-significant) doubling of risk for suspected or proven necrotizing enterocolitis. In the subgroup of infants born at <32 wk gestation, there were no significant differences in neonatal outcomes (respiratory distress syndrome, oxygen dependence, sepsis, necrotizing enterocolitis, abnormal cerebral scan, or death) between antibiotics and placebo.

evidence in support of the efficacy of this intervention in diverse settings is strong, and the practice is routine under certain circumstances (eg, early gestation). Thus, it is prudent to incorporate antibiotic therapy of PPROM in intervention programs wherever feasible, such as at referral-level health facilities. A domiciliary cadre of trained birth attendants potentially can be trained to recognize PPROM and provide referral and, possibly, initial antimicrobial therapy. However, this application of the intervention requires additional assessment and may be difficult in community settings.

TT Immunization and Clean Delivery

BACKGROUND. Despite major advances in understanding of the pathogenesis and risk factors for neonatal tetanus, it is still prevalent in many developing countries. A UNICEF/WHO/United Nations Population Fund survey in June 2000 indicated that 57 countries globally had not achieved elimination of neonatal

TABLE 19. Antibiotics for PPROM

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Kenyon et al (ORACLE I trial)[372]	Urban hospitals in many countries; RPCT	4826 women with PPROM were randomly assigned to receive 250 mg erythromycin (n = 1197), 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid; n = 1212), both (n = 1192), or placebo (n = 1225), 4 times daily for 10 d or until delivery.	Significant prolongation of gestation (40.7% females delivered within 48 hours in the placebo group, vs 34.8% in the erythromycin-only group, P = .004)was seen in mothers treated with any erythromycin combination but no differences were seen in rates of maternal infection or the need for additional antibiotics.	The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. Fewer infants (P = .08) had the primary composite outcome in the erythromycin group (151 of 1190 (12.7%)) than in the placebo group (86 of 1225 (15.2%)). Among the 2260 singletons in this comparison, significantly fewer had the composite primary outcome in the erythromycin group (125 of 1111 (11.2%) vs 166 of 1149 (14.4%), P = .02).
Magwali et al[375]	Zimbabwe; Harare Maternity Hospital; RCT	171 women with PPROM between 26 and 36 wk gestation were randomized to a course of prophylactic Augmentin or no prophylactic antibiotic treatment at all. The calculated sample size was 72 women per group.	Although there was a trend towards higher maternal febrile morbidity rate in the group that did not receive any treatment, no statistical significance was achieved. The women in the treatment group had a significant prolongation of gestation, with 37.8% of the mothers in the this group delivering within 48 hours of membrane rupture compared to 58.1% in the group that received no treatment (P = .01247). More mothers in the treatment group (43.9%) delivered between 48 hours and 7 d after membrane rupture in comparison to the group that did not receive treatment (34.9%). 18% of the mothers in the treatment group delivered after 7 d, as opposed to only 7% of the mothers in the group that received no treatment. (P = 0.01247).	The neonatal outcome measures in the 2 groups (birth weight, Apgar scores, neonatal death due to sepsis, neonatal sepsis) were not significantly different.
Ovalle-Sallas et al[374]	Sites in Chile and USA; urban hospital setting; DBRCT	79 women with PPROM were randomized to receive IV clindamycin plus gentamicin for 7 d (n = 39) or to the control group (n = 40).	Overall, incidence of premature births (<37 wk and <34 wk gestation) was not reduced. In women with infections who received antibiotics, incidence of premature birth (<34 wk) was significantly lower than those patients who received placebo (44.4% vs 88.9%, respectively, P < .05).	Neonatal outcomes were unclear as the trial was stopped after the treatment group showed better maternal outcomes at intermediate analysis.
Almeida et al[373]	Mozambique; urban hospital setting; RCT	106 third trimester pregnant women with PPROM were randomized to either oral amoxicillin (0.75 g, 3 times daily) (n = 50) or placebo (n = 56) in a blinded fashion. The patients were hospitalized in bed for 7 d unless contractions started and delivery ensued.	The average rupture-to-expulsion interval was 68.4 hours in the placebo group and 91.7 hours in the amoxicillin group (P = .28). Hospital stay (3.0 vs 4.3 d, P = .03) was prolonged by 43% in the amoxicillin group. Rates of hemorrhage and postnatal endometritis-myometritis did not differ significantly in the 2 groups.	Birth weight and stillbirth rate did not differ significantly in the 2 groups. There was a trend towards longer duration of hospital stay among newborns in the amoxicillin group suffering neonatal death (1.6 vs 6.5 d, P = .06).

tetanus (defined as <1 case of neonatal tetanus per 1000 live births in every district).[376] Globally, only about half of women of reproductive age are adequately immunized, and it has been estimated that neonatal tetanus accounts for as much as 7% of neonatal deaths globally.[29] Others point out that maternal tetanus may account for at least 5% of all maternal deaths.[377] An additional 90 000 mothers die annually from puerperal infections caused by unclean delivery practices, and sepsis accounts for 14% of all obstetrical deaths.[378] Thus, it is imperative that preventive strategies such as clean delivery and maternal tetanus immunization form a cornerstone of maternal care in any setting and that they go hand-in-hand.

Given the scientific basis for the importance of tetanus prevention and basic hygiene, it would now be unethical to conduct RPCTs assessing such approaches. Hence, much of the evidence for benefit of

TABLE 20. Antenatal TT Immunization and Clean Delivery

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Meegan et al[389]	Kenya and Tanzania; rural setting; QT	During the project period, there were 29 689 births in the intervention areas and 88 471 births in the control areas. In the intervention area, TBAs carried out antenatal, intrapartum and postnatal care. They were supplied with delivery kits and taught clean delivery. No immunization was performed.	The neonatal tetanus rate decreased by 99% in the intervention area compared to the control area (0.75/1000 live births in intervention areas, range = 0–3, vs 82/1000 live births in control areas, range = 74–93).
Tsu[393]	Nepal; rural setting; PCS	Women from 3 districts who had delivered a live infant (defined as a baby that survived at least 24 hours after birth and was born at home between 7 and 28 d prior to the interview) were enrolled in 1 of 4 possible cohorts: 1) kit user with trained attendant (n = 420), 2) kit user with untrained or no attendant (n = 398), 3) kit non-user with trained attendant (n = 404), and 4) kit non-user with untrained or no attendant (n = 438). The data were then collected by interviews with the mothers of the newborns, members of the mother's household who were present for the delivery or were caretakers of the newborn along with some trained TBAs who had participated in some eligible deliveries. Field interviewers also directly observed the newborn's abdomen and cord area, and consulted with medical records if available.	The cohorts in which kits were used had less than half the infection rate (0.45; CI: 0.25–0.81) of kit non-users who did not use a new or boiled blade and clean cutting surface (after adjusting for confounders), but there was no significant difference between kit users and any other group of kit non-users, suggesting that clean cord-cutting is one of the most important practices in preventing infection.
Gupta et al[379]	India; rural setting; PCS	TT vaccination was given IM to pregnant women (n = 1760) as a single booster dose to those who had received 2 doses in the preceding 3 y (n = 762), and TT vaccine was given in 2 doses at 1-month intervals to those who had no previous history of TT immunization (n = 696) or who were previously only partially immunized (n = 230).	Neonatal tetanus prevention attributable to TT vaccine was 88% for complete immunization and 59% for partial immunization compared to nonimmunized. The risk of neonatal tetanus among children born to women who received any dose of TT was one-fifth that of children born to non-immunized mothers (OR: 0.12; CI: 0.02–0.41).
Chongsuvivatwong et al[386]	Thailand; Province-based study; RCT	An education program for TBAs (n = 214) consisting of general midwifery and cord-care training was carried out in 2 provinces with a total population of 500 000, and mass TT immunization was carried out in just 1 of the provinces. Pre- and post-intervention surveys were carried out with randomly selected groups of 210 respondents; the project also interviewed 112 TBAs.	The incidence of neonatal tetanus in both provinces declined sharply, suggesting that reinforcement of routine services and hygienic practices was of primary importance. The NNT death rate was 0.2–0.4/1000 at the end of the intervention, reduced 8- to 10-fold.
Kapoor et al[380]	India; rural setting; QT	TT immunization of pregnant women was initiated in 28 villages in 1970. The second strategy adopted in this area after 1982 was to distribute to every registered pregnant women a sterilized delivery kit containing gauze pieces, half a razor blade and thread.	There was a gradual and sustained reduction in the neonatal mortality rate from 42.3/1000 live births in 1972 to 17.9/1000 in 1987. During this period, neonatal deaths due to tetanus disappeared (14.6/1000 live births in 1972, 0/1000 in 1987). A 22% reduction in NMR occurred after the introduction of birth kits; there is a mixed impact of birth kits and TT.

clean delivery practices and TT immunization comes from observational studies.

COMMUNITY-BASED EVIDENCE. In addition to a host of descriptive studies, our search identified 8 trials conducted in rural settings in developing countries that provided pertinent information on perinatal and/or neonatal outcomes after various interventions to prevent tetanus and provide clean delivery (Table 20). These studies variably involved maternal TT immunization and/or preparation for clean delivery by equipping mothers and/or birth attendants with delivery kits and promoting hand-washing for delivery and newborn care. Thus, in general, it was not possible to determine the impact of individual interventions on outcomes.

Significant reductions in rates of neonatal tetanus, as well as associated case fatality and NMRs, were observed in newborns of mothers immunized for tetanus during pregnancy.[379–385] Even partial immunization was found to be effective in decreasing mortality and tetanus morbidity.[379,382] Hand-washing and use of clean instruments for cord cutting were

TABLE 20. Continued

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Rahman et al[383]	Bangladesh; rural setting; PCS to evaluate an RCT	Neonatal mortality was compared between offspring born from 1978–1979 to women who had received TT prior to pregnancy (n = 956), offspring born to women given TT while pregnant from 1978–1979 (n = 934), offspring born to partially immunized women (n = 729), and offspring born to non-immunized mothers (n = 7237). Women given TT were given 2 doses if immunized in 1974 (non-pregnant), 3 doses of TT if immunized in 1978 (pregnant) and 2 doses if immunized in 1979.	Decreases in the stillbirth rate (44%, $P < .05$) and neonatal mortality rate (49%, $P < .01$) were observed in the women who were fully immunized in pregnancy compared to those who were not.
Rahman [384]	Bangladesh; rural setting; RCT	In 3 unions, TBAs were trained in better maternal nutrition and hygienic newborn care practices; in 3 unions TT was given; and 3 unions were kept as controls. 1760 pregnant women were cared for by these TBAs.	NMR decreased 72% and 54% in the TBA training areas and the TT areas, respectively. The NMR was 38.9/1000 in TT unions compared to 85.2/1000 in control unions. Tetanus neonatorum decreased by 94.6% in the TT area.
Black et al[382]	Bangladesh; rural setting; DBRCT	Volunteer non-pregnant women (n = 46 443) received 0.5 mL of cholera toxin or aluminum phosphate-adsorbed TT by IM injection. 13 220 women received 1 TT injection, while 33 175 received 2 TT injections. Neonatal mortality in infants born 9–32 mo after immunization were compared.	In the first cohort of offspring, neonatal mortality was significantly lower (33%, $P < .01$) among those born after 9–32 mo of mass tetanus vaccination in women (68.4/1000 in controls vs 44.1/1000 in TT area). 75% of the reduction in mortality was attributable to the reduction in neonatal mortality between 4–14 d of age ($P < .001$).

associated with reduced neonatal tetanus incidence,[381,386–389] neonatal mortality,[380,384] and sepsis.[271,384] Training TBAs in clean delivery and making clean delivery kits available were seen as important factors in infection control.[380,385,390–392] In rural Nepal, failure to wash hands before cutting the cord or use of dirty cloths on the umbilical cord were associated with 60% and 70% increased risk of cord infection, respectively.[393] Moreover, failure to use a boiled blade among nonusers of clean delivery kits led to a 2.3-fold increase in risk of cord infections above that of clean delivery kit users. However, use of a clean home-delivery kit did not affect cord infection rates, provided that a new or boiled blade was used to cut the cord.

Thus, tetanus immunization of pregnant women in combination with promotion of hand-washing and clean delivery, including clean umbilical cord care, was protective against neonatal tetanus and resulted in reduced neonatal mortality and morbidity. Among these interventions, the most persuasive data on efficacy are in support of tetanus vaccination strategies. In Sri Lanka, the introduction of the Expanded Programme on Immunization (EPI) vaccination strategy in 1978 led to a dramatic reduction in neonatal tetanus infection rates, which declined from 2.16 to 0.06 cases per 1000 live births.[394] Similar data were reported from Burma,[384] showing that neonatal tetanus mortality rates in non-EPI areas were threefold higher than in EPI areas (9 vs 3 per 1000 live births). Similarly, in Bangladesh, national TT-immunization programs reduced the incidence of deaths from neonatal tetanus by 90% (from 41 to 4 deaths per 1000 live births) over a decade.[29] One study (in 2 sites) compared the efficacy of 3 intervention strategies for reducing neonatal tetanus: maternal TT administration, hospital-based delivery (to promote clean delivery), and home delivery by a trained birth attendant.[395,396] Overall, maternal tetanus vaccination is most effective and seems to offer the single best option for reducing neonatal tetanus in developing countries (Table 21).

CONCLUSIONS. Evidence for the benefits of maternal tetanus immunization on neonatal outcomes is incontrovertible. Maternal TT immunization must be an essential part of antenatal care packages as well as mass-vaccination programs. Similarly, the importance of clean delivery practices, including clean umbilical cord care, must be underscored. Available community-based data suggest that the best gains may be obtained from implementation of a combination of maternal immunization and clean delivery and cord-cutting practices. On the other hand, there is no evidence that as a single intervention, use of a clean delivery kit is necessarily the most appropriate way of ensuring that caregivers and birth attendants pay sufficient attention to antisepsis, nor is there evidence that kit use impacts umbilical cord infection or NMRs. To the contrary, behavior-change communications strategies to promote clean delivery practices, including clean cord cutting, should be im-

TABLE 21. Comparative Efficacy of Interventions to Prevent Neonatal Tetanus

	TT Administration (2 Doses)	Hospital Delivery	Home Delivery by a Trained Birth Attendant
Burma[395]	91.4%	84.6%	32.8%
Egypt[721]	87%	77%	49%

plemented in tandem with introduction of clean delivery kits.

We would underscore the need to undertake an evaluation of the most appropriate, cost-effective, and sustainable clean delivery strategies in community and rural settings in developing countries. If clean delivery kits are promoted, it should be done in the context of broader behavior-change communications regarding clean delivery practices.

Maternal Pneumococcal Immunization

BACKGROUND. The high incidence of infectious diseases in young infants in developing countries suggests that, in many cases, maternally derived antibodies fail to provide adequate protection. For example, infection with *Streptococcus pneumoniae* accounts for 10% of deaths (220 000 deaths per year) globally in infants <90 days old.[397] Although live vaccines are contraindicated in pregnancy, killed or toxoid-based vaccines can be administered safely to pregnant women. These strategies may be particularly useful in circumstances in which background rates of routine vaccinations in childhood and adolescence are low or available vaccines are contraindicated or ineffective in young infants. Thus, although the benefits of maternal immunization against tetanus are well established, there is very little information about the impact of other vaccines administered during pregnancy on pregnancy outcomes.

COMMUNITY-BASED EVIDENCE. One study of maternal pneumococcal vaccination has been reported (Table 22).[398] Although the study took place in an urban hospital setting, we included it in our evaluation because it was based in a developing country and evaluated neonatal outcomes. Infants born to mothers who had been immunized had higher blood levels of antibodies sufficiently protective against pneumococcal antigens. However, the newborn antibody levels depended primarily on the duration between immunization and delivery. Although the level of antibodies decreased at 22 weeks of age postnatally, levels were still higher than those found among control infants. Additional data on clinical outcomes and long-term protection were not available.

CONCLUSIONS. Although limited and preliminary, these data provide intriguing information on the possibility of maternal immunization as a strategy for addressing early neonatal pneumococcal infections. Development of maternal immunizations against group B streptococcus and *Haemophilus influenzae* is similarly of great interest and under active investigation.

Promotion of Smoking Cessation During Pregnancy

BACKGROUND. Inhalation of smoke by pregnant women may occur through several modes of exposure and has been consistently associated with IUGR and LBW in offspring. It is widely recognized that smoking increases the risk of LBW births almost twofold[399] and significantly increases perinatal mortality.[400]

Infants born to women who smoke during pregnancy weigh, on average, 200 g less than infants born to comparable women who do not smoke.[399] Smoking has been shown to double the risk of LBW births among those mothers who smoke, compared with those who do not. In addition to LBW, increased risk of spontaneous abortion, as well as increased risk of perinatal and neonatal mortality, have also been associated with maternal smoking.[401] Recently, new evidence has shown an association of indoor air pollutants with LBW and increased infant and perinatal mortality.[402,403] One study reported an association of LBW with use of wood as cooking fuel.[401,402] The study by Boy et al,[402] using a retrospective cohort design, evaluated the association between LBW and exposure to wood smoke by asking women at the time of delivery about the type of cooking fuel they used. The study results were potentially confounded, however, failing to control for differences in nutritional and socioeconomic variables associated with different fuel types. The study also included a combination of hospital and home deliveries but excluded women living in remote areas due to inaccessibility.

Smoking and use of tobacco in other forms are widespread in developing countries. Moreover, exposure to outdoor air pollution, indoor air pollution, and indoor smoke (either from cooking or secondary inhalation of cigarette smoke) is widespread and may impact the mother as well as the young infant, leading to increased risk for asthma and respiratory infections.[404]

A systematic review of RCTs evaluating the impact of cessation of smoking during pregnancy[405] found that there were significant reductions in the incidence of LBW (OR: 0.8; CI: 0.67–0.95) and preterm births (OR: 0.83; CI: 0.69–0.99) and an increase

TABLE 22. Maternal Pneumococcal Immunization

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Shahid et al[398]	Bangladesh; urban hospital setting; DBRCT	Women 30–34 wk gestation (n = 70) were randomized to receive 23-valent pneumococcal polysaccharide vaccine (n = 36) or meningococcal vaccine containing polysaccharide of groups A, C, Y and W-135. (n = 37).	Among pneumococcal vaccine recipients, there was a high correlation between the maternal pre-immunization and post-immunization antibody titers (Spearman correlation R_S = 0.66 for type 6B and R_S = 0.77 for type 19F, P = .0001).	Infant cord blood antibody titers were highly correlated with the maternal titers at delivery. In the 22 wk postnatal sample, 71% and 63% of the infants of women who had received pneumococcal vaccine had antibody >0.15 μg/ml for types 6B and 19F, respectively (P = .01).

in mean birth weight of 28 g (CI: 9–49 g). However, there was no difference in the incidence of VLBW births or overall perinatal mortality, and the largest cluster-randomized trial reviewed showed no evidence of an impact of reduction in smoking on adjusted mean birth weight.[406]

COMMUNITY-BASED EVIDENCE. Measures to reduce environmental exposure to smoke may improve pregnancy outcomes, but this has not been systematically studied in developing countries. In light of this lack of data, evidence available concerning the impact of smoking cessation on pregnancy outcomes is presented from developed countries in an attempt to evaluate the impact of this potential intervention.

We identified 8 additional studies, the majority of which were undertaken in the United States, primarily in urban settings, that reported on the impact of smoking cessation on pregnancy outcomes (Table 23). No rural-based study could be identified. The studies included several smoking-cessation counseling methods ranging from individual counseling by midwives to counseling by a trained professional counselor, often supplemented with literature about the potential adverse effects of smoking on the developing fetus. In all but 1 study,[407] interventions to promote smoking cessation in pregnant women were found to be significantly effective in increasing smoking-cessation rates[408–411] and reducing the number of cigarettes smoked by mothers.[410,412] In most studies, however, no impact was seen on pregnancy outcomes, including birth weight,[407,408,410,413,414] rates of LBW or preterm delivery,[407–410,413,414] or perinatal mortality.[409,413,414] Some studies, however, demonstrated an increase in birth weight and/or length in subgroups that stopped smoking due to the intervention.[409,411,412]

CONCLUSIONS. Overall, smoking-cessation programs have produced mixed results on pregnancy outcomes such as preterm birth or LBW rates and have failed to impact fetal, perinatal, or infant mortality despite success in reducing smoking rates. Few studies have evaluated the impact of environmental smoke and indoor air pollution on pregnancy outcomes in developing countries or interventions to redress them. However, a recent review by the WHO has highlighted the potential adverse health consequences from indoor air pollution.[403]

Clearly, it is prudent to discourage maternal smoking due to the general harm that smoking does to health. It is important, however, that additional studies on reducing exposure to tobacco and indoor air pollution be conducted in developing countries with direct assessment of pregnancy outcomes and health of the young infant, because evidence for the impact of interventions on health status of newborns in developing countries is currently unavailable. Presently, despite the paucity of studies from community settings in developing countries, there is enough information from developed countries to decry the use of any form of tobacco (smoked or chewed) and addictive drugs such as alcohol, cocaine, and narcotics in pregnancy.

Maternal Care Packages

BACKGROUND. The aforementioned studies and interventions largely evaluated solitary maternal interventions. In most programmatic settings, however, such interventions typically are provided in combinations and as part of a package of care. Although most such studies have examined maternal outcomes, data also exist on the impact of packages of maternal interventions on perinatal outcomes.

COMMUNITY-BASED EVIDENCE. Our review yielded 2 studies that provided maternal care packages in a rural community-based setting and reported information on perinatal outcomes (Table 24). These programs were directed toward identification of high-risk patients and their early referral to a higher-level facility and provided a multilayered series of measures including essential antenatal care, improved referral systems, and facility-based care. The community-based maternal care programs showed significant reductions in perinatal (34%) and neonatal (43%) mortality.[415] Recent data from a perinatal intervention trial in Macedonia indicate that it may be possible to reduce perinatal and neonatal mortality at the national scale through a concerted perinatal education and health worker–training program within the health system setting.[416] Similarly, the introduction of a structured primary care program in Bolivia,[417] coupled with maternal care, led to a dramatic reduction in infant and young child mortality. In 1992–1993, the annual rates of mortality of children <5 years old were 205.5 per 1000 and 98.5 per 1000 in the comparison and intervention areas, respectively. The absolute difference in mortality of 107.0 deaths per 1000 (CI: 72.7–141.3 per 1000) represented 52.1% (CI: 35.2–68.8%) lower mortality among children <5 years old in the intervention areas, compared with the control areas.

CONCLUSIONS. Available evidence suggests that much of the improvement in perinatal and neonatal health in the West preceded the advent of neonatal intensive care and is largely owed to better and comprehensive maternal care and reproductive health.[418] In developing countries, the dependence of infant survival on the survival and health of the mother has been clearly demonstrated.[14] Data on the impact of maternal interventions on perinatal and neonatal outcomes are scarce but robust. Investing in improved maternal health must form the cornerstone of strategies aimed at improving perinatal and neonatal outcomes.

