

Global Maternal and Child Health:

A Research Partnership's Approach for Addressing Challenges and Reducing Health Disparities in Developing Countries

Richard J. Derman, MD, MPH;¹ Shivaprasad S. Goudar, MD, MHPE;² Frances J. Jaeger, AM, MPH, PhD;³ Omar Khan, MD, MHS⁴

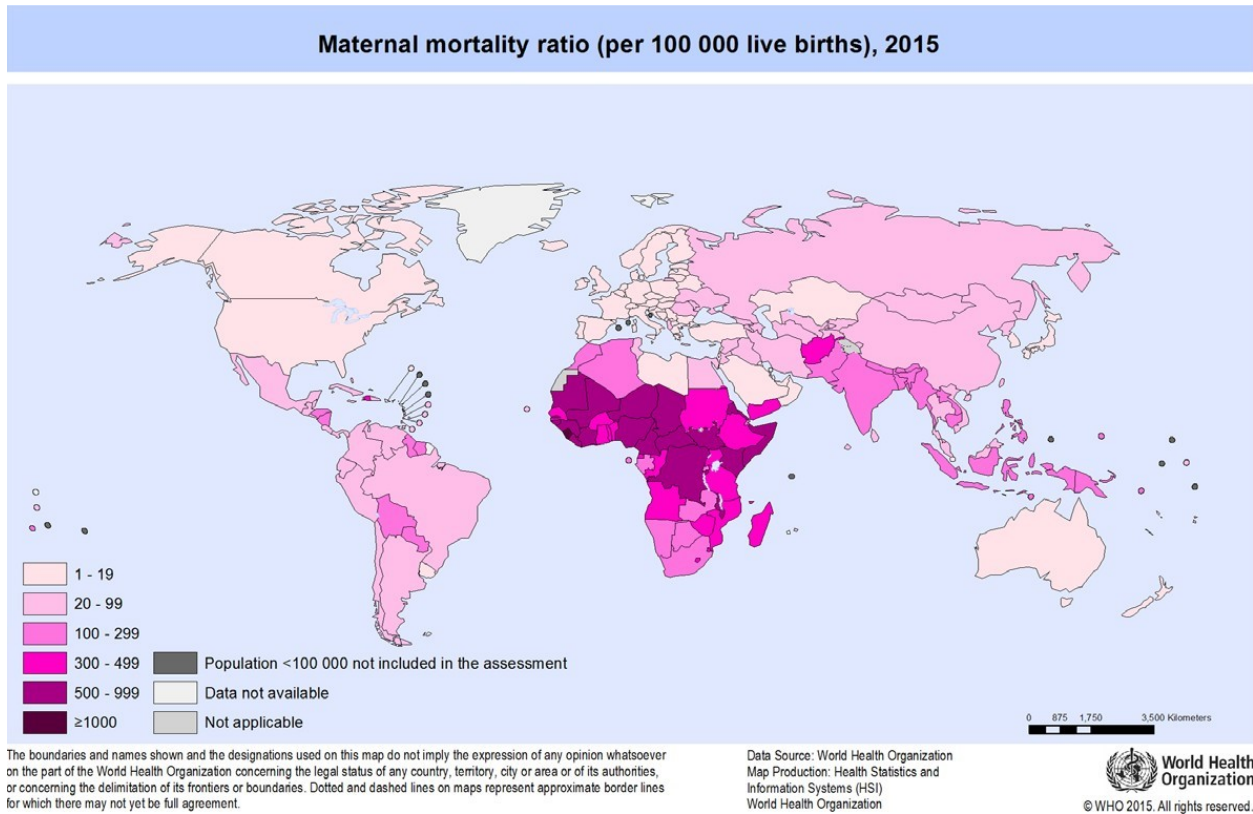
1. Professor of Obstetrics and Gynecology, Associate Provost for Global Affairs and Director, Global Health Research, Thomas Jefferson University
2. Professor of Physiology and Research Coordinator, Women's and Children's Health Research Unit, Jawaharlal Nehru Medical College, KLE Academy of Higher Education, Belagavi, Karnataka, India
3. Consultant (for Research Services) to Thomas Jefferson University
4. Christiana Health Care System and Delaware Health Sciences Alliance

Background

In the midst of significant maternal and child health (MCH) challenges in the United States, it is sobering that the vast majority of MCH deaths occur in developing countries. A report published by the World Health Organization (WHO) on maternal mortality for the period 1990-2015 stated that an estimated 99% of global maternal deaths in 2015—or approximately 302,000 of an estimated 303,000 deaths worldwide -- took place in developing countries.¹ The number of deaths among infants and other children under 5 occurring in developed countries in the same year was estimated as 80,000 by the UN Inter-agency Group for Child Mortality Estimation (UN IGME); but the group estimated that the comparable number for developing regions was 5,865,000 (or 98.6% of the global total).² It is tragic that such disparities exist, and it is particularly disheartening that most maternal and under-5 deaths are associated with preventable causes.