Intrapartum Interventions

Maternal Vaginal and Newborn Skin Antisepsis

BACKGROUND. Maternal intrapartum and postpartum infections are a major cause of maternal morbidity and mortality in developing countries. A large proportion of early-onset neonatal infections in developing countries may also be related to vertically transmitted infections from the maternal genital tract.[21,25,419] Thus, there is interest in evaluating low-cost strategies for preventing and reducing infectious

TABLE 23. Promotion of Smoking Cessation During Pregnancy

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Secker-Walker et al[410]	US; urban setting; RCT	399 pregnant women were recruited for the study. Intervention women (n = 197) received structured advice from their physician and referral to individual behavior-change counseling by trained nurses during prenatal care, while control women (n = 202) received brief advice to stop smoking and a quit-smoking booklet at their first visit.	40% of the women in the intervention group stopped smoking or reduced smoking to ≥50% of the baseline level compared to 25% in the control group (P = .02).	No significant effect of the intervention was seen on birth weight or LBW rate.
Wisborg et al[407]	Denmark; urban hospital setting; QT	3156 women were recruited for the study. Pregnant women in the intervention group (n = 527) were given individual advice and a leaflet about smoking cessation at the first antenatal visit at ~16 wk of gestation. The control group (n = 2629) did not receive this education.	No difference was found between the intervention and control groups in the rate of smoking cessation.	No effect was seen on birth weight or preterm birth rate.
Lefevre et al[414]	Sweden; multi-center trial; RCT	Women in the screened group (n = 7617) had 2 screening ultrasound evaluations to assess fetal growth to assess whether screening would encourage smoking cessation. No specific smoking cessation education was provided in addition to the ultrasound. A control group (n = 7534) was also studied for pregnancy outcomes.		No effect of the intervention was seen on PMR, birth weight or preterm birth rate compared to the control group.
Li et al[411]	US; urban setting; RCT	814 pregnant women were recruited for the study. Women in the intervention arm (n = 400) were given formal counseling, a guidebook, individual smoking cessation reinforcement and social support. Women in the control group (n = 414) received standard written risk information and verbal advice to quit. Women in both groups were subdivided and analyzed according to outcome: quitters (quit smoking), reducers (reduced number of daily cigarettes), and no-changers (no change in smoking habits). Mothers who had never smoked were used as a comparison group.	There was a 14.3% quit rate among women in the experimental group versus an 8.4% quit rate among the control women.	The mean birth weight of infants born to the quitters was 241 g heavier than those born to no-changers (P = .008) and reducers (P = .04). The adjusted mean birth weight of infants born to reducers was 92 g heavier than among the no-changers (P = .08). LBW was about 2 times more likely among the infants born to reducers or no-changers, compared with mothers who never smoked, but this finding was not statistically significant. Interestingly, the percentage of LBW infants born to the quitter group (10.3%) was comparable to the group that had never smoked (10.9%).
Haddow et al[413]	US; multiple sites; RCT	Women in the intervention group (n = 2848 pregnant smokers) were objectively educated (using serum cotinine level for interpretation of the need for smoking cessation), and effectiveness of education was assessed by comparison of cotinine levels in women in the intervention and control groups.		No effect was seen on NMR, IMR, birth weight, LBW or preterm birth rates.
Hjalmarson et al[408]	UK; urban hospital setting; RCT	Women in the intervention arm (n = 492) were given a smoking cessation manual that detailed ways and means of tackling and quitting the habit. Controls (n = 231) were not given the manual.	50% more women in the intervention arm had continuous abstinence.	No significant effect was seen on birth weight, LBW or preterm birth rates.
Macarthur et al[412]	UK; urban hospital setting; RCT	Supplementary health education about smoking in pregnancy was given to women in the intervention group (n = 493) while those in the control group (n = 489) received only routine advice.	The mean daily reduction in number of cigarettes smoked in the intervention group and the control group was 2.2 vs 1.1, respectively.	The firstborn infants in the intervention group were heavier (mean difference 68 g, $P < .06$) and longer (mean difference 0.75 cm, $P < .01$) than those in the control group.
Sexton et al[409]	US; urban setting; RCT	935 pregnant smokers were randomized to either an intervention or a control group. Women in the intervention group received staff assistance for smoking cessation.	The reported quitting rate at the eighth month of pregnancy was 43% compared with 20% in the treatment and control groups, respectively ($P < .01$).	No differences were seen in fetal mortality or gestational age, but infants in the intervention arm were heavier (mean difference 92 g, $P < .05$) and longer (mean difference 0.6 cm, $P < .05$) than those in the control group.

TABLE 24. Maternal Care Packages

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Yan[415]	China; rural setting; PCS	7 of 29 townships were randomly selected. A 3-tiered (village, township and county) Maternal Child Health network was developed in which MCH workers at the community level identified pregnant women and gave them antenatal care, with regular higher-level supervision from doctors. A ward for newborns was available at the county level for emergencies.		NMR declined by 34% (from 26.6/1000 to 17.5/1000 births).
Antia[725]	India; rural setting (Mandwa Project); QT	In collaboration with the elders of the villages, VHWs were trained to take care of pregnant women. A small health center with 10 beds (chiefly for maternity care and tubectomy) was established.	Increased case detection and treatment of leprosy and tuberculosis by VHWs was recorded.	The IMR was lower in the project area compared to the national figures (74/1000 live births vs 114 nationally for that time period).

complications of maternal infections, particularly for settings in which antenatal care may be suboptimal.

A number of antiseptic solutions or preparations may be used for cleansing the maternal genital tract. However, the largest body of evidence and greatest measure of support is available for chlorhexidine. This agent has been used successfully in developed countries for prophylaxis against newborn colonization and infection with group B streptococcus.[420–426]

COMMUNITY-BASED EVIDENCE. A study of the impact of chlorhexidine cleansing was undertaken in Malawi at an urban hospital, at a cost of $0.10 for each maternal-infant pair treated (Table 25).[427,428] Cleansing of the maternal vaginal canal and the newborn skin with a 0.25% chlorhexidine solution resulted in significant reductions in serious postpartum maternal infections ($P = .02$), neonatal admissions (OR: 0.8; CI: 0.79–0.97), neonatal sepsis (OR: 0.5; CI: 0.32–0.76), overall neonatal mortality (28.6 vs 36.9 per 1000; $P < .05$), and neonatal mortality due to infections (OR: 0.5; CI: 0.29–0.88; 2.4 vs 7.3 per 1000; $P < .005$).[428] Among women with rupture of membranes for >4 hours, the HIV transmission rate was decreased by 40% (OR: 0.6; CI: 0.4–0.9). In another study in Kenya comparing intrapartum vaginal lavage with 0.2% and 0.4% chlorhexidine, there was no overall effect on transmission of HIV, but risk of transmission was significantly reduced (OR: 0.1; CI: 0.0–0.9) in the subgroup that had not had rupture of membranes before treatment.[429]

CONCLUSIONS. Chlorhexidine cleansing of both the maternal vaginal canal and the newborn skin has

TABLE 25. Maternal Vaginal and Newborn Skin Antisepsis

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Taha et al[428]	Malawi; urban hospital setting; QT	3635 women giving birth to 3743 babies were enrolled in the intervention phase and 3330 women giving birth to 3417 babies were enrolled in the non-intervention phase. Intervention consisted of manual cleansing of the birth canal and cleansing the baby immediately after birth with a 0.25% chlorhexidine gluconate solution.	The intervention resulted in reductions in maternal admissions related to delivery (29.4 vs 40.2/1000; $P < .02$) and serious postnatal maternal infections (1.7/1000 vs 5.1/1000; $P = .02$).	The intervention resulted in a 22% reduction in NMR and a 67% reduction in infection-associated mortality. The intervention reduced serious neonatal illness requiring admission (16.9% vs 19.3%; $P < .01$), neonatal sepsis (7.8/1000 vs 17.9/1000; $P < .0002$), overall neonatal mortality (28.6/1000 vs 36.9/1000; $P < .06$) and mortality due to infections (2.4/1000 vs 7.3/1000; $P < .005$).
Biggar et al[427]	Malawi; urban hospital setting; RCT	The infection status of infants of 3327 control women (conventional delivery procedures) was compared with that of 3637 infants of intervention-delivered women. Intervention consisted of washing the maternal birth canal and the skin of the newborn with 0.25% chlorhexidine.		Among women with rupture of membranes >4 h before delivery, chlorhexidine reduced HIV transmission rate by 40% (OR: 0.6; CI: 0.4–0.9). No significant effect for women with rupture of membranes <4 h before delivery.

significant potential for reducing maternal and neonatal postnatal infections and improving neonatal (and perhaps maternal) survival. Additional efficacy trials are needed to confirm these results in different facility-based settings, to determine the relative contribution of vaginal cleansing versus newborn skin cleansing, and, thence, to evaluate potential applications and feasibility of the intervention within the community. Evaluation of higher-concentration formulations of chlorhexidine to prevent sepsis with pathogens from the skin[34] and to prevent maternal-to-child transmission of HIV (1%) is also warranted.

Postnatal Interventions

Newborn Resuscitation

BACKGROUND. Intrapartum hypoxia and birth asphyxia are widely regarded as major causes of morbidity and mortality in developing countries.[18,430,431] "Birth asphyxia," or failure to establish breathing at birth, comprises just a portion of the burden of early death from hypoxia. For every neonatal death from asphyxia, there seems to be ~1 additional fresh stillbirth that occurs due to intrapartum hypoxia,[430,432] although the precise burden of stillbirths is not yet well defined.[24] Evidence for birth asphyxia as a major cause of neonatal mortality is well established; however, the contribution of intrapartum hypoxia and birth asphyxia to cerebral palsy and the overall burden of handicap in developing countries is unclear.[433] Previously, it was estimated that for every case of mortality due to asphyxia or intrapartum hypoxia, another 4 newborns survived but suffered sequelae.[434] However, more recent data suggest that this may be a gross overestimation of the burden of handicap, because most newborns in developing countries with severe asphyxia die.[435]

Approaches to improving birth asphyxia-related outcomes may include prevention through improved antenatal care such as birth preparedness; intrapartum care such as the presence of a skilled birth attendant and fetal monitoring (eg, use of a partograph); or improved management (eg, resuscitation) of newborns who do not breathe adequately at birth. The effects of antenatal and intrapartum interventions on birth asphyxia outcomes are thoroughly covered in another recent review[24] and are not included here. The important role of neonatal resuscitation in immediate newborn care is well accepted and forms a cornerstone of immediate newborn care in developed countries,[17] but there are particular challenges to making this intervention feasible in developing-country settings.[24] Recent treatment modalities and interventions such as cerebral hypothermia[436,437] therapy and the role of medications after asphyxia are experimental and have been evaluated only in controlled facility-based situations in developed countries. This latter group of interventions is not evaluated further in this review.

COMMUNITY-BASED EVIDENCE. In addition to a host of descriptive studies, we identified 13 studies from developing countries that evaluated various aspects of neonatal resuscitation, including the feasibility of primary care staff undertaking the interventions (Table 26, see also Table 39). The reported literature suggests that TBAs who are trained and supervised in newborn resuscitation are capable of learning and properly using simple resuscitation techniques[431,438–442] and that resuscitation may be performed successfully by trained health providers using relatively simple equipment (eg, mouth-to-mask breathing)[443,444] and room air.[445,446] Training hospital staff in India[447] and China[448] in newborn resuscitation has been shown to reduce asphyxia-related deaths.

It has been suggested that neonatal mortality may be reduced after training of TBAs in resuscitation,[431,449] although little objective data have been provided. Daga et al[449] reported 41% and 62% reductions in NMR and PMR, respectively, over a 3-year period after introduction of a TBA training program that included mouth-to-mouth resuscitation of asphyxiated infants as a central component of the intervention. Successful resuscitation was reported in 83% of cases of asphyxia. Kumar and Aggarwal[431,442] reported a 70% reduction in asphyxia-specific mortality ($P < .05$) among infants delivered by selected TBAs in rural India trained in advanced resuscitation using a mucus sucker and bag-and-mask compared with TBAs trained in mouth-to-mouth resuscitation. Newborns delivered by TBAs with advanced training also had a 19% lower PMR and a 20% lower case-fatality rate, although neither outcome effect was significant. A recent meta-analysis of the impact of TBA training programs found that neonatal mortality due to asphyxia was reduced 11% (CI: 2–21%).[3] It was uncertain, however, which aspects of the training programs were responsible for the impact. Most programs did not describe neonatal resuscitation as an important part of training; thus, the impact seemed to be due to interventions other than resuscitation.

In northern India, CHWs were trained in essential newborn care (clean cord cutting, maintenance of warmth, breastfeeding promotion); identification and special care, including referral when indicated, of at-risk infants; and mouth-to-mouth resuscitation of asphyxiated infants.[438] The NMR fell 25%, from 51.9 to 38.8 per 1000 live births, during the 2 years of the study, with 18% of deaths attributed to asphyxia. In another trial of home-based neonatal essential and emergency care, including resuscitation of asphyxiated newborns by trained CHWs, Bang et al[439] reported a 48% reduction in asphyxia-specific neonatal mortality. Training of grassroots-level health providers in a Chinese province in methods of newborn resuscitation resulted in a reduction in the case fatality rate from 7.1% to 0.45%.[450]

No data exist on the role of family members in neonatal resuscitation.

CONCLUSIONS. Our review suggests that, although objective evidence for the impact of community-based resuscitation efforts is sparse, there are promising approaches and techniques that seem effective in preliminary trials. Trained TBAs or CHWs seem to be capable of learning resuscitation skills and saving newborn lives; however, the feasibility of scaling up

TABLE 26. Newborn Resuscitation

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Sibley and Sipe[3]	24 countries in 3 regions; meta-analysis of 60 studies			TBA training was associated with a significant (7%; CI: 4–9%) reduction in birth-asphyxia-specific neonatal mortality. This translated into 11% (CI: 2–21%) fewer neonatal deaths due to birth asphyxia among women cared for or living in areas served by trained TBAs.
Deorari et al[447]	India; 14 medical college hospitals; PCS	The National Neonatal Resuscitation Program, begun in 1990, trained and certified 150 pediatricians and nurses as trainers in neonatal resuscitation, providing them with essential equipment. These core faculty trained an additional 12 000 health care providers over 2 y, and resuscitation techniques were added to medical and nursing curricula. Each hospital provided baseline data for 3 mo prior to the intervention, as well as 12 mo of intervention data.		Although overall neonatal mortality was not affected, asphyxia-related deaths declined significantly ($P < .01$).
Bang et al[439]	India; rural setting; RCT	VHWs in 39 intervention villages were trained to provide a package of maternal and newborn care services, including health education, clean delivery, neonatal resuscitation using tube and mask ventilation, breastfeeding promotion, prevention and management of hypothermia, and detection and treatment of local infections (eg, skin, umbilical cord, as well as sepsis) with cotrimoxazole and gentamicin. Results were compared to 47 control villages without trained VHWs. Trained VHWs cared for 1676 neonates from 1995–98.		There was a 48% nonsignificant decrease in the birth-asphyxia-specific NMR in the intervention area (10.5 to 5.5 per 1000 live births) from the first to the third year of the intervention period. Overall NMR dropped from 62/1000 at baseline to 25.5/1000 at intervention end. Stillbirths dropped from 32/1000 to 25.9/1000, and PMR dropped from 68.3/1000 to 47.8/1000.
Saugstad et al[445]	6 countries; RCT	609 infants were enrolled. Newborns requiring resuscitation were randomized to receive room air ($n = 288$) or 100% oxygen resuscitation ($n = 321$).		No difference was seen in mortality in the first 7 d or 28 d of life between the 2 groups. There were 22% fewer infants with Apgar scores <7 after 5 min in the room-air group compared to the oxygen resuscitation group (24.8% vs 31.8%). Median time to first breath was 1.1 (CI: 1.0–1.2) min in the room air group, vs 1.5 (CI: 1.4–1.6) min in the oxygen group.
Kumar[723]	India; rural setting; community-based surveillance	A surveillance system was created for the tracking of births and neonatal deaths in 54 villages. Over a period of 18 mo, trained field workers interviewed the family member who was present at the time of childbirth in 2041 deliveries within 2 wk after the birth. The interviews documented birth history, use of resuscitation, and the training status of the TBA, including advanced training.		Birth asphyxia prevalence was 0.9% among babies delivered by TBAs with advanced training, in comparison to 2.4% in babies delivered by conventionally trained TBAs ($P < .05$). The mortality rate specific to birth asphyxia was 70% less among babies delivered by TBAs with advanced training, in comparison to conventionally trained TBAs ($P < .05$). The fatality rate of asphyxia cases was 20% lower and the PMR was 19% lower (49.4/1000 vs 61.0/1000) among newborns delivered by TBAs trained in use of resuscitation equipment compared to those delivered by TBAs trained for mouth-to-mouth breathing. However, given the small study size the difference did not reach statistical significance ($P > .05$).

TABLE 26. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Zhu et al[448]	China; hospital-based setting; PCS	A prospective study of 4751 newborns, 366 of whom were asphyxiated and managed by a neonatal resuscitation program (NRPG), was conducted over the period of 2 y. This group was compared to a control group comprised of 1722 live-born infants under the traditional resuscitation (TR) program.		The NRPG was associated with a 65.7% reduction in early NMR. During implementation of the NRPG, only 16 infants out of 4751 births (0.34%) died within 7 d, and 2 of the deaths occurred in the delivery room. In contrast, 17 newborns out of 1722 births (0.99%) managed within the TR program, died within 7 d, with 10 of those deaths occurring in the delivery room. As a result of the implementation of the NRPG, neonatal mortality was reduced almost 3 times ($\chi^2 = 10.54$, $P < .01$). 20 of 21 infants with severe asphyxia were normal; 1 had cerebral palsy.
Kamenir[444]	Kenya; rural hospital; open study: retrospective characterization of delivery practices and risk factors and prospective assessment of resuscitation practices	The use of routine resuscitation (including nasal and oropharyngeal suctioning, drying and proper stimulation) was evaluated in newborns with birth asphyxia ($n = 878$). If the neonate remained apneic, bag-and-mask ventilation was started with oxygen (if available).		4% of 878 newborns with asphyxia suffered unfavorable outcomes. Risk factors for unfavorable outcome included deliveries other than spontaneous normal vaginal deliveries and infants weighing <2000 g at birth.
Massawe et al[443]	India and Tanzania; urban university hospitals; QT	Mouth-to-mask (MM) ventilation was compared with bag-and-mask (BM) ventilation. 174 babies were studied; 54 (30 MM and 24 BM) were born in Bombay and 120 (56MM and 64BM) in Dar-es-Salaam.		The MM and the BM methods were equally effective in resuscitation of asphyxiated neonates. There were no significant differences between the 2 treatment groups by Apgar score ≥4 at 5 and 10 min, number of babies with first breath <5 min, number of babies with heart rate >130 beats/min, or number of babies with pulse oximeter values >75% at 5 min. At 5 min, 75% of all infants had Apgar scores ≥4. In Tanzania, low respiratory frequency was associated with a slow increase in heart rate above 130 beats/min.
Kumar[431]	India; rural setting; PCS	Simplified methods of resuscitation were taught to TBAs. An additional group received advanced training on use of the mucus extractor and bag-and-mask ventilation. Overall, 2041 births were reported, some delivered by conventionally trained TBAs ($n = 968$) and some by TBAs with advanced training ($n = 911$). 58 infants were asphyxiated or were fresh stillbirths, 20 of whom were delivered by TBAs with advanced training.		There was a 19% decrease in the PMR among the group of women who were attended to by advanced trained TBAs.
Xiaoyu[450]	China; rural setting; PCS	An exploratory study was created to introduce modern resuscitation to grassroots maternal and child health personnel. This study included training courses on neonatal resuscitation, on-the-spot teaching with repetition of key technical procedures, and the operational sequence of the 5 steps of the ABCDE protocol (airway, breathing, circulation, disability, and exposure). The approach highlighted the importance of endotracheal intubation and practicing neonatal resuscitation in person. In all, 223 newborns in the province were resuscitated.		Asphyxia-specific NMR was reduced 86% by using the strict application of the ABCDE protocol. 223 newborns were resuscitated in the 6 mo of the project with only 1 death (a mortality rate of 0.45%). All 14 cases (100%) of severely asphyxiated babies recovered and were well upon discharge. By contrast, out of 184 babies managed prior to introduction of the program, 13 babies died of asphyxia (a mortality rate of 7.1%) ($\chi^2 = 13.29$; $P < .01$).

TABLE 26. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Ramji et al[446]	India; urban hospital setting; RCT	Consecutive asphyxiated newborn infants (n = 84) were allocated to either resuscitation with room air (n = 42) or 100% oxygen (n = 42).		No significant differences were noted between the 2 groups for a number of outcomes including duration of assisted ventilation, time to first breath and cry and neonatal mortality. Preliminary data indicated that resuscitation with room air may be as effective as 100% oxygen in neonatal resuscitation.
Daga et al[449]*	India; rural setting; training assessment of community-based workers	In Ganjad primary health center, training of *Dais* and Anganwadi workers in newborn care included provision of warmth, resuscitation of asphyxiated newborns, and identification and referral of infants with foot length <6.5 cm in a population of 20 000. Anganwadi workers supported *dais* in identifying and making referrals and worked as a link between *dais* and auxiliary nurse-midwives.		There was a 70% decrease in IMR over a period of 4 y.
Daga et al[441]*	India; rural setting; PCS	*Dais* (TBAs) (n = 67) working in a population of 22 240 were trained to provide warmth to the infant, mouth-to-mouth resuscitation of asphyxiated infants, identification of LBW and preterm infants and safe transportation of high-risk infants to primary health centers. *Dais* reported 30 neonatal asphyxia cases over the 3 y after the program began.	Antenatal registration of pregnant women in 1990 showed a 30% increase over pre-program levels.	The PMR declined by 61.5%, stillbirth rate decreased by 51.4%, and NMR decreased by 42% compared to baseline over a period of 3 y.
Pratinidhi et al[438]	India; rural setting; PCS	CHWs in a study population of 47 000 were trained in risk identification (LBW, small size, preterm birth, feeding problems) and in various techniques of newborn care, including mouth-to-mouth resuscitation. Home visits were done for screening and management of at-risk infants (n = 851) and educating mothers on newborn care. Follow-up visits were fixed for the 8th and 29th day after birth. When only 1 risk factor was present, the TBAs recommended domiciliary care by the mother and CHW using health education under the supervision of nurse or doctor. When more than 1 risk factor was present, the mother and/or infant were referred to the hospital for inpatient care. There were 3083 live births recorded during the 3 y prior to the study, and 2990 live births recorded during the 2 study years.		Risk-detection rate by CHWs was 78%. The stillbirth rate decreased by 25%, from 28.4/1000 births to 21.5/1000 births. The NMR decreased by 25% from baseline over the 2-y project period, from 51.9/1000 live births to 38.8/1000 live births, but this difference was not statistically significant.

* Data are from the same trial.

this approach is unclear. Supervision and maintenance of skills are critical to success, yet formidable challenges exist at the community level. One of the areas of greatest need is to define feasible and cost-effective approaches by which community-level providers (eg, CHWs, community midwives) can prevent fresh stillbirths and neonatal deaths due to intrapartum hypoxia/birth asphyxia. There is evidence that mouth-to-mask and bag-and-mask resuscitation are comparable techniques with regards to neonatal mortality and morbidity[443]; however, the former was deemed more difficult for the providers. Thus, where feasible, bag-and-mask ventilation has become the preferred modality.[439] The evidence that room air could be satisfactorily used for neonatal resuscitation suggests that staff training alone and basic equipment may be sufficient for resuscitation of asphyxiated newborns in developing-country communities.

Additional large-scale effectiveness trials of such intervention strategies with defined criteria and endpoints are clearly required. More precise definitions of "birth asphyxia" at the community level and improved verbal autopsy instruments for identification of fresh stillbirths and neonatal deaths due to acute intrapartum hypoxia are urgently needed. The cost-effectiveness and sustainability of resuscitation using various modalities and the impact of resuscitation on disability rates have not been documented. The various components of resuscitation, such as the role of pharyngeal suction, the need for oxygen therapy, and the role of ventilation by bag-and-mask (as opposed to other modalities such as tube-and-mask, mouth-to-mask, or mouth-to-mouth), also require additional scientific scrutiny. Meanwhile, it is reasonable to promote the basic elements of newborn resuscitation (namely, drying, stimulation, and warming) as a routine part of newborn care and to further evaluate the potential role of trained TBAs and CHWs in using equipment such as the bag-and-mask to ventilate nonbreathing newborns. In addition, all skilled attendants should be trained to provide proper newborn stimulation and ventilation.

Delayed Umbilical Cord Clamping

BACKGROUND. There is little evidence as to whether the current practice of umbilical cord clamping soon after birth, to prevent polycythemia on the one hand or anemia on the other, is based on solid scientific criteria. Some studies have demonstrated that delayed cord clamping (after the cord stops pulsating) may increase neonatal blood volume by approximately one third.[451,452] Thus, delayed cord clamping may increase the newborn infant's iron reserves and reduce the incidence of iron-deficiency anemia in infancy, an issue of considerable public health importance.[453]

COMMUNITY-BASED EVIDENCE. In the course of introducing a program to reduce tetanus incidence in Haiti, it was observed that nearly half of families ceased cutting the cord at home after delivery and instead bundled the infant, placenta, and cord and sought cord care at the hospital.[385] Despite delays in cord cutting for up to several hours, neonatal mortality declined dramatically and no adverse effects on neonatal outcomes were noted.

We identified only 1 comparative trial from a developing country that evaluated this issue in an urban hospital setting (Table 27). Delaying umbilical cord clamping until the cord ceased pulsating was associated with an increase in red blood cell count in the neonatal circulation regardless of whether the infant was level with or below the level of the placenta.[454]

CONCLUSIONS. Despite the potential importance of the timing of cutting the cord, there are little data on its relationship to neonatal health. No data are available from developing countries on whether the common practice of waiting until after the placenta has been delivered to cut the cord has a beneficial or adverse impact on neonatal circulation and health. However, the scarce available evidence does indicate that delayed cord clamping may be beneficial, because it may allow for greater transfer of placental blood to the newborn's circulation before cutting the cord. Additional studies are needed to resolve this issue, because it may have important implications for prevention of anemia in infancy in susceptible populations in developing countries.

Umbilical Cord Antisepsis

BACKGROUND. The importance of clean cord cutting for the prevention of neonatal tetanus was considered in the section on tetanus prevention (see "TT

TABLE 27. Delayed Umbilical Cord Clamping

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Grajeda et al[454]	Guatemala; urban hospital setting; RCT	88 infants were enrolled, out of which 73 were followed up at 2 mo of age. 69 blood samples were available. In group 1 (n = 29) the cord was clamped immediately after birth. Group 2 infants (n = 30) had the cord clamped after pulsations stopped but with the infants kept at the same level as the mother's heart. Group 3 infants (n = 29) had delayed cord clamping at cessation of pulsations but the infants were placed at a lower level.	Infants in the groups with delayed cord clamping had significantly higher hematocrit values 2 mo after delivery compared with the control group. There were no differences between groups 2 and 3.

Immunization and Clean Delivery" and Table 20). Studies of the impact of topical applications of antiseptics to the umbilical cord in the postnatal period generally have shown reductions in bacterial colonization compared with no treatment.[34] However, impact has varied with the specific antimicrobial compound, the mode or frequency of application, and the degree of contamination in the environment. In general, chlorhexidine seems to be the most favorable choice of antiseptic because of its broad spectrum of activity, residual effects on the skin, low toxicity, and results showing overall reductions in cord colonization after treatment.[34,455]

Evidence for the effect of topical antiseptic treatment of the cord in reducing local cord or skin infections or sepsis is less clear because of conflicting reports.[34] Thus, several neonatal skin care reviews have called for discontinuation of routine topical antiseptic care of the cord based on conflicting evidence regarding which topical agent most effectively decreases colonization and the lack of a clear relationship between colonization and infection.[456,457] However, in many cases, when antiseptic treatments have been discontinued, increased rates of cord colonization and infection have been found.[458,459] In general, wide variation in trial design, small sample sizes with insufficient power to assess impact on infections, and inconsistent comparisons between different regimens have contributed to the largely conflicting literature on the impact of cord-care regimens.

A Cochrane review on different methods of neonatal cord care, including the use of topical antimicrobials, suggested that the incidence of omphalitis and skin infections within 6 weeks of observation was not affected by use of antiseptics.[460] There was a trend toward reduced microbial colonization with the use of antibiotics compared with no treatment. Antiseptics such as chlorhexidine, however, prolonged the time to cord separation. It was concluded that simply keeping the cord clean was probably as effective as topical antibiotic use. However, this review was based on 10 RCTs, all conducted in developed countries, none of which reported any systemic infections or neonatal deaths.

In addition to the aforementioned Cochrane review, the WHO[461] also reviewed the evidence from a host of descriptive and physiologic studies and concluded that medical cord-care practice recommendations are overwhelmingly based on research from hospital nurseries in developed countries. It was concluded that, compared with no treatment, application of a topical antimicrobial to the cord stump reduced umbilical colonization by harmful bacteria in hospital nurseries. Chlorhexidine, tincture of iodine, povidone-iodine solutions, triple dye and silver sulfadiazine were all found to be effective in reducing microbial colonization, although caution was issued regarding the need to balance their use with the potential for emergence of antimicrobial resistance. In general, dry cord care was recommended along with the use of soap-and-water solution to clean the cord when visibly soiled.

COMMUNITY-BASED EVIDENCE. There is a large body of literature outlining the increased risk of umbilical infection, mainly due to *Clostridium tetani* colonization, after application of unclean substances such as ash or mud to the cord of neonates in developing countries.[462–464] Observational studies have shown that application of antimicrobial agents to the cord after cutting was protective against tetanus and resulted in reduced neonatal mortality and morbidity[381,387,463] (Table 28). In a large CCS of tetanus deaths in Pakistan, Bennett et al[388] showed that infants who received applications of antimicrobials (type unspecified), both at birth and subsequently, were at significantly less risk of death than those who received dry cord care alone (OR: 0.2; CI: 0.06–0.58), even after adjusting for use of unclean substances such as cow dung, ash, or ghee (clarified butter) (OR: 0.4; CI: 0.21–0.77). In Papua New Guinea, neonates who received daily application of 10% acriflavine in spirit to the umbilical cord were 9.4 ($P < .02$) and 6.7 ($P < .01$) times less likely to have sepsis or fever, respectively, than those who did not receive the antiseptic applications.[463]

CONCLUSIONS. There is no definitive answer to the question of what constitutes the best form of cord care after birth, particularly in domiciliary settings. More research is needed on this issue, especially in situations of limited resources and high potential for environmental contamination of the cord. Although there is evidence to suggest that cord antisepsis may be beneficial, there is insufficient evidence to recommend the widespread use of topical antimicrobials on the cord stump. Nevertheless, the decision to use them may depend on local circumstances.

Rooming-in and keeping the infant with the mother also significantly reduces the incidence of colonization with pathogenic bacteria and cord infections.[465,466] Thus, early colonization of the newborn with commensal flora from the mother, facilitated by early and prolonged contact as with KMC, may be protective and may have contributed to the reduction in infections observed in cohorts who practiced KMC (see "KMC" and Table 35). Similarly, for home deliveries and for cord care after discharge from hospital in developed countries, clean cord care seems to be sufficient, and the application of antiseptics may not be required. However, for developing-country communities in which the majority of newborns are delivered at home and may face severe immunologic challenge from pathogenic bacteria in the environment, the benefits of topical antiseptics remain unknown. Provision of clean delivery kits may increase compliance with clean cord cutting and tying after birth, although this has not been demonstrated (see "TT Immunization and Clean Delivery" and Table 20). Topical antimicrobial applications may be a useful strategy for other instances in which potentially harmful practices such as cow dung application on the cord stump are widely prevalent, even if just for replacement of the harmful practices.[388,461] If chosen, the antimicrobial should have a broad spectrum of activity against Gram-positive

TABLE 28. Umbilical Cord Antisepsis

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Parashar et al[381]	Bangladesh; rural setting; CCS	For each neonatal tetanus case identified (n = 359), 3 living infants matched for gender, residence and date of birth were selected as controls.	Application of antibiotics to the umbilical stump at delivery decreased neonatal tetanus by 79% (OR: 0.21; P = .019). Hand-washing by the delivery attendant and prior immunization with TT were protective in multivariate analyses, decreasing tetanus rates by 36% (OR: 0.64; P = 0.005) and 50% (OR: 0.50; P < .001), respectively.
Bennett et al[388]	Pakistan; rural setting; CCS	Cases (n = 211) were uncircumcised infants diagnosed as having definite or probable neonatal tetanus. 3 controls who survived the neonatal period and whose mothers had not received TT were selected per case (n = 633).	Reported hand-washing by the delivery attendant was highly protective against neonatal tetanus, decreasing rates by 56% (OR: 0.44; CI: 0.29–0.67; P < .0002). Continuous use of antimicrobial agents (antibiotics and antiseptics) on the cord at delivery and during the first few days after delivery was highly protective in univariate testing (matched OR: 0.2; CI: 0.11–0.64; P = .003), and remained significantly protective when other delivery and cord-care practices were controlled for.
Garner et al[463]	Papua New Guinea; rural setting; QT	Newborns (n = 132) were divided into 3 groups. Infants in the control group (n = 64) were born to mothers without birth kits. Infants born the initial part of the intervention phase (n = 33) were born to mothers who had been supplied with a new razor blade and acriflavine 10% in spirit. Infants born during the later part of the intervention phase (n = 34) were born to mothers who had been supplied with a razor blade, acriflavine 10%, and plastic umbilical cord clamps which the women had been instructed how to use.	Of the 9 cases of neonatal sepsis, 8 were in the control group and 1 was in the intervention group (P < .02).
Traverso et al[387]	Pakistan; rural setting; CCS	Tetanus cases (n = 102) were identified at an urban hospital and 3 controls (n = 306) were selected from the village of each case.	Delivery conducted by formally trained personnel was associated with a decreased risk of neonatal tetanus (OR: .28; CI: 0.08–1.0). Use of a topical antibiotic was also associated with a protective effect, decreasing neonatal tetanus rates by 66% (OR: 0.34; CI: 0.18–0.65).

and Gram-negative pathogens and should be inexpensive, culturally acceptable, and widely available.

Additional research is needed to define best cord-care practices in developing-country communities. Meanwhile, efforts must focus also on providing culturally appropriate behavior-change communications to communities and caregivers on proven interventions such as clean cord-care practices, particularly hand-washing and use of a clean blade to cut the cord.

Hypothermia Prevention and Management

BACKGROUND. Hypothermia in the newborn period is widely regarded as a major contributory cause of morbidity in developing countries,[467] although it has been poorly documented. Hypothermia has been associated with increased risk of infection, coagulation defects, acidosis, delayed fetal-to-newborn circulatory adjustment, hyaline membrane disease, and brain hemorrhage.[468,469] At its extreme, hypothermia may manifest as neonatal cold injury[470,471] and be associated with significant mortality.[439] This risk is particularly marked among LBW infants in developing countries and is seen commonly even in countries with tropical climates. Studies in Nepal using continuous temperature monitoring have indicated that thermal stress may be extremely common among newborn infants; 80% of hospital-born infants became hypothermic soon after birth.[472] In another maternity hospital study in Nepal, 85% of newborns had a temperature <36°C within 2 hours of birth.[473] Similarly, in facility-based studies in Ethiopia,[474] Zambia,[475] and Zimbabwe,[476] one half to two thirds of newborns had hypothermia.

Few studies have addressed practices during and after birth, which can put the newborn at risk for hypothermia. In a multicenter evaluation in Latin America, Asia, and Africa, 65% and 73% of health facility workers had adequate knowledge regarding causes and prevention, respectively, of hypothermia, yet interventions to prevent hypothermia were seldom provided (eg, 0% warmed the delivery room, 11% dried and wrapped the infant, and 50% and 61%

provided special protection during transport or to LBW infants, respectively).[477] In 1 village-based study in India, 11% of 189 neonates were found to be hypothermic based on a single temperature reading taken within the first 24 hours after birth. Only 58% of newborns were wiped soon after delivery, the head was covered in 59% in winter and 10.5% in summer, no newborns were kept in skin-to-skin contact, and the room temperature was <24°C in 41% of households.[442] Early bathing and removal of vernix are also recognized but understudied risk factors for hypothermia. However, based on expert opinion, the WHO recommends that bathing be delayed for at least 6 hours after birth to minimize the risk of cold stress during the period of maximum physiologic transition of the newborn.[469]

Although it has been demonstrated that physicians and trained assistants in health facilities are capable of perceiving newborn body temperature by touch with reasonable accuracy,[441,478,479] in a community-based study in India, mothers using touch alone had limited ability to detect hypothermia.[480] Overall, only one fourth (24.6%) of hypothermic infants were correctly identified as such by the mothers. A temperature-indicator device (ThermoSpot) placed on the newborn's skin has been shown to provide an accurate indicator of the presence of hypothermia and is acceptable to mothers in hospital settings,[476,481–484] but additional research on its utility and use in resource-poor communities, especially by mothers, is needed.

It is now well recognized that rapid rewarming of hypothermic newborns in developed-country settings may be entirely safe and result in lower mortality compared with slower methods of rewarming.[485,486] The WHO has recognized the importance of thermal care of the newborn by including it as a priority behavior in the Mother-Infant Package of interventions in developing countries,[14] and the Saving Newborn Lives initiative of Save the Children/USA considers it an essential newborn care practice.[17] Accepted ways to achieve optimal thermal control of the newborn include warming of the room, immediate drying and wrapping after birth, immediate and frequent breastfeeding, delay in bathing until the infant is physiologically stable, close contact with the mother such as skin-to-skin contact, and appropriate swaddling and dressing, including the use of head cover. However, few studies have been conducted to evaluate feasible strategies for the prevention, recognition and management of hypothermia in developing countries. Recent emphasis has been on the use of skin-to-skin contact or KMC in the prevention of hypothermia, and this strategy will be considered separately (see "KMC"). Other potential interventions (eg, incubators, semipermeable plastic sheeting) commonly used to reduce transepidermal water loss (TEWL) and heat loss, particularly in preterm infants in developed countries,[455] have not been adequately evaluated in developing-country settings, are largely impractical for community settings, and will not be considered further here.

COMMUNITY-BASED EVIDENCE. Topical application of products such as paraffin-based ointments or oils aimed to modify skin-barrier function and reduce transepidermal loss of water and heat[455,487–490] has been evaluated in 2 hospital-based studies in developing countries[473,491] (Table 29). In India, topical therapy of preterm infants with corn oil every 4 hours resulted in a significant reduction ($P < .001$) in need for an external source of heat to maintain normal body temperature.[491] Another study in Nepal found that traditional oil massage with mustard oil, swaddling with a plastic swaddler, or KMC was equally effective in preventing hypothermia during the first 24 hours after birth.[473]

During neonatal transport, a simple Styropor box showed promise for preventing hypothermia.[492,493] Other trials have included elements of hypothermia prevention in a package of postnatal interventions,[438,439,494,495] but the specific impact of the thermal control interventions could not be determined.

CONCLUSIONS. Despite the critical importance of maintaining warmth for the newborn, there is a remarkable paucity of studies evaluating and commenting on community-based prevention, recognition, and/or management of hypothermia. There is a clear need for additional research on appropriate and cost-effective strategies for prevention of hypothermia in health system settings, including transport and care of high-risk LBW infants. Approaches such as training TBAs, CHWs, and caregivers to recognize and respond appropriately to warning signs of hypothermia, for example, have not been reported. Although heated cots have been scientifically evaluated in institutional settings,[485] these are too expensive for use in most developing countries.[494] The Styropor box offers an excellent example of simple technology that could be used as an alternative to transport incubators in developing countries, but additional evaluation is warranted to compare it with other options. Preliminary studies suggest that topical applications of skin barrier–modifying products may be beneficial for preservation of body heat.[473,491] Nevertheless, most cases of hypothermia likely could be prevented by a few simple behaviors such as immediate drying and wrapping of the infant, including the head; immediate breastfeeding; delay in the initiation of bathing; close contact with the mother; and keeping the room warm and the infant properly clothed and/or wrapped. In addition, KMC may be a highly cost-effective intervention for preventing hypothermia, especially of LBW infants (see "KMC"). Nevertheless, even when health workers possess knowledge of how to prevent hypothermia, this knowledge may not be translated into practice.[477] Thus, there is a great need to develop and evaluate the impact of culturally appropriate behavior-change communications to promote these healthful domiciliary thermal control practices.

Hypoglycemia Prevention and Management

BACKGROUND. Hypoglycemia after birth is a major cause of morbidity, particularly among intrauterine growth-restricted and preterm infants. The risk of hypoglycemia is significantly greater among preterm

TABLE 29. Hypothermia Prevention and Management

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Gosavi et al[493]	India; urban setting; PCS	32 high-risk newborn infants of varying disease severity were transported using the Styropor box.	None developed hypothermia (all had temperatures >36.5°C before and after transport). No other complications occurred during the transportation.
Daga et al[492]	India; rural setting; PCS	1 normal birth weight infant (2.6 kg) and a LBW infant (1.8 kg) were sequentially studied using KMC and then a Styropor box.	The temperature of the 2 infants was comparable using the 2 methods of care.
Johanson et al[473]	Nepal; rural setting; RCT	A prospective observational study of postnatal neonatal body temperature was followed by a randomized controlled intervention study using KMC, traditional "oil massage" and a "plastic swaddler." There were 500 infants in the initial observation study and 300 in the intervention study. In the observation study, 85% (420/495) of infants had temperatures <36°C at 2 h and nearly 50% (198/405) had temperatures <36°C at 24 h (14% were <35°C). Most of the infants who were cold at 24 h had initially become cold at the time of delivery (only 7 infants had been both well-dried and wrapped). In the intervention study, all infants were dried and wrapped before random assignment to 1 of the 3 intervention methods.	All 3 methods were found to be equally effective. Overall, 38% (114/298) and 18% (41/231) of the infants had a temperature <36°C at 2 and 24 h, respectively. None were <35°C.
Fernandez et al[491]	India; rural setting; PCS, controls matched for weight and gestational age	Preterm babies ($n = 25$) between 28 and 36 wk gestational age were treated with corn oil applied every 4 h to the entire body. An equal number of preterm infants ($n = 25$) were matched for weight and gestational age and served as the control group.	The study group required the use of the warmer to maintain rectal body temperature for significantly less time ($P < .001$) than the controls. Serum triglyceride levels also rose significantly ($P < .01$) in the study group from baseline to 72 h after initiation of treatment.

infants because of their reduced energy and glycogen reserves and inability to mobilize alternative metabolic fuels.[496] Hypoglycemia is also relatively common among LBW infants and macrosomic infants of diabetic mothers.[497] Prevention and management of neonatal hypoglycemia have been the subjects of a major review by Williams.[498]

Little data on hypoglycemia incidence or impact on newborn health are available from developing countries, in part due to difficulties in detection, which requires proper processing in a well-functioning laboratory. Studies in Nepal indicated that 38% of term infants had hypoglycemic episodes after birth.[499,500]

The most cost-effective strategy for preventing hypoglycemia is early feeding (continued every 2 to 3 hours on demand day and night) with breast milk, which is superior to milk formula in that it can promote relatively greater ketogenesis[501] and has a relatively lower insulinogenic effect.[502] The benefits of breast milk feeding are comparatively more marked in preterm infants.[503] Although nasogastric feeding may be difficult in primary care settings, there is evidence that cup and/or spoon feeding in larger preterm infants may be entirely feasible.[504,505] Although the cornerstone of prevention and management of neonatal hypoglycemia is early colostrum and breast milk feeding, other options may be needed for circumstances in which breast milk is not available, insufficient, or contaminated with HIV.

COMMUNITY-BASED EVIDENCE. We identified 2 studies from India for which alternative strategies for prevention of hypoglycemia were used[506,507] (Table 30). Both studies, conducted in urban hospital settings, indicated that the addition of granulated sugar to formula feeds in a sterile fashion was satisfactory for prevention and treatment of hypoglycemia. The osmolality of the sugar-fortified formula, however, was significantly higher than standard feeds. Thus, in the absence of follow-up information on risk of enteric infections and diarrhea with such an approach, sugar fortification of formula cannot be recommended for widespread implementation in programs.

CONCLUSIONS. The use of artificial formulas fortified with glucose polymers[508] or lipids such as medium-chain triglycerides,[509,510] has been shown to be effective in the prevention and management of hypoglycemia in developed-country studies. It is highly unlikely, however, that these strategies would

TABLE 30. Hypoglycemia Prevention and Management

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Singhal et al[507]*	India; urban hospital setting; RCT	110 term SGA infants without complications were enrolled in the study. Infants in the intervention group ($n = 55$) received fortified feeds that were prepared by adding 1 sachet containing 1.5 g of powdered sugar to 30 mL of standard milk formula. Infants in the control group ($n = 55$) received standard milk formula.	There was an 85% decrease in the incidence of hypoglycemia among newborn infants in the intervention group compared to controls ($P < .01$). No other morbidity was reported.
Singhal et al[506]*	India; urban hospital setting; RCT	130 term large-for-gestational-age infants without complications were enrolled in the study. Infants in the intervention group ($n = 65$) received fortified feeds that were prepared by adding 1 sachet containing 1.5 g of powdered sugar to 30 mL of standard milk formula. Infants in the control group ($n = 65$) received standard milk formula.	There was a 77% reduction in rates of hypoglycemia among intervention group infants compared to controls. The incidence of hypoglycemia was reduced significantly ($P < .05$) by the sugar-fortified feeds. The mean blood sugar level in babies receiving fortified feeds was significantly ($P < .001$) higher at all ages as compared to those receiving standard feeds. No other morbidity was reported.