The world's estimated Maternal Mortality Rate (MMR), or the number of deaths per 100,000 live births, for 2015 was 216. This global ratio, however, masks the massive difference between the MMR of developed countries (12) and that of countries classified as developing (239). For example, Sub-Saharan African countries, with a mean MMR of 546, bear the disproportionately large burden of maternal deaths. South Asia, while statistically a distant second with an MMR of 176, nevertheless experiences significant, unnecessary mortality (see Figure 1). In countries with relatively large populations, the burden of the absolute number of MCH deaths can be staggering despite MMRs lower than the global ratio. In 2015, India's population of more than 1.3 billion was second highest in the world, and the 45,000 maternal deaths occurring that year resulted in India achieving second place for such deaths. India followed only Nigeria, which had 58,000 maternal deaths. Together these two countries accounted for approximately one-third of global maternal deaths in 2015.¹

Figure 1. Maternal mortality ratio (per 100,000 live births), 2015



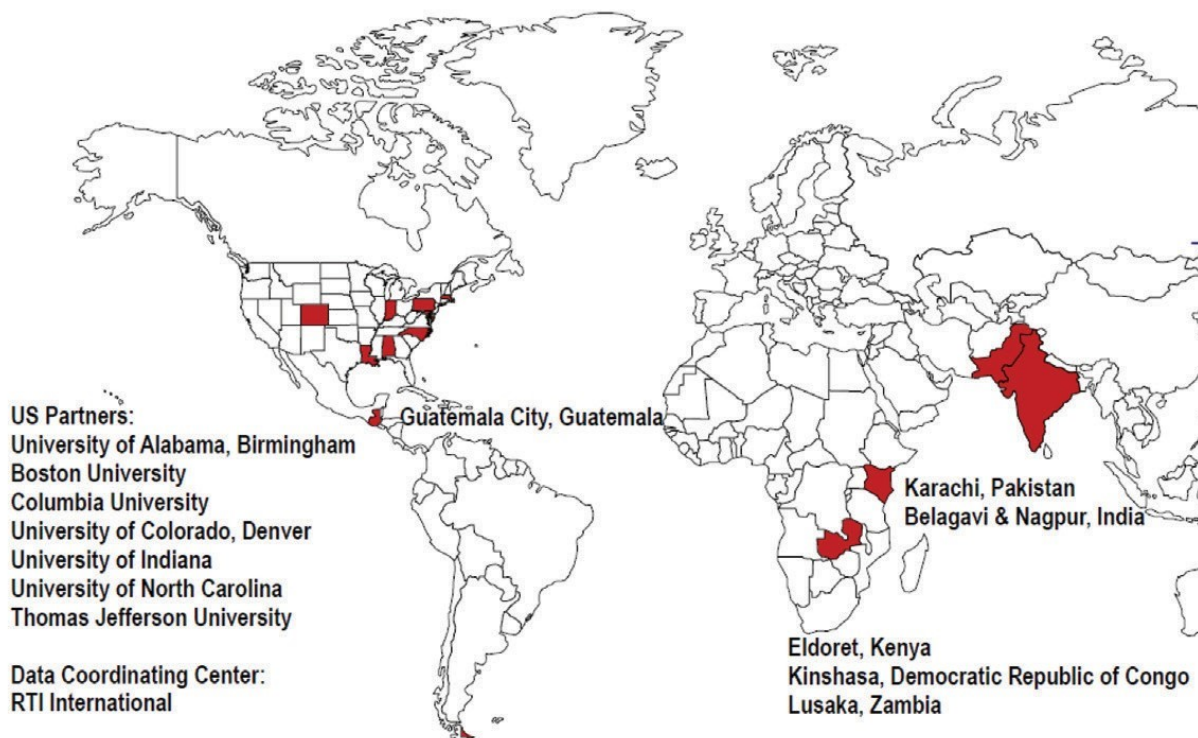
The under-5 mortality rate (U5MR) reflects the probability of a child (including an infant) dying before age 5, expressed per 1,000 live births based upon the current age specific mortality rates.^{2,3} While under 5 deaths are trending downward, the 2017 report with UN IGME child mortality estimates indicated a 2016 global U5MR of 41 deaths per 1,000 live births. However, the least developed countries had a U5MR of 68 compared to a U5MR of 6 for highly developed countries. The U5MR of 79 for Sub-Saharan African countries means that nearly 8 (or 7.9%) of 100 babies born live in the region die before their 5th birthday.³ Those of us in the US would consider most of these under 5 deaths to be unnecessary, preventable and treatable by means available in any developed country setting.⁴