* Data are from the same trial.

find favor in developing countries with significantly higher risk of infection. Although the data on use of sugar-fortified milk supplements in India are interesting,[506,507] these studies did not evaluate the efficacy of this intervention in comparison with colostrum and breast milk feeding, nor would it have been ethical to do so. These alternative strategies to breast milk feeding cannot be recommended presently but merit careful controlled evaluation with appropriate endpoints and outcomes as possible interventions in settings in which breast milk feeding is not possible or is inadvisable. Thus, consonant with the recommendations of the WHO,[498] the mainstay of prevention and treatment of hypoglycemia in developing countries must clearly remain early and exclusive breastfeeding and the use of expressed breast milk in other circumstances.

Breastfeeding

BACKGROUND. Breastfeeding is a foundational practice for appropriate care and feeding of newborn infants. A wide variety of benefits of breastfeeding have been well documented, including reduced risk of hypothermia, hypoglycemia, necrotizing enterocolitis, omphalitis, acute respiratory infections (ARIs), diarrhea, and septicemia.[511] Benefits of breastfeeding on infant and child health and development have also been extensively reviewed recently.[60,512] Several studies have effectively demonstrated reduced rates of morbidity and mortality in early infancy with exclusive breastfeeding in community settings in developing countries.[513–519] However, there are relatively few studies that have principally evaluated the impact of breastfeeding on neonatal outcomes. Huffman et al[511] recently reviewed the evidence in this regard and concluded that early and exclusive breastfeeding played an important role in reducing neonatal mortality, particularly after the first week of life. There is also additional evidence linking lack of exclusive breastfeeding with increased risk of early-onset[520] and late-onset neonatal sepsis.[521]

COMMUNITY-BASED EVIDENCE. Our review identified several studies that addressed the issue of impact of breastfeeding practices on perinatal and neonatal outcomes in developing countries. These studies were mostly from developing-country hospital-born cohorts[220,505,522–525] (Table 31), although 2 other reports principally provided community-based data.[526,527] These studies consistently showed reduced rates of morbidity (eg, diarrhea, pneumonia) and mortality associated with breastfeeding. The largest systematic review available on the relationship of breastfeeding to infectious disease outcomes in developing countries is the WHO multicountry pooled analysis.[528] This study clearly indicated that those infants <2 months old who were not breastfed had significantly higher mortality (OR: 5.8; CI: 3.4–9.8) due to infectious diseases than breastfed infants.

Although a number of barriers to effective breastfeeding in the neonatal period have been identified,[529–532] including reduced tendency to breastfeed LBW infants,[533] there is ample evidence that culturally appropriate behavior-change communications strategies can increase immediate and exclusive breastfeeding rates[59,61,62,531,532,534–536] (Table 32). In particular, recent data from India convincingly demonstrate the benefit of community strategies for promotion of breastfeeding in terms of reducing diarrhea morbidity and preventing growth faltering.[537]

CONCLUSIONS. Despite the lack of RCTs evaluating the impact of breastfeeding on neonatal outcomes, there is overwhelming evidence in support of a variety of perinatal and neonatal health benefits from breastfeeding. All newborn infants in developing countries, especially in domiciliary settings, must receive colostrum and exclusive breastfeeding, and intervention programs must place substantial em-

TABLE 31. Breastfeeding

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
WHO Collaborative Study Team[528]	Studies from Brazil, The Gambia, Ghana, Pakistan, The Philippines and Senegal; pooled analysis of existing studies	Multiple studies evaluating exclusive breastfeeding versus mixed or formula feeding and providing data on outcomes in infancy were combined in this pooled analysis.	Pooled OR for mortality in nonbreastfed individuals was 5.8 (CI: 3.4–9.8) for infants <2 mo of age.
Coutsoudis et al[724]	South Africa; urban hospital setting; PCS	549 women-infant pairs were studied; 1 cohort of infants was never breastfed ($n = 156$), a second cohort was exclusively breastfed ($n = 103$), and a third cohort received mixed feeding ($n = 288$). Among 549 infants, 3 distinct groups were studied: (1) those who were exclusively breastfed, (2) those who were given mixed feeds, and (3) those who were never breastfed.	Breastfed and nonbreastfed infants had comparable rates of HIV infection (acquired from mothers who were HIV positive). Exclusive breastfeeding to 3 mo or longer was associated with a significantly lower risk of infection (hazard ratio: 0.52; CI: 0.28–0.98, $P < .04$). Never having breastfed also carried a risk of infection similar to mixed feeding (0.85, CI: 0.51–1.42, $P = 0.53$).
Kumar et al[525]	India; urban hospital setting; PCS	50 newborns were enrolled in the study. group 1 ($n = 25$) was exclusively breastfed (EBF); group 2 ($n = 25$) was mixed fed (MF).	Although birth weights in both groups were comparable, group 1 infants had significantly greater weight gain from the second month of life onwards ($P < .01$). EBF infants had 40 sickness episodes per 100 child-mo as compared to 69 per 100 child-mo in group 2. Diarrheal episodes were 20 per 100 child-mo in group 2 as compared to 6 per 100 child-mo in group 1 ($P < .01$). Cases of pneumonia, otitis media and hospitalization were also more common among MF infants than EBF infants (4 vs 3; 3 vs 1; and 5 vs 2, respectively), although the sample size was too small to measure significance.
Augustine et al[524]	India; hospital setting; RCS	Mortality and morbidity statistics using the records ($n = 169$) of all the infants (60 preterm and 109 term) admitted during the first 7 d of life in a rural pediatrics ward over 1 y were analyzed.	Exclusive breastfeeding was associated with the lowest rate of mortality (29%), compared with infants not yet fed (64%) or those receiving sugar water or cow's milk with or without breastfeeding (43%).
Singh et al[526]	India, urban and rural settings; Cross-sectional survey	Data from a cross-sectional survey on the relationship between colostrum and neonatal and post-neonatal deaths, in which a cohort of newborn infants ($n = 826$) were followed up, was analyzed for mortality patterns.	In the rural high socioeconomic group, no neonatal deaths were found among the subgroup that received colostrum, and 8.2% of neonates died in the subgroup that did not receive colostrum. As a general conclusion, 1.7% of urban neonates and 2.6% of urban postneonates who received colostrum died, compared with 6.3% and 7.1%, respectively, who did not receive colostrum. In rural areas, comparable neonatal and postneonatal death rates were 1.7% and 1.7%, respectively, for infants who received colostrum, and 7.4% and 3.5%, respectively, for infants who did not receive colostrum.
Victora et al[523]	Brazil; urban hospital setting; CCS	Cases ($n = 357$) in which young infants had died of infections were identified through coroner's records. 2 controls were matched to each case for age and socioeconomic status ($n = 714$).	Compared with infants who were exclusively breastfed, those who were mixed-fed (given formula or cow's milk in addition to breast milk) had 4.2 times the risk of death from diarrhea (CI: 1.7–10.1), whereas those who were completely weaned (not receiving any breast milk) had a risk 14.2 times higher (CI: 5.9–34.1). Compared with exclusively breastfed infants, mixed-fed infants and completely weaned infants had 1.6 times (CI: 0.7–3.6), and 3.6 times (CI: 1.7–7.5) the risk of death from respiratory infections.

TABLE 31. Continued

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Habicht et al[527]	Malaysia; urban and rural settings; RCS	Sample consisted of 5357 births between 1940 and 1975, with an average IMR of 47.8 infant deaths per 1000 live births. Sample was restricted to babies who could have lived until the end of the at-risk period. 83% of infants were fully breastfed.	The effects of breastfeeding on infant mortality were reported for 3 sub-periods of infancy: 8–28 d, 29 d-6 mo, and 7–12 mo. Reductions in deaths per 1000 infants per added month of full breastfeeding were 68.6 (CI: 41.1–96.1), 24.9 (CI: 13.4–36.4), and 3.4 (CI: 1.6–5.2) for the periods 8–28 d, 29 d-6 mo, and 7–12 mo, respectively. Reductions in deaths per 1000 infants per added month of partial breastfeeding were 21.9 (CI: –7.9–51.7), 11.2 (CI: 0.2–22.2), and 1.7 (CI: 0.4–3.0) for the 3 time periods, respectively.
Narayanan et al[505]	India; urban hospital setting; RCT	A total of 226 LBW infants were randomly assigned to 1 of 4 intervention groups. Group 1 (n = 57) was fed raw expressed human milk only; group 2 (n = 56) was fed human milk subjected to holder pasteurization. Group 3 (n = 56) was fed raw milk from 9 AM until 9 PM (5 feeds) and formula for 3 feeds at night. Group 4 (n = 57) was fed pasteurized human milk from 9 AM until 9 PM and formula for the remaining 3 feeds.	There was a 68% reduction in neonatal infection rates in group 1 (10.5%) compared to group 4 (33%); however, sample size was too small for statistical significance.
Clavano[522]	Philippines; urban hospital setting; PCS	9886 newborn infants were followed up to assess the relationship of neonatal mortality and diarrhea to feeding patterns.	Of the 138 infants with diarrhea, 90% were formula fed, 6% were partially breastfed, and 4% were exclusively breastfed. Mode of infant feeding was also significantly related to mortality. Of the 67 infants who died, 96% were formula fed, 1% was partially breastfed, and 3% were exclusively breastfed. After rooming-in and formal breastfeeding policies were introduced, the proportion of infants exclusively breastfeeding increased by 135%, and the incidence of death among clinically infected newborns dropped by 95.3%.

phasis on this component. Several authors have demonstrated that it is possible to improve breastfeeding practices through culturally appropriate behavior-change communications. There is a need, however, for enhanced understanding of barriers to early, exclusive breastfeeding in many settings, leading to effective development and implementation of breastfeeding promotion programs.

Prevention and Treatment of Ophthalmia Neonatorum

BACKGROUND. Ophthalmia neonatorum is caused primarily by *Neisseria gonorrhea* or *Chlamydia trachomatis*. The prevalence of ophthalmia neonatorum in developing countries is uncertain. Before the introduction of preventive therapy, this condition was recognized to affect between 1% and 15% of newborn infants in Europe and 9% of newborn infants in the United States.[538] Transmission rates from mothers with gonococcal cervicitis to their offspring range from 30% to 50% in the absence of prophylactic ocular treatment,[14] whereas transmission ranges from 18% to 61% for chlamydia.[539] In developing countries such as Kenya, where rates of maternal STDs are high, rates of gonococcal ophthalmia range from 15% to 34%.[540,541]

A variety of interventions have been evaluated for prevention of ophthalmia neonatorum in developed countries, mostly in hospital settings, and have largely focused on the prevention of gonococcal infections.[542–545] These studies have suggested that silver-nitrate, tetracycline, or erythromycin ointments given prophylactically are equivalent in efficacy.[546,547] The WHO recommends 1% silver-nitrate solution, 1% tetracycline ointment, or 2.5% povidone-iodine within 1 hour of delivery.[14,16,548] The American Academy of Pediatrics also considers 0.5% erythromycin ointment as standard therapy, in addition to silver nitrate or tetracycline.[549] In the presence of proper prophylactic treatment, gonococcal ophthalmia develops infrequently. However, silver nitrate is not effective if used after infection has been established, which may help to explain the higher risk of gonococcal eye infections observed in association with PROM. For infants born to mothers with confirmed gonorrhea, parenteral treatment with

TABLE 32. Breastfeeding Promotion and Education

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Jakobsen et al[62]	West Africa; suburban setting; RCT	1226 pregnant women who gave birth to 1250 children were randomized to 1 of 2 groups. Mothers in the intervention group (n = 659) were given individual health education sessions at the local health center on their routine visits (ie, first antenatal visit, vaccination sessions in weeks 6, 10 and 14, and when the child reached the age of 9 mo). Mothers in the control group (n = 591) were not exposed to these messages. Intervention messages encouraged breastfeeding for 2 y, avoidance of introducing weaning foods and water for 4–5 mo, and continued breastfeeding for ill children. Family-planning information was also included.	Significantly more mothers in the intervention group had had an intrauterine device inserted (rate ratio = 2.45 (CI: 1.27–4.70) compared with the control group. However, mothers who had an intrauterine device inserted did not breastfeed longer compared with mothers who reported not to have had an intrauterine device inserted.	Introduction of weaning foods was significantly delayed in the intervention group compared with the control group (incidence rate 1.22; CI: 1.05–1.42). More children in the intervention group (31.1%) compared to controls (24.8%) were almost exclusively breastfed at 4 mo of age (OR: 1.18; CI: 1.03–1.38).
Morrow et al[61]	Mexico; periurban setting; RCT	130 pregnant women were randomized to 1 of 3 groups. Group 1 (n = 44) received 6 visits by a peer counselor. Group 2 (n = 52) received 3 visits by a peer counselor. Group 3 (n = 34) was the control group; women in this group were referred to a physician for lactation problems.	There were significantly more females who were exclusively breastfeeding their infants in the intervention groups than the control group. Duration of any breastfeeding (>3 mo or >6 mo) was significantly greater in the intervention group than the control groups (P = .024).	Control infants had a significantly higher risk of diarrhea than those in the intervention groups (OR: 2.1; 90% CI: 1.11–4.04; P = .029).
Lutter et al[59]	Brazil; urban hospital setting; PCS	442 women were enrolled in the study; 236 women delivered at the program hospital and 206 delivered at the control hospital. The intervention hospital had an active breastfeeding promotion program, characterized by rooming-in, early initiation of breastfeeding and breastfeeding assistance and talks during hospitalization. The control hospital had no such programs.		The median duration of exclusive breastfeeding was 75 d among women in the program hospital compared with 22 d in the control hospital. At 1 mo, the probability of exclusive breastfeeding was 0.64 in the program group compared with 0.39 in the control group.
Haider et al[531]*	Bangladesh; urban setting; cross-sectional knowledge, attitudes, and practices survey	Study area covered 30 000 households; a random sample of households with infants ages 0–6 mo (n = 1100) were selected. Mothers were interviewed at home. The WHO classification was used to describe infant feeding practices.		93% of mothers fed their infants colostrum during the first 3 d of life. However, only 8% fed colostrum as the first food. 97% claimed they had heard the term "exclusive breastfeeding" and understood it but 70% wrongly perceived it to mean giving the baby breast milk and water. 33% and 5% of infants in their first and fifth mo of life, respectively, were breastfed exclusively.
Haider et al[532]*	Bangladesh; urban setting; community-based RCT	40 adjacent zones were randomized to control or intervention groups. Women were enrolled during the last trimester of pregnancy. 15 house-based counseling visits were scheduled, with 2 visits in the last trimester, 3 during the early postnatal period (1 within 48 h, 1 on day 5, and 1 between days 10 and 14), and every 2 wk until the infant was 5 mo old. Peer counselors were local mothers who received 10 d of training.		363 women were enrolled in each group. Peer counseling significantly improved breastfeeding practices. For the primary outcome, the prevalence of exclusive breastfeeding at 5 mo was 202/228 (70%) for the intervention group and 17/285 (6%) for the control group (mean difference: 64%; CI: 57–71%; $P <$ .0001). For the secondary outcomes, mothers in the intervention group initiated breastfeeding earlier than control mothers and were less likely to give prelacteal and postlacteal foods.

* Data are from the same trial.

ceftriaxone is recommended as first-line therapy by the WHO[548] and the American Academy of Pediatrics,[549] although penicillin G can be considered if resistant strains are unlikely. Silver nitrate has been shown to be equivalent to tetracycline or erythromycin ointments for prevention of chlamydia conjunctivitis.[539,545] Thus, systemic treatment with erythromycin is also needed to prevent progression to chlamydial pneumonia.

COMMUNITY-BASED EVIDENCE. Our search identified 2 studies from developing countries (see Table 33) on prevention and treatment of ophthalmia neonatorum. Both were undertaken in urban hospital settings.[541,550] In 1 study, povidone-iodine was superior to silver-nitrate drops and to costlier erythromycin ointment.[550] In another study, tetracycline ointment was superior to silver-nitrate drops.[541]

CONCLUSIONS. Evidence for the benefit of prophylaxis with silver-nitrate drops, tetracycline ointment, or erythromycin ointment to prevent ophthalmia neonatorum is well established, based largely on developed-country studies. Scarce data from developing countries suggest that povidone-iodine is also effective, and this agent is recognized by the American Academy of Pediatrics as a first-line prophylactic therapy. Thus, choice of agent may be less important than wide-scale implementation of this intervention, which must form part of primary neonatal management packages, particularly in areas endemic for sexually transmitted diseases (STDs) due to gonorrhea. In areas with low rates of gonococcal infections in pregnancy, the benefits of routine prophylaxis relative to other newborn interventions may be questionable. Although local gonococcal resistance rates should be considered, local availability, acceptability, and cost of the various agents generally will be primary determinants in choice of agent. Overall, the evidence in support of prophylaxis for chlamydial infections is less clear.

Vitamin K Prophylaxis

BACKGROUND. Vitamin K prophylaxis in neonates for prevention of IVH is well established. Two Cochrane reviews have addressed the role of vitamin K prophylaxis in neonatal health. Puckett and Offringa,[551] in a Cochrane review of prophylactic vitamin K for prevention of IVH, also concluded that a single dose (1.0 mg) of intramuscular (IM) vitamin K after birth is effective in the prevention of classic hemorrhagic disease of the newborn (HDN), and IM or oral (1.0 mg) vitamin K prophylaxis improves biochemical indices of coagulation status at 1 to 7 days. However, neither IM nor oral vitamin K has been tested in randomized trials with respect to the effect on late HDN, and oral vitamin K, in either single or multiple doses, has not been tested in randomized trials for its effect on either classic or late HDN. Crowther and Henderson-Smart,[552] in a Cochrane review of vitamin K administration to pregnant women before preterm delivery, concluded that antenatal vitamin K was associated with a nonsignificant trend toward reducing all grades of periventricular hemorrhage (RR: 0.82; 95% CI: 0.67–1.00), particularly severe (grades 3–4) disease (RR: 0.75; CI: 0.45–1.25). This trend disappeared when poorer-quality trials were excluded. It was concluded that vitamin K administered to women before very preterm birth has not been shown to significantly prevent periventricular hemorrhage.

Although well established in developed countries, the incidence and implications of vitamin K defi-

TABLE 33. Prevention and Treatment of Ophthalmia Neonatorum

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Isenberg et al[550]	Kenya; urban setting; RCT	3117 newborns were enrolled and randomized to 1 of 3 groups to receive 2.5% povidone-iodine solution ($n = 1076$), 0.5% erythromycin ophthalmic ointment, ($n = 1112$), or a drop of 1% silver-nitrate ophthalmic solution ($n = 929$).	13% of the infants in the povidone-iodine group, vs 17.5% of the infants in the silver-nitrate group ($P < .001$), and 15.2% of the infants in the erythromycin group ($P = .01$) had infectious conjunctivitis. Povidone-iodine was more effective against *Chlamydia trachomatis* than was silver nitrate ($P < .001$) or erythromycin ($P = .008$). Noninfectious conjunctivitis was less frequent among povidone-iodine-treated infants (9.7%) than those treated with silver-nitrate (13.9%, $P < .001$) or erythromycin group (13.3%, $P = .004$). Incidence of *N gonorrhoeae* and *Staphylococcus aureus* infections was similar in the 3 groups.
Laga et al[541]	Kenya; urban setting; QT	2732 infants were enrolled in 1 of 2 groups to have either 1% silver nitrate ($n = 1233$) or 1% tetracycline ($n = 1499$) instilled in their eyes. A historical cohort of newborns who did not receive eye prophylaxis were included as controls.	Infection rates of gonococcal ophthalmia neonatorum in newborns exposed to *N gonorrhoeae* at birth were 7.0% in those receiving silver nitrate and 3.0% in those receiving tetracycline (CI: −3.4 to 11.4%). As compared with historical controls, the incidence of gonococcal ophthalmia neonatorum decreased 83% and 93% among infants treated with silver nitrate and those treated with tetracycline, respectively.

ciency in developing countries has received little attention. In a national hospital-based survey in Thailand, the incidence of vitamin K deficiency was found to be 35 cases per 100 000 births.[553] In contrast, a community hospital–based study in rural Thailand found the incidence to be as high as 72 cases per 100 000 births.[554] There are very few community-based data on vitamin K deficiency or HDN from either Africa or south Asia.

COMMUNITY-BASED EVIDENCE. Our review could not identify any community-based vitamin K intervention trials.

CONCLUSIONS. Vitamin K prophylaxis is a well-established intervention for prevention of IVH and early HDN in newborns in developed countries. The preferred route is IM administration, whereas the efficacy of the oral route needs additional investigation. There is no definitive evidence that administering prenatal vitamin K to pregnant women entering preterm labor can prevent IVH in the neonate, but this intervention warrants additional investigation. Moreover, studies are needed in developing-country community settings to identify cost-effective methods of implementing vitamin K interventions.[555]

Hepatitis B Vaccination

BACKGROUND. Disease due to hepatitis B virus (HBV) infection is one of the most prevalent public health problems worldwide. An estimated 350 million people are HBV carriers, and >1 million deaths each year are attributed to the virus.[556,557] The hepatitis B surface antigen (HBsAg) carrier rate in the general population in Taiwan was reported to be 15% to 20%,[558] whereas the prevalence of HBsAg positivity in Bangladesh was highest in 5- to 9-year-olds (8.5%), and simultaneous infection with hepatitis D virus was common (24.4%), particularly in older age groups.[559] Dusheiko et al[560] reported a hepatitis B carrier rate of 5.5% to 14% in the southern African population.

Hepatitis B immunization prevents chronic HBV carrier states and, subsequently, chronic liver disease in adulthood. However, Wong et al[561] found that the incidence of preterm birth, PPROM, SGA births, neonatal jaundice, fetal distress, perinatal asphyxia, congenital abnormalities, gastrointestinal tract abnormalities, and perinatal mortality were similar among pregnant women with and without serologic HBsAg positivity. Thus, the benefits of hepatitis B vaccination are long-term and most evident well after the neonatal period.

COMMUNITY-BASED EVIDENCE. Seven studies were identified that discussed programs implementing hepatitis B vaccination in developing-country communities; the 2 main studies were conducted in Taiwan and The Gambia[558,562–567] (Table 34). In general, incorporation of hepatitis B immunization into the EPI program of various countries was highly successful and effective. Hepatitis B vaccination programs were not only effective in preventing perinatal and early horizontal transmission of HBV but also resulted in decreasing mortality due to fulminant hepatitis and reduced development of childhood hepatocellular carcinoma. One study in South Africa,[568] however, determined that the intervention was not effective. Some reasons for the lack of effectiveness were given, and the authors proposed that the problems they identified were likely to be faced by other programs in developing nations. Importantly, they found that program participants had difficulty in complying with WHO recommendations that the first dose of hepatitis B vaccine be given as soon as possible after birth. Administering all 3 doses within reasonable limits of the recommended vaccine schedule is often difficult in rural areas, where distances to clinics are great and mobile outreach clinics are impeded by poor road conditions. Moreover, the birth dose may be particularly difficult given various proscriptions against seeking care for newborns outside the home in the formal health sector, particularly for early postnatal care.[439,569–571] Providing appropriate training to village health workers (VHWs) in The Gambia to deliver heat-stable vaccines in a Uniject device, however, was shown to be a cost-effective and reliable method for hepatitis B vaccination in rural settings.[572] This alternative means of delivering the intervention may facilitate resolution of the above-mentioned problems with traditional hepatitis B vaccination and may be an effective way to improve coverage and seroconversion rates.