Hemorrhage, hypertensive disorders and sepsis cause more than half of the maternal deaths worldwide. Certainly, lack of access to safe pregnancy termination services and safe/hygienic services in general affect the incidence of maternal mortality, as does lack of access to primary health care, including prenatal care.⁵ When accounting for under-5 deaths, the link to maternal health is clear. In 2016, the major causes of under-5 deaths identified in the 2017 UN IGME report, based upon provisional estimates of the WHO and the Maternal and Child Epidemiology Estimation Group, included preterm birth complications (18%), intrapartum related events (12%), and neonatal sepsis (7%). Other major causes of under-5 deaths included pneumonia (16%), diarrhea (8%), and malaria (5 per cent).³ Clearly, an integrated approach to maternal, neonatal, and child health (MNCH) is warranted. Interventions directed at ensuring healthier pregnancies and safer delivery can benefit pregnant women and mothers and have favorable effects on the offspring--certainly immediately at the time of delivery, most likely during early childhood, and quite possibly on a long-term basis as the interventions may impact survival and development.

The Global Network Mission

In 2001, the National Institutes of Health (NIH), specifically the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), in collaboration with the Bill & Melinda Gates Foundation, funded the Global Network for Women's and Children's Health Research. The objective of this initiative was to expand scientific knowledge, develop sustainable research infrastructures, and improve health outcomes for pregnant women and young children in developing countries. Since the initial selection of partnerships between a Principal Investigator based at a US institution and researchers based in a developing country, several Global Network re-competitions have occurred. Currently, 7 sites in the US are paired with research sites in Central America (Guatemala); Sub-Saharan Africa (the Democratic Republic of the Congo, Kenya and Zambia); and South Asia (two locations in India and one in Pakistan) [see Figure 2]. The funding mechanism is a cooperative agreement that requires substantial involvement of NICHD researchers and program officials in Global Network research-related activities. Additionally, RTI International serves as the Global Network Data Coordinating Center.

Figure 2. Current Global Network Membership



While single-site studies were conducted by the early partnerships, priority shifted to the funding of multi-site clinical trials addressing major causes of maternal and newborn morbidity and mortality in low and lower middle-income countries. Substantial US federal funds have flowed to partner institutions since inception of the Global Network, and the success in building solid research infrastructures at Global Network foreign sites has resulted in financial support for studies consistent with the research agenda characterized in Table 1. Financial resources have been provided by a variety of sources, including (but not limited to) other NIH agencies, governmental and non-governmental organizations of other countries, the World Health

Organization, private foundations, health professional organizations, and for-profit businesses supporting research initiatives.

Table 1. Global Network Research Agenda

Maternal Issues	Postpartum Hemorrhage Hypertensive Disorders of Pregnancy Maternal Nutrition
Newborn Issues	Birth Asphyxia Preterm Birth Infant Neurodevelopment
Maternal and Newborn Issues	Emergency Care Neonatal Care

Highlights of Women’s and Children’s Health Research Implemented by Global Network Partnerships

This section discusses a selection of the many studies carried out by Global Network sites as well as women’s and children’s health research unique to the partnership with which three authors of this editorial are associated—i.e., the partnership between Thomas Jefferson University, Philadelphia and Jawaharlal Nehru Medical College (JNMC), Belagavi (also known as Belgaum), Karnataka, India. A Web site (<https://globalnetwork.azurewebsites.net/>) is maintained by RTI International that summarizes completed and active research carried out by partners under the sponsorship of the Global Network for Women’s and Children’s Research.

Maternal Newborn Health Registry (MNHR)

The Registry is a prospective, population-based observational study to quantify trends in pregnancy outcomes, including stillbirths and neonatal and maternal mortality rates, in geographically defined low-resource areas. It has operated since 2008, enrolling all pregnant women residing in defined study clusters and tracking birth outcomes through 6 weeks post-delivery. The average number of pregnant women enrolled each year by all participating Global Network research sites is more than 60,000 women. Thus, the MNHR Monthly Report prepared by RTI International in early January 2018 reflected more than 604,000 Registry records with delivery outcomes and more than 596,000 records with outcomes at 42 days post-delivery.⁶ Since birth and death registration systems are often deficient in developing countries, the MNHR has been an essential component of the Global Network, facilitating the evaluation of the impact of Global Network research and identifying the factors that support or impede improved maternal and perinatal outcomes.