CONCLUSIONS. Hepatitis B vaccine is administered universally at birth in developed countries. Considering the high risk of hepatitis B infection in many developing countries and the efficacy of the hepatitis B vaccine, policies regarding routine immunization need to be developed and implemented urgently in developing countries endemic for HBV infection. It is important to recognize, however, that evaluating the success of integrating hepatitis B vaccination into the EPI is more complex than for many other diseases. Because many infected children do not have any recognizable signs of illness, serologic surveys, rather than disease surveillance, will be needed to monitor the success of immunization programs. The appropriate field methodology for such surveys must be developed and standardized. The true benefit of such programs also requires measurement of the reduction in long-term sequelae of infection.

The total financial burden derived from both the direct and indirect costs of HBV detection and vaccination must be weighed critically in light of multiple health problems and competing agendas in resource-poor countries. However, support from donor agencies such as the Bill & Melinda Gates Foundation and the Children's Vaccine Program, which has initiated aid for hepatitis B vaccination in a number of countries, could help to make immunization against HBV, a proven intervention for benefit later in life, a reality.

Neonatal Vitamin A Supplementation

BACKGROUND. The significant public health benefits of vitamin A supplementation on child mortality in developing countries[210] are well established. There is much interest in the potential benefit of neonatal vitamin A supplementation on neonatal and infant outcomes, given the widespread subclinical vitamin A deficiency that exists among pregnant

TABLE 34. Neonatal Hepatitis B Vaccination

Source	Location and Type of Trial	Intervention	Program Impact
Chen et al[562]; Kao et al[567]; Chen et al[563]	Taiwan; community-based QT	In July 1984, a nationwide vaccination program was started. Preparatory work was done 1 y before the program started. It included education of doctors, allied health workers and public laboratory facilities in testing HBsAg and hepatitis B virus "e" antigen (HBeAg). A confidential registration data bank was formed. Infants born to HBsAg-positive mothers were given the vaccine at ages 1, 5, and 9 wk and then a booster at 12 mo. Infants born to mother testing positive for both antigens received a hepatitis B immunoglobulin within 24 hours along with the vaccines.	87% of the children received at least 3 doses of vaccine. The overall prevalence rate of HBsAg decreased from 9.8% in 1984 to 1.3% in 1994 in children <10 y of age. A statistically significant decrease was observed in every age group between 1 and 10 y. The overall prevalence rate of HBeAg was 26% in 1984, 15% in 1989 and 4% in 1994. The average annual incidence of hepatocellular carcinoma in Taiwanese children aged 6–14 y declined from 0.7 per 100 000 children in 1981–1986 to 0.36 per 100 000 in 1990–1994. The average mortality associated with fulminant hepatitis in infants from 1975–1984 was 5.36/100 000 infants (range: 2.9–6.7), which decreased to 1.71/100 000 (range: 0.3–4.6) for the period 1985–1998. Thus, the mortality rate decreased threefold after the vaccination program.
The Gambia Hepatitis Study Group[566]; The Gambia Hepatitis Study Group[565]; Montesano[564]	The Gambia; community-based QT	Children (n = 60 000) were divided into 2 groups. 1 group received routine EPI vaccination, and the other received routine EPI vaccination plus the hepatitis B vaccine. This continued from 1986–1990, after which all children were given hepatitis B vaccine and it became a part of the standard EPI. The first dose was given at the same time as BCG vaccine (ie, during the first month of life). The second dose was given along with a first dose of triple antigen at 2 mo of age or later. The third dose was given with the third dose of triple antigen at 4 mo of age or later. A minimum interval between doses was fixed at 4 wk. A cohort of 1000 children was followed long-term to measure immunogenicity.	The coverage survey showed that 98% of children aged 12–18 mo had received the first dose, 94% had received the second dose and 74% had received the third. In 94% of children, immunization produced protective levels of antibodies at 1 y of age. As a result of the vaccination program, protection against infection was >80% and the protection against carriage status was >90%.
Odusanya et al[725]	Nigeria; community-based QT	Immunization and preprimary health care services were commenced for children (n = 327) in a rural community in Nigeria. Hepatitis B vaccine was administered at birth and then in a single injection with diphtheria-tetanus-pertussis vaccine at 6 wk of age and another at 3 mo of age.	2 y after the program was started, the immunization coverage rates were 94% for BCG, 88% for diphtheria-tetanus-pertussis vaccine (third dose) and 82% for measles. Hepatitis B coverage for all 3 doses was 58%.
Ariwan[726]	Indonesia; community-based QT	Healthy Start Program in Indonesia involved a visit by the village midwife between 1 and 7 d after birth to provide Hepatitis B vaccination and maternal care/education.	Hepatitis B vaccination rate increased from 0% in 1990 to 84% in 1996. IMR decreased from 73/1000 to 55/1000 live births, due to other aspects of the maternal care and education program.
Poovorwan et al[727]	Thailand; community-based QT	Hepatitis B vaccination has been an integral part of the EPI since 1992. In each of 5 representative provinces, 400–488 healthy immunocompetent infants ranging from 6 to 18 mo of age were evaluated by examining their sera for viral hepatitis markers.	The coverage rate of hepatitis B vaccine was 71.2% to 94.3%. The number of individuals undergoing complete course of hepatitis B vaccination increased fourfold. Only 0.7% of children born after the implementation of the EPI strategy were HBV carriers.
Sutanto et al[572]	Indonesia; community-based QT	During the study, village midwives (n = 110) used Uniject devices, rather than the standard disposable or reusable syringes. The midwives were provided with these devices in an outreach carrier box. After they picked up these boxes the midwives were allowed to keep them under ambient conditions (27°C average, range of 25−32°C) for 1 mo. Nurses administered 10 000 sterile injections in home-based settings during the trial.	Potency test of the Uniject compared to the standard injection after 1 month showed that the TT vaccine had lost 6% of its potency, while the hepatitis B vaccine had suffered a 1% drop in potency. Seroconversion rates were identical in children immunized using the Uniject vs the standard vaccine method. Total cost per child immunized using the Uniject device was US $6.57 vs US $7.19 using a standard disposable syringe at the health center.
Schoub et al[568]	South Africa; rural setting; community-based QT	All infants born in 1989 in a self-governing region of the Transvaal were immunized according to 2 schedules: (1) early schedule = birth, 3 mo and 6 mo and (2) late schedule = 3 mo, 4.5 mo and 6 mo. Those who were not given vaccine according to any 1 of these schedules were classified as unscheduled.	Only 6.6% of vaccine recipients were vaccinated according to the schedules, whereas 93.4% were given vaccines in an unscheduled manner. There was no difference in seroconversion to the surface antigen between the 2 groups.

women and lactating mothers in many developing-country settings, the demonstrated positive impact of antenatal vitamin A supplementation on maternal mortality[218] (see "Antenatal Vitamin A Supplementation"), and the demonstrated benefits of vitamin A supplementation during infancy and childhood.[94]

Vitamin A supplementation has been investigated in selected subsets of newborns in developed countries, such as in VLBW infants, to prevent chronic lung disease.[573–575] However, the benefit and cost-effectiveness of such interventions in developing-country settings, in which survival rates of VLBW infants are low, remain unclear; few VLBW infants survive to develop chronic lung disease.[419]

COMMUNITY-BASED EVIDENCE. We identified 3 studies that evaluated the impact of vitamin A supplementation during the neonatal period on neonatal and/or infant outcomes in developing countries in both rural and urban settings (Table 35). No study showed a reduction in mortality during the neonatal period,[576,577] and the 3 studies showed a mixed impact on infant mortality.[576–578] Results are forthcoming from an additional large-scale trial of neonatal vitamin A supplementation in Zimbabwe.

CONCLUSIONS. Neonatal supplementation with vitamin A holds some promise for reducing mortality during or shortly after the neonatal period, and there is some evidence of reduced mortality during infancy.[576] These results, coupled with emerging evidence that antenatal vitamin A supplementation may reduce maternal mortality,[218] indicate the need for additional research in this area. A critical factor may be the timing of vitamin A supplementation, with potentially increased impact with early administration.[577] The role of supplementation in populations with relatively high rates of HIV infection also requires investigation.

KMC

BACKGROUND. KMC refers to the technique of positioning and skin-to-skin care of LBW infants after birth and was pioneered by Rey[579] from Colombia. After initial skepticism,[580] the technique has now found widespread acceptance and has been used extensively in both developed and developing countries. Despite numerous intervention studies evaluating the technique, however, very few have used rigorous (eg, RCT) designs. A recent Cochrane review of KMC[581] identified 3 studies that met criteria for inclusion in their analysis, but the analysis was based largely on just 1 RCT.[582] The review found that neonates who were given KMC versus standard care had lower risk of nosocomial infection (OR: 0.49; CI: 0.25–0.93), severe illness (OR: 0.3; CI: 0.14–0.67), and lower respiratory tract disease (OR: 0.37; CI: 0.15–0.89) at 6-month follow-up. In addition, the proportion of infants who were not exclusively breastfeeding at discharge was reduced (OR: 0.41; CI: 0.25–0.68), as was the rate of maternal dissatisfaction with method of care (OR: 0.41; CI: 0.22–0.75). Infants given KMC also had gained more weight per day by discharge (weighted mean difference: 3.6 g per day; CI: 0.8–6.4). Despite these interesting data, because the results were largely based on a solitary RCT, it was concluded that there were insufficient data to recommend its routine use in LBW infants.

Since the Cochrane review noted above, Charpak et al[583] reported another RCT of KMC impact in a hospital setting. The intervention consisted of continuous skin-to-skin contact and nearly exclusive breastfeeding, and infants were followed until 12 months' corrected age. Risk of death tended to be lower in the infants given KMC (OR: 0.57; CI: 0.17–1.18) but was not significantly lower than the control infants given routine incubator care. Infection rates

TABLE 35. Neonatal Vitamin A Supplementation

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Humphrey et al[576]	Indonesia, urban hospital setting; RPCT	2067 newborn infants were allocated to receive 1 oral dose of 52 μmol vitamin A plus 23 μmol vitamin E (n = 1034) or placebo (<0.1 μmol vitamin A plus 23 μmol vitamin E) (n = 1033), on the first day of life.	Supplementation had no effect on NMR. The probability of survival during the first year of life, however, was greater in the vitamin A-supplemented than the control infants (OR: 0.36; CI: 0.16–0.87).
West et al[578]	Nepal, rural setting; DBRPCT	Newborns (n = 11 918) were randomized to either an intervention group (n = 6086) or a placebo group (n = 5832). Newborns in the intervention group received a single oral dose of vitamin A (15 000 retinol equivalent [RE] [~3 drops of oil]); newborns in the placebo group received 75 RE (250 IU).	The cumulative OR of death after 4 mo of the supplementation trial suggested a modest protective effect for vitamin A (OR: 0.9) but this pattern then changed in the second year and the OR returned to 1.11 (CI: 0.86–1.42) after 24 mo; no impact overall on neonatal mortality was observed.
Rahmathullah et al[577]	India; rural setting; DBRCT	Infants (n = 11 619) were randomly assigned to receive either 24 000 IU of vitamin A twice within a 24-h interval beginning within 48 h of birth, or to receive a placebo.	Infants in the vitamin A group had a 22% reduction in total mortality (CI: 4–37%) compared with those in the placebo group. Vitamin A had an impact on mortality between 2 wk and 3 mo after treatment, with no additional impact after 3 mo.

were similar, although severity was judged to be higher in the control infants, and there was no difference in disability rates. Total days in the hospital were decreased in infants who weighed ≤1500 g at birth and received KMC.

An earlier 2-cohort study by Charpak et al[584] reported a higher RR of mortality in infants given KMC (RR: 1.9; CI: 0.6–5.8), although this risk reversed after adjusting for weight at birth and gestational age (RR: 0.5; CI: 0.2–1.2). Infants given KMC grew less in the first 3 months and had a higher proportion of developmental delay at 1 year. No significant differences were found in overall mortality rates between the 2 groups. The cohorts in the study, recruited from 2 different tertiary hospitals, showed many social and economic differences.

A nonrandomized, controlled study conducted in a remote Zimbabwe mission hospital without incubator care reported that survival of infants born weighing <1500 g improved from 10% to 50%, whereas that of infants 1500 to 1999 g improved from 70% to 90%.[585] Similar results were shown by another nonrandomized study from a secondary hospital in Mozambique. Of 32 infants weighing <1800 g, survival was 73% in 22 infants given KMC and 20% in 10 infants not given KMC ($P < .01$). It also has been suggested that infants given KMC discharged during the cold season may be more vulnerable to severe illness, especially lower respiratory tract infections, than those discharged during the warm season.[586] Another study on a small number of newborn infants with mild respiratory distress suggested that early introduction of KMC might have beneficial effects.[587]

Ramanathan et al[588] reported from their RCT in Delhi, India, that KMC neonates demonstrated better weight gain after the first week of life (15.9 ± 4.5 vs 10.6 ± 4.5 g/day in KMC and control groups, respectively; $P < .05$) and earlier hospital discharge (27.2 ± 7 vs 34.6 ± 7 days in KMC and control groups, respectively; $P < .05$). The number of mothers exclusively breastfeeding at 6-week follow-up in the KMC group was double that of the control group (12 of 14 [86%] vs 6 of 14 [43%]; $P < .05$).

COMMUNITY-BASED EVIDENCE. There are no data on the impact of KMC from community-based settings in developing countries. All studies reported from developing countries were conducted among medically stable LBW infants (typically <2000 g) in urban hospital settings (Table 36).

Two reports describe adaptation of the technique for use in the community.[589] In a pilot study in Bangladesh, CHWs were trained in community-based application of KMC (CKMC) and subsequently taught expectant and new mothers how to give KMC. Women were interviewed 1 month postpartum to evaluate their experience with CKMC. In all, 77% of mothers initiated skin-to-skin care, and 85% with LBW infants did so (37% were LBW). CKMC was adopted quickly and popularly in this community. Similarly, in Uttar Pradesh, India, promotion of CKMC through a community mobilization and behavior change communication program resulted in adoption of skin-to-skin care of newborns by >70% of families.[590]

CONCLUSIONS. Studies to date have suggested that KMC had a variety of beneficial effects on the health of LBW infants, including increased weight gain and exclusive breastfeeding rates and lower risk of nosocomial infection and severe illness. The literature also suggests that KMC promotes mother-infant bonding, improves newborn thermal control, shortens duration of hospital stay, results in earlier stabilization of physiologic and behavioral functioning, and may improve survival. This last claim is unproven and may be unrealistic, given that studies have all included medically stable infants.

Limited experience with adaptation of skin-to-skin care for use in the community in developing countries has been encouraging. There is an urgent need, however, to adapt the approach for various cultural settings and to further evaluate its acceptability, safety, and efficacy in developing-country community settings.[26,591] We feel that KMC must be viewed in its wider application to include even culturally appropriate variants such as co-bedding with the mother and skin-to-skin practice by caregivers other than the mother herself, particularly the father, because fathers, too, can provide effective thermal control in newborn infants to reduce the risk of hypothermia.[592] Given the paucity of resources and risk of hypothermia in domiciliary settings in developing countries, this intervention (or mode of newborn care) may be suitable for essential care of all newborns in the community as well as for high-risk situations such as the care of preterm, VLBW infants, and transport of sick newborns.

Topical Emollient Therapy

BACKGROUND. The skin barrier of preterm infants is compromised for a variety of reasons including developmental immaturity[455] and lack of vernix, which is produced near term during gestation and serves as a naturally protective cutaneous biofilm.[593] In addition, the skin barrier of preterm infants is easily injured,[594] and particularly in developing-country situations, the skin barrier of even term infants may be compromised as a result of intrauterine malnutrition.[595] Thus, the skin may serve as an important portal of entry for serious bacterial infections.[596] However, evidence from laboratory studies in animals and clinical trials in humans suggests that it may be possible to enhance skin-barrier function through application of topical emollients or oils, thereby improving health outcomes.

In experimental conditions, compromised epidermal barrier function and dermatitis in essential fatty acid (EFA)-deficient rodents was reversed by topical application of either purified EFAs or EFA-rich vegetable oils, particularly sunflower-seed oil.[597,598] Cutaneous absorption and metabolism of linoleic acid seemed largely responsible for the beneficial effects of sunflower-seed oil.[490,598–600] Topical therapy with sunflower-seed oil has also been found to correct cutaneous signs of EFA deficiency (ie, normalization of TEWL, resolution of dermatitis) in humans, including premature infants.[598,601,602] It has been ad-

TABLE 36. KMC

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Cattaneo et al[731]	Ethiopia, Indonesia, and Mexico; multicenter urban hospital setting; RCT	149 LBW neonates were randomly assigned to KMC (almost exclusive skin-to-skin care after stabilization), and 136 LBW neonates to conventional methods of care (warm room or incubator care).	Overall scores on mother's sense of competence were better in the KMC than in the control group (weighted mean difference: 0.31; CI: 0.13–0.50) On the other hand, overall scores on mother's perception of social support during the infant's stay in the NICU were worse in the KMC group than in the control group (weighted mean difference −0.18; CI: −0.35 to −0.01).	Lower rates of not exclusively breastfeeding were recorded at discharge (RR 0.41; CI: 0.25–0.68).
Charpak et al[582]*	Colombia; urban hospital setting; RCT	In an urban tertiary hospital, 746 newborns were randomized to receive either KMC (n = 382) or traditional care (n = 364).		Significantly lower rates of nosocomial infection (OR: 0.49; CI: 0.25–0.93) and severe illness at 6 mo follow-up were found in the KMC group. The risk of dying was similar in both groups (RR = 0.59; CI: .22–1.6), and no differences were found in growth indices. Hospital stay after eligibility was shorter in the KMC group, primarily for infants ≤1800 g.
Sloan et al[732]	Ecuador; urban hospital setting; RCT	300 newborns were randomized to KMC (n = 140) or incubator/thermal cot care (n = 160).		Trial was stopped early because of a significantly lower rate of severe morbidity in the KMC group ($P < .005$ at 6 mo).
Charpak et al[583]*	Colombia; urban hospital setting; RCT	A group of 746 newborns were randomized when eligible for minimum care, into KMC (n = 382) and "traditional" care (n = 364). Information on vital status was available for 93% of infants at 12 mo of corrected age. KMC consisted of skin-to-skin contact on mother's chest 24 h/d, nearly exclusive breastfeeding, and early discharge, with close ambulatory monitoring. Controls remained in incubators until the usual discharge criteria were met.		There was a "trend" toward lower risk of death among the KMC group, although the result was not significant (KMC: 11 [3.1%] of 339 infants died; control: 19 [5.5%] of 324 infants died; RR: 0.57; CI: 0.17–1.1). Growth index of head circumference was significantly greater in the KMC group, but the developmental indices of both groups were similar. Infants weighing ≤1500 g at birth and given KMC spent less time in the hospital then the group given standard care. There were similar numbers of infections in both groups, but infections in the KMC group were of lesser severity.
Ramanathan et al[588]	India; urban hospital setting; RCT	28 neonates with birth weights <1500 g were randomized into 2 groups, 1 receiving KMC and 1 receiving incubator care. The KMC group (n = 14) received KMC for 4 h per day in not more than 3 sittings. Infants received KMC after shifting from NICU and at home. Control infants received standard care. A Likert scale was used to assess mothers'/nurses' attitudes towards KMC.	The number of mothers exclusively breastfeeding at 6-wk follow-up was double in the KMC as compared to the control group (12/14 [86%] vs 6/14 [43%], respectively; $P < .05$).	KMC neonates demonstrated better weight gain after the first week of life (15.9 ± 4.5 g/d vs 10.6 ± 4.5 g/d in the KMC and control groups, respectively; $P < .05$) and earlier hospital discharge (27.2 ± 7 vs 34.6 ± 7 d in KMC and control groups, respectively, $P < .05$).
Kambarami et al[730]	Zimbabwe; urban hospital setting; RCT	74 infants (37 in each of 2 groups) were consecutively allocated to receive either KMC or incubator care.		KMC infants gained twice as much weight per day (20.8 vs 10.2 g; $P = .0001$); had shorter stays in the hospital (16.6 vs 20.7 d; $P = .0457$); and had a better survival rate (0% vs 9% deaths; sample size too small for significance).

vanced that these beneficial effects may be due to increased metabolism of lipids in the epidermis, including active fatty-acid transport by keratinocytes, which makes it possible for even the immature epidermis of preterm infants to metabolize lipids derived from topically applied emollients and to utilize them as nutritional building blocks for the formation of a healthy, functional epidermal barrier.[455,490,603,604]

TABLE 36. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Lincetto et al[731]*	Mozambique; urban hospital setting; PCS	2 cohorts of LBW (<2000 g) infants (n = 246) were enrolled. The first cohort (n = 149) was selected during the cold season and a second cohort (n = 122) was enrolled in the hot season. The intervention encouraged KMC at home. In 64%, routine follow-up exams after discharge were performed until infants reached a weight of 2500 g.		No seasonal differences in weight gain or the risk of complications were found in infants treated with KMC in the hospital. Risk of serious complications, including death (RR: 1.96; P = .02) and readmission (RR: 2.77; P = .04), was higher after discharge in the colder season because of mother's incomplete compliance with KMC and exposure to low temperatures.
Bergman[585]	Zimbabwe; mission hospital setting; PCS	KMC was introduced as the exclusive means of treating LBW infants (n = 126), without incubators and standard equipment for care of LBW neonates. Survival with KMC were compared to hospital survival data prior to the intervention, from 1983 to 1987.		The survival of babies born <1500 g improved from 10% to 50%, whereas that of infants 1500–1999 g improved from 70% to 90%. Overall survival rate was 63%.
Christensson et al[475]	Zambia; urban university hospital NICU; RCT	80 consecutive low-risk hypothermic infants with admission weight of >1500 g admitted in the NICU were randomly assigned treatment with skin-to-skin (STS) care by the mother (n = 41) or in an incubator (n = 39).		At 240 min, 90% of babies in STS group reached normal temperature (37.1–37.2°C), compared with 60% in the incubator group (P < .0001).
Lincetto et al[586]*	Mozambique; provincial hospital setting; PCS	KMC for LBW infants (n = 32) was introduced with limited resources and without an intensive care unit. Care included post-discharge follow-up visits to all infants <1800 g. Mothers of infants in the intervention group (n = 22) were taught skin-to-skin care and asked to observe other mothers to facilitate compliance. Control infants (n = 10) were given standard non-KMC care in the maternity ward.		Out of 32 LBW infants (<1800 g) admitted in 3 mo, survival was 73% in KMC and 20% in non-KMC infants (P < .01).
Charpak et al[584]	Colombia; 2 tertiary care hospitals, 1 offering traditional care and the other KMC; PCS	332 newborns weighing <2000 g and eligible for care in the minimal care unit were enrolled in either of 2 groups: 1 receiving KMC (n = 162), and 1 control group (n = 170). KMC infants eligible for MCU were discharged regardless of gestational age or weight, were kept 24 h/d in an upright position, attached to the mother's chest and receiving skin-to-skin contact until KMC was not tolerated anymore. Control babies from another facility were kept in incubators until they were discharged. Both groups were followed periodically up to the age of 1 y.		RR of death was found to be higher in KMC infants (RR: 1.9), though the reverse was found after adjusting for weight at birth and gestational age (RR: 0.5). There were no significant differences in overall mortality rates among the 2 groups. KMC infants grew less in first 3 mo and had a higher proportion of developmental delay at 1 y.

* Data are from the same trial.

Darmstadt et al[490] used a hairless-mouse model to demonstrate that the impact of topical therapy varies markedly with the product applied. A single application of sunflower-seed oil significantly improved skin-barrier function within 1 hour, and the effect was sustained 5 hours after application. In contrast, other vegetable oils tested (mustard, olive, and soybean oils) significantly worsened skin-barrier function (ie, increased TEWL) 1 and 5 hours after application and delayed recovery of a compromised skin barrier compared with control- or Aquaphor-treated skin. Moreover, a single application of mustard oil resulted in a variety of adverse ultrastructural changes in the epidermis under transmission electron microscopy, suggestive of toxicity.[490,605] Thus, given the widespread use of mustard oil for massage

of newborns, as documented in south Asia,[488,606] it seems that millions of newborns each year are being treated with potentially toxic applications to the skin.[488,490]

In clinical trials in developed countries, topical applications of epidermal barrier-enhancing emollients have been shown to decrease TEWL, improve skin condition, and minimize skin injury in extremely preterm infants.[490,594,607–609] However, topical therapy has had a variable impact on risk of infection. A pilot study at Stanford University (Stanford, CA) showed that twice-daily application of the ointment Aquaphor for the first 2 weeks of life to premature infants <33 weeks' gestational age resulted in improved skin condition and a reduction in episodes of culture-proven sepsis due to coagulase-negative staphylococci.[608] In another trial, Aquaphor therapy in neonates weighing <1500 g decreased the nosocomial bloodstream infection rate to 5.4 per 1000 patient-days, compared with 12.7 per 1000 patient-days during the preceding 16 months.[610] In contrast, a small CCS suggested that extremely preterm infants weighing <1000 g who were treated with topical petrolatum ointment were at increased risk for *Candida* infections,[611] and another report suggested that topical applications of Aquaphor might serve as a source for nosocomial infections with coagulase-negative staphylococci and Gram-negative organisms.[612] A recently completed multicenter US-based trial showed that Aquaphor therapy increased risk of sepsis with coagulase-negative staphylococci among neonates weighing 501 to 750 g (OR: 1.60; CI: 1.07–2.39); no effects were seen in neonates weighing 751 to 1000 g.[613] A Cochrane review of studies in developed countries concluded that prophylactic topical-ointment therapy increases the risk of coagulase-negative staphylococcal infection and any nosocomial infection.[614]

COMMUNITY-BASED EVIDENCE. Oil massage of neonates is a nearly universal practice in south Asia.[488,606] The typical timing (from the first days of life), frequency (typically 1–3 times daily), pattern (total body), and duration (throughout infancy and early childhood) of use suggest that the practice is an important event in daily child care, that significant time and resources are devoted to it, and that exposure of the infant's skin to the oil is significant. The most commonly used oil for infant massage is mustard oil, which, as noted above, is potentially toxic[490] and, when tainted with seeds of the weed *Argemone mexicana*, may cause the neurologic syndrome coined "epidemic dropsy."[615,616]

In India, topical therapy with corn oil improved thermoregulation (see also "Hypothermia Prevention and Management") of 5- to 7-week-old infants in the community,[491] and growth of hospitalized preterm infants was improved with sesame-seed oil therapy.[617] In Nepal, it was found that traditional oil massage with mustard oil, swaddling with a plastic swaddler, or KMC was equally effective in preventing hypothermia during the first 24 hours after birth (see Table 29).[473]

No community-based data are available on the effect of topical therapy on neonatal infections or mortality. Hospital-based studies have been concluded in Egypt and Bangladesh, and data have been reported from Egypt (Table 37). In Egypt, topical application of sunflower-seed oil 3 times daily to preterm infants <34 weeks gestational age (n = 51) at the Kasr El-Aini neonatal intensive care unit at Cairo University significantly improved skin condition (P = .037) and reduced the incidence of nosocomial infections (incidence rate ratio: 0.46; CI: 0.26–0.81; P = .007; adjusted for weight on admission, gestational age, and gender) compared with infants not receiving topical prophylaxis (n = 52) (see ref 732). In Bangladesh, preliminary data analysis suggested that emollient therapy of preterm infants <33 weeks gestational age 3 times daily with sunflower-seed oil or Aquaphor reduced the odds of neonatal mortality (OR: 0.75; C:I 0.57–0.98). Among infants weighing ≤1250 g, emollient therapy reduced the odds of mortality by 35% (OR: 0.63; CI: 0.46–0.87).[618]

CONCLUSIONS. Emollient therapy is a promising intervention, particularly for LBW infants in devel-

TABLE 37. Neonatal Topical Emollient Therapy

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Ahmed et al[618]	Bangladesh; urban hospital setting; RCT (preliminary report)	In a Special Care Nursery, neonates (n = 385) were randomized to topical application of sunflower oil or Aquaphor 3 times a day, or to the control group, which received standard nursery care.	Treated infants (sunflower-seed oil and Aquaphor-treated infants combined) had a significantly reduced risk of neonatal mortality (25%) (OR: 0.75; CI: 0.57–0.98). Among infants weighing ≤1250 g, emollient therapy reduced the odds of mortality by 37% (OR: 0.63; CI: 0.46–0.87).
Darmstadt et al[732]	Egypt; urban hospital setting; RCT	Neonates were randomized to 3 times daily topical application of sunflower oil (n = 51) or to usual nursery practice (control group) (n = 52).	Treatment with sunflower-seed oil resulted in a significant improvement in skin condition (P = .037) and a highly significant reduction in the incidence of nosocomial infections (adjusted incidence ratio: 0.46; CI: 0.26–0.81; P = .007) compared with infants not receiving topical prophylaxis (n = 52).

oping countries, although data to date are hospital-based. Data thus far are also restricted to LBW infants <33 to 34 weeks' gestational age, in whom the skin barrier is likely to be most highly compromised. Additional research is needed on the impact of this therapy in the community and among all newborns (without restriction based on birth weight).

Emollient therapy is inexpensive (~ $0.20 [US dollars] for a course of therapy in a preterm infant weighing 1.5 kg)[490] and technologically simple and can be delivered readily by health care workers and caregivers. Research suggests that the practice of oil massage is nearly universal in south Asia, and caregivers indicate a willingness to modify their behavior and apply an alternative oil that has skin barrier–enhancing properties.[488,606] Behavior-change communications may be an effective way to introduce the intervention more broadly by modifying what is already a well-entrenched traditional practice. Furthermore, in many communities, cadres of workers such as the *domin* or *naún* in India (and similarly, in Nepal) are designated to apply oil massage in the community to newborns, and working with them could enhance the feasibility and scalability of the intervention.[606]

Choice of emollient is important. Emollients containing a physiologic balance of epidermal lipids (3:1:1:1 molar ratio of cholesterol/ceramide/palmitate/linoleate) are optimal for barrier repair,[604,619] and tests of impact on neonatal outcomes are warranted using topical products with optimized effects on skin-barrier function. However, natural vegetable oils are readily available worldwide and may provide a simpler, inexpensive alternative that also warrants additional investigation as a more readily scalable and affordable intervention, particularly for use in the community.

Hyperbilirubinemia Screening

BACKGROUND. Hyperbilirubinemia is widespread among newborns. Almost 97% of all healthy newborn infants have biochemical hyperbilirubinemia (ie, serum bilirubin >17.1 μmol/L), and almost 65% may be overtly jaundiced. Jaundice tends to occur in term infants with serum bilirubin levels above ~85 μmol/L.[620] Although hyperbilirubinemia may not be a major direct cause of mortality in developing countries, delayed detection and therapy may predispose infants to bilirubin encephalopathy and kernicterus,[621,622] both of which are common causes of handicaps in developing countries.[419,623]

It is not the purpose of this review to discuss the numerous options for management of hyperbilirubinemia but rather to evaluate strategies for its early recognition in community settings. Management of this condition has been reviewed extensively, and interventions such as phototherapy and medical therapy (eg, phenobarbital, exchange transfusion, and management of underlying conditions such as sepsis, hemoglobinopathies, and blood-group incompatibilities) largely pertain to hospital settings.[624] Nevertheless, of the known risk factors for jaundice and bilirubin encephalopathy, prematurity and past history of hemolytic disease of the newborn are important. Frequent and exclusive breastfeeding must be encouraged, because it has been shown to reduce the propensity for hyperbilirubinemia, due at least in part to improved hydration status.[625,626]

Early detection of jaundice in developing countries would be significantly facilitated if first-line health workers at peripheral health facilities were able to accurately identify young infants with clinically significant jaundice who needed care at a referral-level facility. Several studies, mostly from developed countries, have found that bilirubin levels determined with a simple hand-held icterometer correlated to varying degrees with measures made by using more expensive and sophisticated instruments and standard techniques (ie, serum bilirubin measurement).[627–632] However, there has been considerable debate, even in developed countries, about whether the presence of jaundice can be determined reliably by using visual assessment and what cadres of individuals can perform visual assessments reliably. Although some investigators have found that clinical estimation of jaundice in newborns by neonatologists[633] or physicians or nurses[631,634,635] was highly correlated with serum bilirubin levels, others have questioned the ability of health care providers, including physicians and nurses, to diagnose clinical jaundice by visual estimation.[628,636]

COMMUNITY-BASED EVIDENCE. Our review identified 5 studies from developing countries that evaluated strategies for the early detection of neonatal hyperbilirubinemia (Table 38); however, none of these studies were in a rural setting (all were conducted in urban hospitals). Only 1 of these studies tested the accuracy of visual estimation of jaundice; Riskin et al[633] reported that neonatologists' visual estimates were highly correlated to measurements using a spectrophotometer (r: 0.682; $P < .001$).

All the other studies tested the accuracy of noninvasive techniques (eg, use of a hand-held icterometer or bilirubinometer) relative to laboratory serum bilirubin measurement. Bilgen et al[632] and Kumar et al[627] compared transcutaneous bilirubin readings by using a bilirubinometer to serum bilirubin, and both reported strong evidence of a linear correlation (r = 0.83 and 0.91, respectively). Two studies, 1 in Turkey and 1 in India, also found a significant positive correlation between icterometer measurement and serum bilirubin levels.[630,632] However, in Pakistan, Bhutta and Yusuf[629] found that transcutaneous bilirubinometry was much less effective than standard biochemical testing in accurately identifying hyperbilirubinemia, particularly among dark-skinned infants.

CONCLUSIONS. Simple methods including visual assessment of degree of jaundice by health workers and use of simple, hand-held icterometers hold promise for use at the community and primary care levels in developing countries, but additional studies are warranted. The role of visual inspection in the home by caregivers, particularly in areas with a relatively high prevalence of hyperbilirubinemia, has never been evaluated.

TABLE 38. Neonatal Hyperbilirubinemia Screening

Source	Location and Type of Trial	Intervention	Neonatal Hyperbilirubinemia Detection
Bilgen et al[632]	Turkey; urban hospital setting; QT	Transcutaneous measurements were obtained from newborns ($n = 96$) with a Minolta AirShield bilirubinometer and an Ingram icterometer and compared to serum bilirubin measures.	A linear correlation existed between serum bilirubin values and the readings on both the Minolta bilirubinometer ($r = 0.83$) and the Ingram icterometer ($r = 0.78$).
Riskin et al[633]	Israel; urban urban hospital setting; PCS	4 neonatologists were asked to estimate visually the level of bilirubin in a group of term clinically jaundiced infants ($n = 283$) before discharge from the nursery on the third day of life. Their clinical estimation was compared with actual measurement of serum total bilirubin from samples drawn simultaneously.	Clinical visual estimation of serum total bilirubin had a high correlation to actual serum bilirubin levels as measured by spectrophotometer ($r = 0.682$; $P < .001$).
Kumar et al[627]	India; urban hospital setting; RCT	Term babies ($n = 100$) were randomly selected for estimation of transcutaneous bilirubin (by Minolta AirShield bilirubinometer 101) and serum bilirubin levels by conventional diazo method. Babies needing phototherapy ($n = 40$) were randomized into 2 groups: (1) those having their transcutaneous bilirubin level measured from a covered area on the forehead, and (2) those who did not have a covered area on the forehead.	There was a linear correlation ($r = 0.9090$; $P < .001$) between serum bilirubin level and transcutaneous bilirubin level. In the babies requiring phototherapy, there was significant ($P < .001$) linear correlation between prephototherapy and postphototherapy readings, group 1 ($r = 0.69$) and group 2 ($r = 0.80$).
Bhutta et al[629]	Pakistan; urban hospital setting; QT	Transcutaneous bilirubinometry was compared with standard laboratory estimation of bilirubin level in normal jaundiced newborns ($n = 65$).	Transcutaneous bilirubinometry was not very effective in recognizing hyperbilirubinemia in comparison with biochemical testing, especially among dark infants. Although the correlation between the 2 methods was significant ($r = 0.66$; $P < .01$), the scatter was wide and the specificity was only 53%.
Narayanan et al[630]	India; urban hospital setting; QT	Effectiveness of the icterometer was evaluated in detecting neonatal hyperbilirubinemia in newborn infants ($n = 158$).	There was positive correlation between the readings on the nose and serum bilirubin levels ($P < .05$).

TBA/CHW Training

BACKGROUND. Although there is consensus that increased access to skilled health care, including a skilled birth attendant during delivery, is widely desired and likely to improve pregnancy outcomes,[16,24] approximately half of women and newborns lack access to skilled care.[18] Moreover, nearly two thirds of births worldwide take place in the home, and a large percentage of births in developing countries take place in the hands of untrained or trained TBAs. Given the projected absence of adequate cadres of skilled birth attendants in many countries for years to come and a potential role for TBAs and/or CHWs in health service delivery for newborn care, we evaluated the available evidence for the impact of TBA and CHW training on perinatal outcomes. CHWs typically differ from TBAs in education (higher) and age (younger) and are perceived by many as being more amenable to training.[24] However, we considered them together for the purposes of this review.

COMMUNITY-BASED EVIDENCE. A number of studies have assessed changes in knowledge and attitudes after the training of TBAs.[440,637–642] An observational study showed that trained TBAs were more likely than untrained TBAs to give advice on breastfeeding as well as on immunizations and oral rehydration therapy.[643] Trained TBAs also had better skills in neonatal resuscitation relative to untrained TBAs but did not have any impact on maternal behaviors. Kumar et al[640] stressed that continued training of TBAs was important in sustaining improved maternal and newborn care practices.

Table 39 (see also Tables 26, 41, and 42) summarizes the evidence from studies that examined the effect of TBA and CHW training on perinatal and neonatal health status outcomes in community settings. The CHWs were community based in all settings and had varying levels of training and linkage to the health system. Their relationship to the health system ranged from close association that facilitated referral of high-risk infants and/or those with complications to settings in which care was entirely home based.[439]

The 1 randomized trial in The Gambia[644] showed a reduction in neonatal mortality of 61% in the villages to which primary health care was introduced and TBAs were trained. However, neonatal mortality also fell by 35% in the control villages, rendering the 26% comparative fall in neonatal mortality nonsignificant. There was a significant increase in the number of women receiving antenatal visits and tetanus immunization during pregnancy, although the number of women whose births were conducted by a

TABLE 39. TBA/CHW Training

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Alisjahbana[733]	Indonesia; urban slums; PCS	TBAs (n = 20) were provided with a weighing scale with color codes and also a pictorial chart depicting maternal and child conditions. Using these, the TBAs determined the risk of a poor pregnancy outcome for the mothers and their neonates (n = 178 mother-infant pairs).	The weights determined by the TBAs using the colored scale were as accurate as the weights determined by midwives.	
Kumar[639]	See Table 26			
Rashid et al[643]	Bangladesh; rural setting; CCS	TBAs in the intervention group (n = 28) were provided 3 mo of basic training and 36 mo of supervised follow-up training. They were compared to a cohort of untrained TBAs (n = 27).		Although there was a significant difference between the trained and untrained TBAs in the advice provided to mothers regarding immunization, oral rehydration therapy use and breastfeeding practices, there was no associated change in behavior of the mothers.
Greenwood et al[644]	The Gambia; rural setting; RCT	TBAs were trained to provide antenatal care (especially malarial prophylaxis), risk assessment and subsequent referral, intrapartum care (especially safe and clean delivery) and neonatal care. Mortality and morbidity data for 1913 women over the 3 y of the program were compared to baseline data from 673 women.	There was a 62% decrease in maternal mortality in the intervention area compared with the preintervention period. Such a decrease was not observed in the non-intervention areas. There was also a significant increase in maternal tetanus immunization rates, maternal antenatal attendance and mothers who went to a trained TBA for delivery.	There was a significant 33% decrease in NMR in the intervention area compared to the nonintervention area. This change was mainly attributed to a decrease in rates of late neonatal deaths, especially those of infectious origin.
Daga et al[441]*	See Table 26			
Daga et al[449]*	See Table 26			
Smith et al[648]	Ghana; rural setting; cross-sectional household survey with TBA clients	The program was designed to improve working relationships between TBAs and other health providers in 2 districts of Brong-Ahafo Region. TBAs received comprehensive training covering care during antepartum, intrapartum, and postnatal periods and were provided with a kit containing midwifery and public health items. 2-week training contained instructions on care/management of normal pregnancy, recognition of complications and referral, care of the newborn and 5 nonobstetric primary health care topics; family planning, infant feeding, growth monitoring, immunization and control of diarrheal diseases.	Training was protective against postnatal fever (OR: 0.30; CI: 0.14–0.65), retained placenta (OR: 0.35; CI: 0.13–0.96), and labor >18 h (OR: 2.57; CI: 1.13–5.81).	Authors concluded that "the evidence for a beneficial impact of TBA training on the health of mothers and newborns is not compelling. Some moderate beneficial effects may be forthcoming, but it is unlikely that TBA training will result in large reductions in maternal and perinatal morbidity and mortality."

* Data are from the same trial.

trained midwife fell by 7% during the trial, confounding precise interpretation of the effect of TBA training. In another study, perinatal mortality decreased by 19% among offspring of women delivered by TBAs who had been trained in essential newborn care and advanced resuscitation, including use of the mucus extractor and bag-and-mask ventilation.[639]

In an uncontrolled study in India,[438] CHWs identified and managed high-risk neonates in the home, including preterm and LBW infants and those with feeding problems, illness, or a history of prolonged and difficult labor. Interventions included resuscitation of asphyxiated newborns, including cleaning of the mouth and pharynx and mouth-to-mouth respiration; antiseptic cord care, including cutting; promotion of breastfeeding; minimal handling to reduce

TABLE 39. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Janowitz et al[647]	Brazil; rural hospital setting; RCS	Data was collected from a random sample of women who had recently delivered over a 1-y period (n = 1961) to compare outcomes of deliveries by family members, by TBAs, and in hospitals. TBAs in the study were trained in local hospitals or in the home of a centrally located TBA following the official training plan of the local teaching hospital, and had regular supervision from a physician or nurse. TBAs primarily provided assistance only during delivery but were also given training in prenatal and postpartum care, as well as referral criteria.	Over the course of 1 y, 139 out of 1057 women who were being seen by TBAs planned to deliver at home but were referred to a hospital instead. An additional 119 women gave birth at home without the assistance of a TBA.	While the survival rate among births to women having their first delivery in a hospital was 4 times that of a first delivery in a home, hospital intervention did not have a statistically significant impact on the survival of infants born to women who were most likely to be referred.
Berggren et al[385]	Haiti; rural setting; RCS	Training programs for TBAs with Haiti's maternal and child health family-planning program were integrated in order to reduce maternal and newborn mortality. As a result, a manual for training to be used by professionals was created based upon recommendations by personnel from government and private institutions who had extensive experience in training indigenous women as midwives. The number of midwives reached by the training program increased from 36 in 1968 to 175 in 1970.	In the Trou Chouchou area, maternal mortality seemed to be unaffected.	Neonatal mortality was eliminated once the integrated training program had been implemented. Training of traditional midwives at the Albert Schweitzer Hospital resulted in an increased acceptance of prenatal consultations (80% after the program was introduced, compared with 37% at baseline) along with fewer deaths from neonatal tetanus (1 neonatal death from tetanus post-introduction, vs 15 neonatal deaths from tetanus at baseline; sample too small to reach significance).
Sibley and Sipe[3]; Bang et al[439]	See Table 26			Neonatal, infant and PMRs in the intervention area were significantly reduced (62%, 46%, and 71%, respectively) compared to the control area. Case fatality resulting from neonatal sepsis significantly declined, from 16.6% before treatment to 2.8% after treatment by VHWs.
Pratinidhi et al[438]	See Table 26			
Rahman[384]	See Table 20			
Meegan et al[389]	See Table 20			
O'Rourke et al[642]	Guatemala; rural setting; training program report	A TBA training program to improve relations between hospital staff and TBAs, as well as to improve standards of care, was implemented at a rural hospital. Mothers referred by TBAs were surveyed to evaluate the program.		Apgar scores improved and PMR declined, but the change was not statistically significant.

the risk of infection; postnatal home visitation and provision of anticipatory guidance about routine newborn care; and referral of sick newborns and those with feeding problems to a hospital. Home care of preterm and LBW infants also included keeping the room warm and feeding with a dropper if nec-

essary. In the absence of management of sepsis, newborn mortality declined by 25% during the intervention year compared with the year before implementation of the program.

Similar but less stringently evaluated success has been reported by Daga et al[441,449] from the Rural Neonatal Care Project in Dahanu, India, where NMR and PMR fell 41% and 62%, respectively, over a 3-year period. The project used TBAs as the means for delivery of neonatal care. Maintenance of the "warm chain," resuscitation of asphyxiated newborns, and appropriate, early referral of high-risk mothers and newborns (eg, LBW) were recognized as the most important interventions.[441] Anganwadi workers also played an important role in bridging the gap between TBAs and formal health workers.[449] Overall, the IMR in the block to which these services were introduced declined 70% over a 4-year period, from 148 to 45 per 1000.[449]

As part of the Narangwal Nutrition Study, a controlled trial in a rural area of Punjab, India, the Rural Health Research Centre trained a cadre of villagers as family health workers (FHWs) (lady health visitors) to provide health services in the villages in which they lived. All were given special training in comprehensive primary care and surveillance techniques and provided prevention, early diagnosis, management of illnesses (including penicillin injections for suspected pneumonia in infants), and referral services in village clinics and homes.[645] FHWs were the principal providers of nutrition and medical care in the study and were data collectors for longitudinal fertility and dietary surveys. They had detailed, written standing orders and were given weekly supervision by a doctor and a public health nurse to provide support, facilitate referrals, and ensure quality data collection. FHWs spent at least half their time performing home visits, which helped them identify pregnancies early and provide basic prenatal care to all women in service villages.[244,645] The interventions significantly reduced perinatal mortality. Analysis of service records revealed that 90% of patient contacts were handled capably by FHWs, and the remainder were safely referred to physicians.[244]

In another study in India, Society for Education, Action and Research in Community Health (SEARCH) trained TBAs in elements of clean delivery and CHWs in a variety of antenatal and postnatal interventions including provision of health education to caregivers in the home, promotion of breastfeeding, management of birth asphyxia, identification of premature and LBW (ie, high-risk) infants, prevention and management of hypothermia, treatment of skin and cord infections, identification of sick newborns, and administration of oral and injectable antibiotics for cases of suspected sepsis.[646] Although the precise impact of the TBAs versus the CHWs cannot be determined, there was little to no input from the formal health sector; thus, the impact apparently was largely facilitated by these trained village-level workers alone. The NMR fell by 62%, the PMR fell by 71%, and stillbirths were reduced by 18%.

A community-based trial conducted in Tanzania and Kenya demonstrated that, for areas in which maternal immunization was not a feasible method of decreasing tetanus morbidity and mortality, measures such as TBA training for safe and clean delivery and cord care were effective in decreasing perinatal, neonatal, and infant mortality[389] (Table 20).

Janowitz reported that trained TBAs in rural Brazil identified and appropriately referred most high-risk women.[647] In another study evaluating the impact of TBA training in Ghana, Smith et al[648] found reductions in intrapartum fever, labor >18 hours, and retained placenta, but the number of perinatal deaths and tetanus cases were too low to evaluate. Clients of trained TBAs were more likely than those of untrained TBAs to be referred for tetanus immunization (58% vs 28%, respectively), and immunization rates in both groups were high (87% vs 77%, respectively). In this setting, in which health providers other than TBAs were the primary antenatal care contacts, the value of training TBAs in clean cord care was questioned.[648]

O'Rourke[642] reported a twofold increase over a nearly 3-year period in referrals of women with pregnancy complications after introduction of a TBA training program in Guatemala. A 27% nonsignificant reduction in PMR was reported using a before-after comparison.

A recent meta-analysis of TBA training showed that there were statistically significant decreases of 11% in neonatal complications and 6% in perinatal deaths in areas served by trained TBAs compared with areas without trained TBAs.[3]

CONCLUSIONS. The overall effects of TBA training on perinatal and neonatal outcomes were generally beneficial. Little evidence was found to support the widely held notion that TBA training is futile. On the contrary, training was associated with improved behaviors (ie, advice, skills) among birth attendants, although it did not necessarily translate into improved maternal behaviors regarding newborn care. In some cases, caregiver behaviors did improve: the meta-analysis by Sibley and Sipe[3] showed improvements in overall TBA and caregiver knowledge as well as behaviors. Although there has been little evaluation of the impact of TBA training on perinatal and neonatal health outcomes, the weight of evidence suggests that TBAs may make positive contributions to newborn care, and further definition of TBA and CHW roles and evaluation of the impact of TBA training on perinatal and neonatal outcomes are merited.

TBA training need not be seen in isolation from other interventions, particularly interventions that improve the skills of other caregivers. The Gadchiroli trial successfully used both TBAs and CHWs working as a team along with the mother and other caregivers, particularly the mother-in-law, to improve domiciliary care for the mothers and newborn infants.[439] These interventions, therefore, may be considered for settings in which TBAs and CHWs will remain an important group of care providers for the foreseeable future. However, additional research is

needed to define the interventions that TBAs and/or CHWs can be trained to provide most effectively in programs at scale, to delineate criteria for selection of TBAs to be trained, to develop appropriate preservice and in-service training programs, and to evaluate the cost-effectiveness of such training programs.

Pneumonia Case Management

BACKGROUND. The true incidence of neonatal pneumonia or ARI at the community level is not known; however, a significant proportion of newborn infants diagnosed with sepsis or serious infections may have associated pneumonia, and the clinical presentations of these conditions have significant overlap in the newborn. Recommended treatment of serious systemic bacterial infections, including pneumonia, in neonates in developed countries includes parenteral administration of antibiotics in a health care facility. Similarly, in developing countries, the WHO recommends parenteral antibiotic therapy (eg, benzylpenicillin or ampicillin plus an aminoglycoside such as gentamicin) in a health facility for treatment of serious neonatal infections.[16,25,649,650] In resource-poor countries, however, the majority of births and neonatal deaths take place in the home, and families are often reluctant to seek care outside the home for neonatal illness.[439,569–571] In these settings, facility-based care with use of parenteral antibiotics is currently infeasible for many neonates, and alternative management strategies are needed. Insight into the role of oral antibiotic therapy as a potentially simpler and more feasible regimen for treatment of serious neonatal infections for situations in which referral to a health facility for quality care and parenteral therapy is not possible may be gained by reviewing pneumonia case management trials that included treatment of neonates.

COMMUNITY-BASED EVIDENCE. We identified 6 reports[654] and 2 meta-analyses of community-based trials of pneumonia case management that included neonates (Table 40). Sazawal and Black[651,652] conducted a meta-analysis of community-based intervention trials on case management of pneumonia in unselected preschool-aged children in developing countries. The impact of pneumonia case management on total neonatal mortality and pneumonia-specific neonatal mortality was determined. The 5 studies comprising the neonatal mortality analysis compared concurrent control and treatment groups.[653–660] In 4 of the studies, neonates with suspected pneumonia were treated with oral co-trimoxazole,[653–656,659,661] and another used both injectable penicillin and oral ampicillin.[660] Uncorrected analysis showed a 27% reduction in all-cause neonatal mortality (CI: 18–35).[652] After correction for perceived biases that may have affected the study results, the estimated reduction in total and pneumonia-specific neonatal mortality was 30% (CI: 15–42%; OR: 0.70, 0.59–0.84) and 42% (CI: 20% to 64%; OR: 0.56, 0.37–0.83), respectively.

In an additional study in Indonesia, use of ampicillin plus supportive care (eg, continued breastfeeding, clearing of the nose, fever control) in children with pneumonia had no measurable impact on cure rates of mild disease at 1-week follow-up, and did not halt progression to moderate disease at 1 week compared with the use of supportive care alone in the control group.[662]

CONCLUSIONS. Several studies have shown that it is possible to train CHWs to recognize and successfully treat pneumonia in newborn infants in community-based settings.[653–660,663] The impact of such training on reducing neonatal mortality and morbidity in community settings in developing countries is significant. Available data clearly indicate that a case management approach emphasizing essential newborn care along with prompt recognition of serious bacterial infections and treatment with oral antibiotics is superior to no case management. In fact, the reduction in neonatal mortality found in the meta-analysis was comparable to estimates of the proportion of neonatal deaths due to infections (ie, 32%[18]), suggesting that a substantial proportion of these deaths were averted through case management that primarily included oral antibiotic therapy in the home. However, the impact has its limits, given that it is impossible in many cases to distinguish pneumonia from sepsis on clinical grounds, and these conditions frequently coexist during the neonatal period. Thus, pneumonia case management alone, including use of oral antibiotics, will lead to undertreatment of many infants with more widespread infections (ie, sepsis) that require parenteral therapy. It was this realization that led the group at SEARCH to provide more comprehensive detection and management of serious neonatal infections with a combination of oral and parenteral antibiotics (see "Neonatal Care Packages"). A host of factors, including feasibility and cost-effectiveness of implementation, as well as ethical standards, must be considered when weighing the relative merits of neonatal pneumonia versus more comprehensive sepsis case management.

Neonatal Care Packages

BACKGROUND. Given that the majority of births take place at home in developing countries, frequently in the hands of relatively untrained birth attendants, there is considerable interest in the potential of developing locally adapted packages of newborn care in community-based settings. Whereas the previous sections reviewed trials that focused on use of trained TBAs/CHWs and on pneumonia case management, this section discusses more comprehensive packages of care that may or may not have included management of sick newborns.

COMMUNITY-BASED EVIDENCE. We identified 9 studies that were undertaken in community settings and included a comprehensive neonatal care plan rather than solitary interventions (Table 41). Several of these studies used TBAs and/or CHWs to provide care and thus were discussed in detail in "TBA/CHW Training" (Table 39).

In India, Pratinidhi et al[438] used VHWs to identify and manage high-risk neonates in the home. Interventions addressed birth asphyxia, hypothermia prevention, clean cord care, breastfeeding promotion, postnatal visitation, and identification and referral of

TABLE 40. Neonatal Pneumonia Case Management

Source	Location and Type of Trial	Intervention	Perinatal/Neonatal Outcome
Bang et al[658]*	India; rural setting; RCT	The project trained 86 TBAs in diagnosis and management of under-5 children with pneumonia ($n = 2568$ attacks). They were initially trained in visual judgment of fast breathing or difficult breathing; later in the project, 10 TBAs were trained in the use of simple breath counters. Training in safe and hygienic delivery and newborn care was also given. Community acceptance of case management by different workers was assessed. Surveys were conducted every 6 mo and causes of death in children were determined by verbal autopsy; see also Bang et al.[656,657]	A significant decline in neonatal mortality due to pneumonia (44%) was noted. The proportion of error-free case management by TBA increased continuously as the program progressed from 56.7% in the first year, to 68.6% in the second year, and 83.4% in the third year ($P < .0001$). The proportion of correct diagnoses by 10 TBAs increased from 60% to 82% when the breath counter was used.
Bang et al[657]*	India; rural setting; RCT	TBAs in the intervention area were trained to diagnose and treat pneumonia, and care-seeking for suspected pneumonia was encouraged in families. Management of neonatal pneumonia cases ($n = 65$) included continued breastfeeding, administration of cotrimoxazole syrup, and paracetamol for fever. Severe cases were promptly referred.	Case management led to a 40% reduction in pneumonia-specific mortality in the neonatal period, and a 78% reduction in mortality in the second month of life. 80% reduction in mortality was observed during the rest of infancy.
Bang et al[656]*	India; rural setting; RCT	TBAs, VHWs and paramedics diagnosed and treated pneumonia in the community. TBAs were also trained and provided with necessary equipment to conduct safe deliveries and to resuscitate asphyxiated newborns using mouth-to-mouth breathing. 2180 women in villages were interviewed to evaluate the effectiveness of the program.	Pneumonia-specific mortality rate decreased by 53.8% in the intervention area, and the case-specific fatality rate declined by 62% in the intervention area compared to the control area.
Datta et al[568]	India; rural setting; PCS	Primary health care workers in the intervention area of 38 villages were identified and trained in recognition, treatment and referral of ARI. Additional training material including self-learning educational aids were developed and field tested to ensure their suitability and simplicity. Infants with moderate or severe ARI were administered penicillin orally in 2 equal daily doses of 125 mg for 5 d.	Primary health care workers were contacted in 38% of cases of ARIs in the intervention area as opposed to 1% in the control area. Mean duration of infections in the intervention area was significantly lower ($P < .01$), whereas case fatality was ~33% of that in the control area.
Pandey et al[659]	Jumla, Nepal; rural setting; controlled intervention trial.	13 404 children were enrolled. Active case detection by CHWs trained in WHO pneumonia case management strategy. Principal criteria for establishing a diagnosis of pneumonia were a respiratory rate of 50 breaths per minute or greater or chest indrawing, measured through a specially developed battery-operated beeper timer to assess respiratory rate accurately. Emphasis was placed on maternal education for early detection of signs of pneumonia. Parents of presumed cases were given free cotrimoxazole pediatric suspension (8 mg trimethoprim/kg per d for 5 d) with detailed instructions and workers watched as parents administered the first dose. Workers revisited households on the third and sixth days to assess compliance and the child's status. Children who did not improve after 4 doses of cotrimoxazole, or relapsed, were treated with chloramphenicol suspension as the sole second-line antibiotic.	Case referral by mothers increased from 15% during the first year to 56% by the third year. 80% of pneumonia episodes were appropriately detected and treated. A statistically significant decreased risk of death (RR: 0.72; CI: 0.63–0.82) was observed and by the third year of the program. The greatest RR reduction was seen in infants between 6 and 11 mo and those between 1 wk and 5 mo. In addition to reduction in the deaths resulting from pneumonia, significant reductions in deaths due to diarrhea and measles were recorded, indicating that reduction in pneumonia morbidity had considerable carryover effects.
Sazawal et al[652]	India, Tanzania, Pakistan, Bangladesh, and Nepal; meta-analysis of community-based neonatal pneumonia case management trials		Meta-analysis found reduction in total under-5 mortality of 27% (CI: 18–35%), 20% (CI: 11–28%) and 24% (CI: 14–33%) among neonates, infants and children 0–4 y of age, respectively. Pneumonia-specific mortality was reduced by 42% (OR: 22–57%), 36% (20–48%) and 36% (20–49%), in the same groups, respectively.

* Data are from the same trial.

TABLE 41. Neonatal Care Packages

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Bang et al[439]	See Tables 26 and 39			
O'Rourke et al[734]	Bolivia; rural setting; PCS	Groups followed a 4-stage community action cycle to identify needs and practical solutions to problems that led to maternal and perinatal mortality. The impact of this intervention was evaluated by comparing PMRs and obstetric behavior among community women (n = 409) before and after the intervention.	There was an increase in the users of contraceptives from an estimated baseline of ~0–1% to 27%. There was a 71% increase in tetanus immunization in women. An increase in attendance at antenatal clinics was observed. Women resorted more to trained *Dais* (trained birth attendants) as opposed to untrained *Dais* for delivery.	There was a 63% decrease in PMR after the intervention compared to baseline (44 deaths/1000 births vs 117 deaths/1000 births, respectively; $P < .001$).
Manandhar et al[665]; Osrin et al[69]	Nepal; rural setting; RCT	Local female facilitators in intervention villages were trained to lead discussions within village development committees and women's groups about perinatal health issues. The groups then developed participatory action plans to solve perinatal health problems in an iterative process to reach 28 000 married women of reproductive age. Common goals of the action plans included surveillance of birth outcomes, caregiver recognition of danger signs, improved health worker knowledge and skills, clean delivery, early breastfeeding, and improved referrals.	Maternal mortality was significantly reduced in the intervention clusters compared to the control clusters (OR: 022; CI: 0.05–0.90).	A 30% reduction in IMR was observed in the intervention clusters compared to the control clusters (OR: 0.70; CI: 0.53–0.94).
Daga[492]	India; rural setting; PCS	6 babies with a foot length of <6 cm, whose mothers were not willing for hospital care, were managed at home using trained health workers.		All 6 newborn infants survived and did not require admission to the hospital.
Schieber et al[735]	Guatemala; rural setting; CCS	100 cases were obtained through a random sample of all perineonatal deaths. 120 controls were selected by enrolling the next registered birth after the study case in which the infant lived for at least 28 d). Mothers were interviewed, and data were reviewed by physicians to identify probable cause of death. 2 analyses were performed, first to identify predictors of perineonatal mortality and, second, to compare baseline characteristics between women who elected traditional as opposed to modern care.		Population-based attributable risks related to prematurity, malpresentation, and prolonged labor demonstrated that these complications account for significant proportions of observed perineonatal mortality.
Daga et al[449]*	See Tables 26 and 39			
Daga et al[441]*	See Tables 26 and 39			
Bartlett et al[664]	Guatemala; rural setting; PCS	All pregnant women identified in the community over a period of 1 y were enrolled. Newborns (n = 320) were seen weekly in the first month and biweekly in months 2 and 3. Mothers were taught routine newborn care by fieldworkers. A physician examined the infants biweekly in the first month and monthly in months 2 and 3. For minor illnesses, physicians provided treatment in the community. For complicated cases, physicians provided immediate treatment in the community, followed by referral.		Mortality rate in the first 3 mo of life was reduced by 85%, compared to historical controls.

TABLE 41. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Pratinidhi et al[438]	See Tables 26 and 39			
Greenwood et al[644]	See Table 39			
Kielmann et al[118]*	See Table 6			Morbidity duration was shorter in villages with MC (or NUT + MC) than in NUT or control villages ($P < .02$). Postneonatal mortality was lower in villages receiving MC or NUT + MC (23.3/1000 and 35.2/1000 live births for MC and NUT + MC groups, respectively) than the control villages (50–52/1000). Difference between combined mortality of villages receiving medical care (MC and NUT + MC) and the control villages was statistically significant ($P < .05$). The difference between 1 and 7 d mortality in the 3 intervention groups relative to the control group was highly significant (1 d: 28/1000; 7 d: 52.1/1000; $P < .005$).
Kielmann et al[244]*	India; rural setting; PCS	Groups and interventions were the same as Kielmann et al (See Table 6).	Mothers in the intervention group prolonged breast-feeding by about 2 mo because of nutrition education given to them.	IMR was lowest in the MC group (70/1000 live births), second in the MC + NUT group (81/1000 live births) and third in the NUT group (89/1000 live births) as compared to the control group (129/1000 live births).

* Data are from the same trial.

sick newborns and those with feeding problems to health facilities. Newborn mortality declined by 25% during the intervention year, compared with the year before implementation of the program (Tables 26 and 39).

In Narangwal, a town in Rural Punjab, India, 3 service groups received nutrition care (nutrition education, surveillance, and food supplementation of 1674 J and 11 g/day of protein through special feeding centers), medical care (immunization, health education, and early diagnosis and treatment of illness through frequent surveillance), or both nutrition care and medical care.[118,244,645] A fourth group served as the control group. Results showed significant improvements in growth (weight and height) and Hb levels of children. Medical care significantly reduced postneonatal morbidity and mortality in the 1- to 3-year-old age groups and decreased illness duration of all 6 conditions examined in this study. Prenatal nutrition care to pregnant women was most effective in preventing perinatal deaths, followed by medical care for infants (Table 41).

Two decades ago in a rural area of The Gambia, a package of primary health care interventions was introduced by the Gambian government to improve maternal and neonatal birth outcomes.[644] A VHW and a TBA from each village were trained to provide antenatal care (especially malarial prophylaxis), risk assessment and subsequent referral, intrapartum care (especially safe and clean delivery), and neonatal care. Alongside significant declines in maternal mortality over the 3 years after the program was introduced (from 2716 to 1051 of 100 000; χ^2: 5.9; $P < .05$), the program documented statistically significantly lower rates of neonatal deaths in intervention villages relative to nonintervention villages (46.6 vs 69.6 of 1000, respectively; χ^2: 4.3; $P < .05$), primarily due to a reduction in late neonatal deaths due to infections.

In Guatemala, pregnant women were taught routine infant care and care seeking for illness, and when symptoms of severe illnesses were detected, immediate empiric treatment was begun in the community with accompanied referral to an area hospital.[664] The mortality rate among infants enrolled in the study was reduced by 85% compared with historical controls.

In rural India, Daga et al[441,449,492] emphasized re-

suscitation of asphyxiated newborns, prevention of hypothermia, and referral of sick newborns and achieved 41% and 62% reductions in NMR and PMR, respectively, compared with baseline data over a 3-year period. The administration cost of the program was considered "affordable," because it was based on inexpensive domiciliary neonatal care by TBAs supported by relatively low-cost facilities for neonatal care. This intervention was acceptable to the community and the TBAs because it was simple to carry out and did not involve technology that causes "culture shock"[441] (Tables 26, 39, and 41).

An uncontrolled trial (the "Warmi" Project) to improve maternal and child health in the rural province of Inquisivi, Bolivia, included training TBAs, offering tetanus immunizations to women of reproductive age, ensuring a clean birthing surface and hygienic cord care, providing antibiotic eye drops, encouraging immediate breastfeeding, and ensuring thermal control.[642] Family-planning services and community funds and mechanisms for transport of women in need of care to secondary health facilities were established also. The program emphasized community participation in identifying and solving problems. This approach led to a 67% reduction in perinatal mortality over a 3-year period, an increased proportion of women receiving prenatal care, and an increased number of women initiating breastfeeding on the first day after birth compared with baseline (from 25% to 50%).

In rural India, SEARCH trained VHWs in intervention areas to provide a package of home-based neonatal care, including health education to pregnant women, diagnosis and management of birth asphyxia, identification of high-risk (premature and LBW) neonates for more intensive surveillance, temperature maintenance, promotion of breastfeeding, administration of vitamin K, treatment of skin infections, and identification of sick newborns suspected of having septicemia, meningitis, and/or pneumonia and administration of antibiotics (oral co-trimoxazole and IM gentamicin) in the home.[439] Neonatal mortality due to sepsis was reduced 76% and overall neonatal mortality declined by 62%, compared with the control, nonintervention area.

More recently, in the rural district of Makwanpur, Nepal, Osrin et al[69] conducted a cluster-randomized trial to evaluate a community-based participatory intervention to improve essential newborn care. The intervention, which covered a population of 28 000 married women of reproductive age, trained local female facilitators in intervention villages to lead discussions within village-development committees about perinatal health issues. These facilitators also helped the groups develop participatory action plans in an iterative process. Mothers' groups within each village-development committee met monthly to identify perinatal health problems, design and implement solutions, monitor birth outcomes, and share results with others. Common goals of the action plans included community surveillance of births and birth outcomes, improved caregiver recognition of danger signs, proper care seeking, improved knowledge and skills of health workers, clean delivery practices, increased rates of early breastfeeding, and improved referral patterns. Infant mortality was reduced by 30% (OR: 0.70; CI: 0.53–0.44) and maternal mortality was reduced by 78% (OR: 0.22; CI: 0.05–0.90).[665]

CONCLUSIONS. These data strongly support implementation of packages of essential newborn care. For settings in which health facility capacity is limited and referral is not possible, the data also support the utilization of trained community-based workers in the screening and preventive and curative care of newborn infants. These interventions have not been evaluated in effectiveness trials using available staff and infrastructure. Thus, there are legitimate concerns regarding the replicability and sustainability of these comprehensive programs of care. Additional cost-effectiveness evaluations of this approach must be undertaken in larger trials in diverse geographic locations.

Creation of linkages to referral facilities and facilitation of referral pathways and improvement in quality of care at referral facilities were essential aspects of most community-based newborn care programs reporting improved survival. Nevertheless, some programs[118,244,439,642,665] reduced neonatal mortality with little health systems, capacity, primarily through provision of improved antenatal and neonatal care in a context of community empowerment.

Care in Peripheral Health Facilities

BACKGROUND. In many settings, a primary strategy to improve neonatal outcomes will be to increase healthful essential newborn care practices in the home, while also seeking to improve care seeking for newborn illness, and stabilization and referral of sick infants to health care facilities as close to the community as possible, where better-quality care may be available.

COMMUNITY-BASED EVIDENCE. We identified 9 studies that described and evaluated various postnatal interventions in primary or secondary health facilities in community settings (Table 42). Most of the facilities described were community-based and had limited resources. Also included was a study that evaluated postdischarge follow-up of neonates in a community setting.[666]

Various approaches to improving neonatal care and outcomes were evaluated in these studies, which focused primarily on training caregivers and health providers in essential newborn care. Although no study used a randomized, controlled design, improvements were reported in survival[441,494,667–669] and immunization rates,[669] and reductions were noted in length of hospitalization and number of readmissions after discharge.[666]

CONCLUSIONS. Strengthening health facilities and health systems is an essential aspect of community-based programs to improve neonatal health. However, given the barriers that exist to care seeking for neonatal illness,[439,569–571] it is unlikely that utilization of facility-based services for newborn care in many communities will increase in the absence of demand creation, improved referral pathways, and quality of

TABLE 42. Neonatal Care in Peripheral Health Facilities

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Arif et al[736]	Pakistan; urban hospital setting; RCT	362 babies were randomly assigned to either an incubator or heated cot by the mother's side ($n = 151$), or to the special care baby unit ($n = 211$). Mothers were trained by nurses.		Weight gain from admission to discharge was significantly higher among newborn infants in the maternal care group ($P < .001$). Mortality in the fair and poor babies was significantly lower (44%) in the maternal care group ($P < .001$). Overall, mortality in the maternal care group was 57% lower than the special care unit, irrespective of condition at admission.
Bose et al[666]	India; rural setting; RCS	At the Community Health and Development Hospital, a low-cost nursery for newborns ($n = 175$) was established with facilities for phototherapy, heat cradles and other basic nursing facilities.		Of 175 newborns admitted, 6 died and 8 were transferred to nurseries in a tertiary care or government hospital.
Borulkar et al[737]	India; rural setting; PCS	Staff at a community hospital was taught special care for newborns ($n = 2266$), comprised of provision of optimal warmth, resuscitation of asphyxiated neonates, proper feeding and oxygen administration when indicated.		For a 5-y period, survival was 61.5% in the 1000–1500 g birth weight category and 92.5% in the 1520–2000 g category of admissions. No comparable historical data was reported.
Dutt et al[669]	India; rural setting; PCS	Jawaharlal Institute Rural Health Center served as a treatment as well as a referral center in the rural area for births ($n = 356$).	94% of the deliveries were conducted by trained personnel, as compared to 16% in 1967. All mothers were immunized against tetanus.	IMR decreased by 68% (comparative neonatal mortality rates were not specified). In the postnatal period, >98% of the children had received the full courses of DPT, oral polio, and BCG immunizations. There were no deaths due to neonatal tetanus.
van der Mei et al[667]	Ghana; rural hospital setting; PCS	Care of neonates ($n = 567$) was done under limited resources by training mothers and nurses in basic newborn care		Survival rates of infants weighing ≤1500 g and for those weighing 1500–2000 g were 52% and 90%, respectively.
Wilkinson[668]	South Africa; rural hospital setting; QT	The pilot study was based on an analysis of consecutive hospital and clinic deliveries ($n = 640$). A subsequent study included 2193 consecutive hospital and clinic births. Basic interventions (including a community obstetrics guide for local midwives, a policy change to admit all pre-eclamptic women with high diastolic blood pressure to the hospital, a managed system for blood collection and result delivery, and training for midwives and skilled birth attendants in neonatal resuscitation and management of labor emergencies) were introduced in the hospital to tackle problems identified through a pilot study.		A 32% decrease in NMR was seen during the intervention period.

care. Although it is unlikely that interventions based in facility settings alone will make a major difference in situations in which the bulk of deliveries take place in domiciliary settings, they are nevertheless an essential adjunct to such care.

There are few existing guidelines for the care of sick newborn infants in health care institutions with limited facilities and manpower.[548,670] Thus, there is an urgent need to improve and strengthen referral pathways and linkages between domiciliary-based interventions and facility-based care for sick neonates. There are considerable opportunities to reduce cost of care and improve efficiency by such an approach. Despite the limited information, we would strongly endorse incorporation of basic guidelines for improved secondary care of newborns in health facilities as an essential adjunct to community-based and domiciliary interventions.

COST-EFFECTIVENESS OF COMMUNITY-BASED INTERVENTIONS

BACKGROUND. During the last few decades, significant reductions in perinatal and neonatal mortality have been achieved in the context of studies evalu-

TABLE 42. Continued

Source	Location and Type of Trial	Intervention	Maternal Outcome	Perinatal/Neonatal Outcome
Bhakoo et al[738]	India; urban hospital setting; RCS	Changes were made to the admission and discharge criteria in the neonatal special care unit (NSCU), to encourage keeping the baby with the mother and early hospital discharge for home care. Rather than be kept in the NSCU (where mothers were not allowed), more high-risk babies stayed with their mothers. Outcomes for infants kept in the NSCU (n = 165) were compared to infants who were cared for alongside their mothers (n = 127).		After changes were made to the admission and discharge criteria, fewer newborn infants who were cared for outside the NSCU alongside their mothers died (7/127), as compared to those admitted to the NSCU (57/165). Neonatal mortality in babies weighing <2 kg declined significantly over a 13-y period (7.94% in 1986 vs 12.88% in 1973; $P < .005$), and over the same period, mortality fell among preterm babies from 26.88 to 11.5% ($P < .001$). This was achieved despite a two- to threefold increase in the high-risk babies and without any increase in the number of neonatal special care beds or nurses.
Daga et al[494]	India; urban hospital setting; QT	A conservative neonatal care unit was established in J J Hospital, Bombay, having 4 main features: 1) room warming, 2) exclusive breastfeeding, 3) maternal involvement in infant care, and 4) minimum handling and minimum intervention. Birth outcomes for a cohort of infants (n = 21) in 3 different weight groups (1000–1250 g, 1260–1500 g, and 1510–2000 g) were measured and compared to historical controls.		3 neonates were admitted with birth weights of 1000–1250 g, and the survival was 33% in this group compared to a previous best of 50%. In the birth weight group of 1260–1500 g, 8 neonates were admitted and their survival was 75%, compared to 66% as a previous best in this weight group. For the weight group 1510–2000 g (n = 10 admitted), a 90% survival rate was found, compared to 92.5% as a previous best.
Cooper et al[739]	South Africa; urban hospital setting; RCT	A group of VLBW infants (n = 19) was fed a formula specifically developed for such infants, while another group (n = 20) was fed expressed breast milk (EBM).		Time to reach a weight of 1800 g was 28 d for the formula-fed group, vs 40 d for those receiving EBM. The allocation groups were not strictly randomized for severity of illness.

ating a variety of interventions in developing-country communities, as reviewed above. For some interventions or packages of care, promising results in efficacy trials have included, or subsequently led to, evaluations of their cost-effectiveness.[671,672] In general, however, attempts at costing interventions have included posthoc data collection or extrapolation, which are not optimal for this kind of analysis.[673]

Studies in developed countries have shown that early initiation of antenatal care is among the most cost-effective strategies for reducing neonatal mortality. In contrast, neonatal intensive care, despite its impact on mortality of the sickest patients, has been found to be one of the least cost-effective and feasible approaches.[81,674] Several interventions in pregnancy such as the preterm birth–prevention program in urban Los Angeles[675] and management of gestational diabetes mellitus[676] have also been shown to be cost-effective. Well-defined efforts in developed countries to estimate the cost-effectiveness of various other interventions have been reported, such as prevention of preterm births,[675] reorganization of perinatal services,[677] and establishment of perinatal databases.[678] In addition, certain specific postnatal interventions such as neonatal resuscitation,[679] indomethacin therapy for premature infants,[680] surfactant replacement therapy,[681] prevention of respiratory syncytial virus infections,[682] or therapy for apnea of prematurity[683] have been shown to be cost-effective interventions in the context of developed countries. Most available information on cost-effectiveness of interventions refers to hospital or facility-based interventions, and these cost-effectiveness evaluations have used variable methods; only rarely have maternal and infant benefits together been evaluated.

COMMUNITY-BASED EVIDENCE. Cost-effectiveness models and analyses of interventions to improve perinatal and neonatal outcomes have been infrequently applied in emerging economies[684] and are rarer still in developing countries. Examples of cost-effectiveness assessment of intervention strategies in developing countries have largely included hospital-based interventions such as routine ultrasonogra-

phy,[685] surfactant replacement therapy,[686] prevention of respiratory syncytial virus infections,[687] and (more recently) the successful WHO-modified antenatal care package.[84,688] In other instances, organization of basic neonatal care services in referral hospitals has been shown to be cost-effective.[689]

Cost-effectiveness data are also available from developing-country communities for selected interventions focusing on antenatal interventions to prevent infectious complications of pregnancy and their impact on neonatal outcomes. These interventions include antenatal screening and treatment for syphilis,[324] syphilis prevention,[690] toxoplasmosis treatment,[691,692] TT-immunization administration,[693] malaria-prevention programs,[694] and screening and treatment for asymptomatic bacteriuria.[695] These evaluations reported a wide range of cost-benefit ratios, with estimates ranging from $14 to $115 per neonatal death or adverse outcome averted (Table 43).

There has been much interest in recent years in the cost-effectiveness of community-based strategies for perinatal care. Such data, however, are almost exclusively available from developed countries and include the institution of community-based nurse-midwifery services, culturally adapted perinatal care,[696] and earlier discharge and community care for premature infants.[697,698] The strongest body of evidence for the impact and cost-effectiveness of community-based interventions in developed countries pertains to smoking-cessation[699–701] and other LBW-prevention programs (for example, nutrition-related interventions such as the WIC program),[702–704] indicating substantial benefits.

In contrast, there are almost no systematic studies of the cost-effectiveness of community-based interventions to improve perinatal and neonatal outcomes in developing countries, with the exception of studies in Nepal and rural India[439,665] and several evaluations of malaria prophylaxis and therapy.[283,694,705] Studies to evaluate even well-established strategies for the improvement of perinatal and neonatal health outcomes, such as breastfeeding promotion in large effectiveness trials, are only now being commissioned.[706]

CONCLUSIONS. Critical steps in the development of effective community-based health interventions include the demonstration of efficacy and effectiveness. To convince policy makers to support the programmatic implementation of promising interventions, however, cost-effectiveness data are needed to inform the feasibility of the intervention at scale and its expected benefits relative to other services. Even for interventions considered to be of proven benefit for perinatal and/or neonatal health, little such data are available and are primarily from facility-based evaluations and, moreover, from developed countries. Cost-effectiveness data for community-based perinatal/neonatal health interventions in developing countries are almost nonexistent. However, with the recent development of guidelines for costing of maternal and newborn interventions by the WHO[709] and the Saving Newborn Lives Initiative (Saving Newborn Lives, Saving Newborn Lives Initiative: Project Costing Guidelines, Washington, DC, Save the Children/USA, unpublished data) and with the establishment of Marginal Budgeting for Bottlenecks and CHOICE activities to inform public health resource allocation, more such data are expected.[707,708] For example, several trials of the impact of antenatal, intrapartum, and postnatal interventions on perinatal and neonatal health that are currently underway have included evaluation of cost-effectiveness as a key objective. Moreover, data are beginning to emerge from Marginal Budgeting for Bottlenecks on the marginal costs of introducing certain interventions relevant to perinatal and neonatal health to existing programs.

SUMMARY

Implications for Programs

This review of evidence from developing-country community-based trials for the impact of antenatal, intrapartum, and postnatal interventions on perinatal and neonatal health outcomes has highlighted the paucity of available information, particularly from RCTs. Only 31 studies were RCTs that reported primary perinatal/neonatal health status outcomes (eg, stillbirth rate, PMR, NMR), and only 40 were RCTs that reported secondary perinatal/neonatal health outcomes (eg, LBW, preterm births, morbidities, or breastfeeding rates) (Table 1). Still fewer (only 10) were interventions conducted in health system settings or were effectiveness trials.

TABLE 43. Available Cost-effectiveness Data for Antenatal, Intrapartum, and Postnatal Interventions

Intervention	Cost-Effectiveness Data	Evidence of Cost-Effectiveness*
Malaria chemoprophylaxis or intermittent therapy	2-dose regimen of SP cost $9.66 per case of LBW averted[705]	3
Malaria prevention using PIBs	$4–43 per discounted life-year lost[740]	3
Syphilis screening and treatment	$1.05 per neonatal discounted life-year gained[324]	4
TT immunization	$27–115 per neonatal death averted[693]	4
Package of antenatal, intrapartum and postnatal interventions	1 y of care cost $5.30 per newborn and averted 1 neonatal death for every 18 neonates cared for[439]	3
Participatory neonatal care women's groups	$3442 per neonatal death averted ($4397 including health services strengthening); $111 per life-year saved[665]	3

* Rankings are based on a scale of 1–4 as follows: 1 indicates evidence of poor cost-effectiveness (leave out of programs); 2, uncertain evidence of cost-effectiveness (need additional data before including in programs); 3, some evidence of cost-effectiveness (may include in programs, but further evaluation is warranted); 4, strong evidence of cost-effectiveness (include in programs). Note that cost-effectiveness data from community-based trials was available only for selected interventions (see cost-effectiveness section).

To broaden the relevance of the conclusions that can be drawn from the available data, we placed the evidence in the context of biological plausibility, data from studies in developed countries, programmatic experience, and recommendations by the WHO and other leading child health agencies. Recommendations based on this review are broadly applicable to developing-country communities but are particularly germane to the most impoverished populations with high NMRs (eg, >40 per 1000 live births).

It is clear that the level of evidence for benefit of a number of interventions (Table 2) warrants their broad programmatic implementation (Fig 1). Interestingly, this group of evidence-based interventions closely resembles those identified through a strategic planning process at the international and multiple-country levels and outlined in a conceptual framework for community-based maternal and newborn care recently advanced by Save the Children/USA.[17] Moreover, these elements of essential newborn care are highlighted in recent recommendations for routine and sick newborn care by the WHO.[14–16] Thus, there seems to be broad convergence of expert opinion and the evidence base regarding priority interventions to advance perinatal and neonatal health and survival at the community level in developing countries. Considering past experience of child health programs in implementation of various interventions, and current recommendations of the WHO and leading child health agencies, a few additional interventions not covered in this review have been added to Fig 1 (marked with an asterisk). These interventions include birth preparedness and recognition of and appropriate response to danger signs in the antenatal and intrapartum periods; skilled health care at delivery (evidence reviewed elsewhere); early postnatal visitation for provision of anticipatory guidance and recognition and management of maternal and newborn illness; and birth spacing. Many of these interventions have been included in comprehensive packages of maternal and newborn interventions but have not been rigorously evaluated per se for their specific contribution to the total impact of the package of care.

Effective interventions span maternal and neonatal care, as anticipated when one considers that pregnancy-related causes, delivery-related causes, and infections each account for approximately one third of neonatal deaths.[18] Moreover, although not emphasized here, many of the interventions of proven benefit for neonates also lead to improved maternal health (detailed in Tables 4–42),[45,710] which serves to illustrate the importance of integrating maternal and neonatal care while avoiding vertical programs for either the mother or the newborn. Although data on cost-effectiveness are particularly lacking, an approach that integrates maternal and neonatal health into Safe Motherhood and Child Survival programs and bridges the gap between these programs will not only establish continuity of care across the life cycle but will also enhance the cost-effectiveness of intervention packages.

Research Gaps

Although a number of interventions have been shown to reduce perinatal and/or neonatal mortality and to have the potential to reduce global neonatal mortality by approximately half through wide-scale implementation of evidence-based interventions,[10] there are fundamental gaps in our knowledge of how to most effectively improve perinatal and neonatal outcomes in developing-country communities.[711] Although we know that implementation of comprehensive neonatal care programs can reduce perinatal and/or neonatal mortality substantially, failure to empower and mobilize communities to accept interventions[712] and lack of understanding of community practices and culture are major barriers. Thus, there is an urgent need to adapt and evaluate culturally and regionally appropriate packages of interventions in a variety of settings. Pivotal questions regarding implementation of neonatal health care programs that demand additional operational research include: Which cadre of health workers in various settings can most effectively deliver the needed services for mothers and newborns at the community level? How will these workers be trained and supervised in a sustainable manner at scale, and what are the most effective methods for preservice and in-service training? What will be the scope of their service delivery (eg, with regard to client age, breadth of services, and geographic reach)? Is a team of skilled birth attendants and newborn care providers needed at the community level to provide simultaneous care for the mother and newborn during the critical intrapartum period, particularly to address birth asphyxia?

The conceptual framework for newborn care at the community level advanced by Save the Children/USA[17] calls for provision of both preventive and curative care, particularly for birth asphyxia and infections. However, in many settings, provision of curative care for these major causes of neonatal mortality is beyond the capacity of current health care systems. Thus, critical unanswered questions are: Can effective implementation of a behavior-change communications package at the domiciliary level, without active case management of newborn illness by health workers, improve neonatal outcomes? What is the added benefit and cost-effectiveness of active identification and management of neonatal illness, particularly serious bacterial infections and intrapartum hypoxia/birth asphyxia? What are the most feasible and effective ways to deliver life-saving newborn resuscitation and antibiotic therapy in the community? How can barriers to care seeking for newborn illness be overcome most effectively so that home-based care and care seeking can be effectively linked with referral-level care at facilities? What is the impact and cost-effectiveness of postnatal visitation for promotion of healthful behaviors and recognition of neonatal illness? Can the same worker address the postnatal needs of both mothers and newborns? What is the optimal timing and number of routine visits with a health care provider?

Skilled care during delivery is universally recognized as a major long-term priority for improving the

care of mothers and newborns, and plans for advancing health system capabilities for providing this care are paramount. Based on a consideration of the fact that most births and neonatal deaths in developing countries still occur at home during the early neonatal period, due to birth asphyxia and/or infections and primarily among LBW infants, the following emerge as major research gaps:

1. Understanding and improving household and community practices and their determinants: Local formative research is needed to better understand local beliefs and practices and the reasons behind them so that effective behavior-change strategies can be developed and evaluated.[23] This must be followed by appropriate research to develop intervention strategies to improve care-seeking behaviors at the household and community levels.
2. Improving the capacity of health systems for providing essential preventive and special curative neonatal health care: As noted above, some of the most challenging questions in neonatal health care relate to how to deliver services most effectively to newborns in an integrated way within existing programs for maternal and child health.[20–22] Although difficult, answering these questions requires that many packages and combinations of interventions be tested through effectiveness trials in health system settings.
3. Preventing and improving recognition and management of birth asphyxia: Identification of sustainable interventions for management of intrapartum hypoxia/birth asphyxia is urgently needed at the community level.[24] Solutions must allow for immediate response at the time of delivery in a cost-effective manner and necessarily will require integration with skilled health care for mothers at delivery and links with referral facilities.[16]
4. Preventing and improving recognition and management of infections: There is an urgent need to identify how the burden and severity of maternal infections relate to perinatal outcomes. These infections may range from subclinical intrauterine infection and bacterial vaginosis to overt genital tract infections that may lead to preterm labor. The true burden of bacterial neonatal infections in community settings is also unclear, because many clinical bacterial infections may represent viral infections. Narrowing this information gap is vital: to devise optimal antibiotic-treatment strategies for neonatal infections,[25] we need to know the agents of life-threatening infections in the community and their antibiotic-susceptibility patterns.[26] There is additional need for validated algorithms for accurate and rapid identification of infected neonates by CHWs and caregivers. We also must advance antibiotic-treatment strategies for serious infections, which may include simplified antibiotic-delivery systems and/or regimens. The potential development and evaluation of simplified oral treatment regimens that include oral administration will be a major advance for public health programs.
5. Preventing and improving care for LBW infants: Given that the majority of newborns who die in many developing countries are LBW, improved strategies for both prevention of and care for LBW infants are urgently needed. These strategies include interventions to reduce preterm births, reduce the incidence of IUGR, or a combination of both. Prevention may be achieved by improved maternal nutrition and detection and treatment of maternal infections. Improved postnatal care of LBW infants may be achieved in part by behavior-change communications, topical emollient therapy, breastfeeding promotion, and widespread implementation of culturally adapted methods for skin-to-skin care (or variations thereof) with the mother and, when indicated, other household members. The development, validation, and availability of low-cost technology for the care of LBW infants in primary and secondary health care facilities are important adjuncts to community-based management strategies.
6. Improving information on the magnitude and causes of neonatal mortality: Lack of accurate global, regional, and country-specific data on the magnitude and causes of perinatal and neonatal morbidity and mortality currently is limiting advocacy and program planning in newborn health. Strengthening of information systems, including birth and death registration and dissemination of information at local levels about causes of newborn morbidity and mortality (and their determinants), are needed to guide resource allocation and program and research priorities. Moreover, as programs incorporate newborn care, their impact must be monitored and accurate data fed back to those involved in health policy and program decision-making to enable them to use scarce resources more effectively. Integral to documenting and monitoring newborn health status is the need for improved verbal autopsy instruments to enable more accurate determination of causes of perinatal and neonatal deaths in the community and to assess the contribution of sociocultural and logistic factors. Perinatal audit may also be a powerful tool for identifying avoidable factors in deaths, and mobilizing change in communities to improve maternal and neonatal health care.
7. Cost-effectiveness analyses: Assessment of cost-effectiveness must be incorporated into neonatal health research to guide selection of interventions and stimulate investment in neonatal health.
8. Development of indicators and simple management tools for assessing and monitoring health system performance for perinatal and newborn care at the national level: An important impediment to wider implementation of neonatal health programming is lack of inclusion of perinatal and neonatal health indicators among global indicators for measuring progress in Child Survival (eg, Millennium Development goals). Moreover, programs too often fail to monitor adequately and demonstrate the effectiveness of their programs.

Tools for rapid situational analysis, prioritization of program activities, and accurate monitoring and documentation of program effectiveness are urgently needed.

A major factor currently limiting our ability to identify effective interventions is the wide variation in study designs and indicators for assessing impact and the almost complete absence of cost-effectiveness data. In 2001, a group of neonatal health researchers met to discuss a common agenda and methodologies for neonatal health research in developing-country communities.[27] This review further highlights the need, as recommended at the 2001 meeting, for dialogue among researchers, policy makers, program managers, and donors regarding the selection of research priorities; the use of common (and, whenever possible, rigorous) study designs; and for sharing of data-collection instruments and research results. Reporting of indicators of neonatal health at global and national levels is essential for monitoring large-scale success.

CONCLUSIONS

A paucity of community-based data are available from developing countries on health status impact, principally perinatal and/or neonatal mortality, for many interventions that are currently being considered for inclusion in neonatal health programs. However, a review of the evidence and consideration of the broader context of knowledge, experience, and recommendations regarding these interventions enabled us to categorize the interventions according to the strength of the evidence base and confidence with which the intervention could be included now in programs. As a result, a package of priority interventions for inclusion in programs was identified, and research priorities for advancing the state-of-the-art in neonatal health care were formulated. Thus, this review can serve as a guide for development of evidence-based maternal and newborn health care programming at the community level and for selection of research to advance the state-of-the-art in community-based neonatal care. It also may facilitate dialogue with policy makers about the importance of investing in neonatal health.

Clearly there is ample evidence for benefit of a number of antenatal, intrapartum, and postnatal interventions. Operational questions of how to implement the intervention(s) in an affordable and acceptable manner at scale were an overriding concern for many interventions. Thus, although there is great need for continued research on the cost-effectiveness of a number of interventions, particularly for prevention and care of LBW infants, prevention of fresh stillbirths, and prevention and management of birth asphyxia, it must not hamper implementation now of many interventions of known impact at a wider scale. For many of these proven interventions, however, critical questions remain regarding how to implement them in a cost-effective manner at scale. Close monitoring of the impact of these programs is imperative. Finally, close communication between program managers who document experience with intervention implementation; the researchers who generate answers to operational questions and devise new, innovative interventions and approaches; and the donors who promote the research will be critical to advancing maternal and neonatal health care at the community level.

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