Misoprostol and Other Uterotonics to Prevent Postpartum Hemorrhage

Initially, the National Institute of Child Health and Human Development (NICHD) selected ten partnerships for Global Network membership and funding. The Research Unit established in India in cooperation with Jawaharlal Nehru Medical College (JNMC) was designated *Site 8*; this numerical reference has been maintained although there presently are only 7 partnerships. The JNMC research team, under the leadership of the partnership’s Principal Investigator and his sponsoring institution (at the time, the University of Missouri-Kansas City), implemented the partnership’s first Global Network study within the Belgaum District of Karnataka. The study,

the first ever community-based randomized, placebo-controlled clinical trial of oral misoprostol, was designed to determine if administration of misoprostol after delivery could decrease postpartum hemorrhage (PPH), a leading cause of maternal death in developing countries. Prior to delivery, the Site 8 research team enrolled 1,620 pregnant women in the study. When the trial was implemented, almost all deliveries occurred in the home and many were assisted by traditional birth attendants. However, per the study protocol, an auxiliary nurse midwife (ANM) was called to the home when a subject was about to deliver. The ANM administered either 600 µg of misoprostol in tablet form or a placebo. Misoprostol was selected as the study drug because, unlike the preferred uterotonic used in hospitals (oxytocin), it did not require refrigeration and could be carried in the ANMs delivery bag and easily administered orally in the home setting. This trial resulted in nearly a 50% decrease in PPH and an 80% decrease in severe PPH.⁷ Study findings supporting the effectiveness of misoprostol for PPH reduction provided the critical evidence for the inclusion of misoprostol on the WHO Model List of Essential Medicines⁸ in 2011 as well as identification of misoprostol in a UN Commission on Life-Saving Commodities 2012 report, which stated that thousands of maternal lives could be saved if barriers to misoprostol use were removed.⁹ Site 8's misoprostol study has been referenced in seven systematic reviews per a PubMed sidebar notation for the trial's abstract.⁷ And importantly, the study stimulated registration and expansion of misoprostol use, at low-cost, for PPH prevention, and resulted in the design and use of a drape (the BRASSS-V drape) for measurement of blood loss following delivery.¹⁰ The drape was made available to public sector health facilities in Karnataka State, included in delivery kits, and used in subsequent PPH research in India and elsewhere.

Following publication of findings, the misoprostol trial led to implementation of other studies to reduce, if possible, the reported side effects of misoprostol (fever and shivering) and to compare different primary and secondary approaches for managing PPH. JNMC researchers conducted a subsequent misoprostol trial that found secondary prevention of PPH with misoprostol to be non-inferior to universal prophylaxis based on the primary outcome of postpartum hemoglobin and the finding that the rate of PPH and the need for patient transfer were no worse in secondary prevention clusters than in primary prevention clusters.¹¹ The JNMC research team also participated in a WHO-sponsored, multisite, randomized-controlled trial that concluded that the prophylactic administration of a uterotonic within 1 minute of birth of the baby is perhaps the most important of the three components of the active management of the third Stage labor.¹²

The quest to find an "ideal uterotonic" matching the efficacy of oxytocin and lacking the need for refrigeration continued as a WHO-sponsored randomized trial was conducted in partnership with Merck for Mothers and Ferring Pharmaceuticals. The study, involving a total of 12 countries, was designed to evaluate a new, proprietary uterotonic--a room-temperature stable (RTS) formulation of carbetocin.¹³ Notably, the Belagavi Research Unit led the trial in six centers spread across different regions of India and contributed nearly a quarter (or 7,100 subjects) of the total sample size of approximately 30,000 subjects. If the results of the study indicate that RTS carbetocin is a safe and effective alternative to oxytocin, and if this form of uterotonic can be produced and made available for those women that could benefit from its use, the study could have a substantial impact on the prevention of postpartum hemorrhage and maternal survival worldwide.

Community Level Interventions for Pre-Eclampsia

The JNMC research team became engaged in a series of studies collectively referred to as the Community Level Interventions for Pre-Eclampsia (CLIP) Trials that included a study to determine baseline rates of preeclampsia in Karnataka State,¹⁴ an assessment of community health worker knowledge and management of preeclampsia,¹⁵ and a community-based cluster randomized, controlled trial (RCT) to determine if a community-based package of care for women with hypertensive disorders of pregnancy can improve maternal and neonatal outcomes.¹⁶ The Site 8 Research Unit enrolled nearly 15,000 Karnataka State subjects in the RCT, which was implemented in India during the period of February 1, 2014 to October 31, 2016. Several successes identified by the JNMC research team and associated with the India RCT include:

- Registration of all eligible pregnancies
- Improved early detection of pregnancy hypertension
- Community health workers (ASHAs) demonstrated ability to task share
- Increased referral and timely intervention
- Safe community administration of MgSO₄ and methyl dopa
- Improved vertical integration of health system
- Continuous professional development activities
- Recognized benefit to the community

Data analysis was recently completed for the RCTs of all participating sites. Therefore, publications and dissemination meetings are planned to share study results.

CRADLE Trial

India and other countries with unacceptably high maternal mortality recognize the need for earlier detection and prompt treatment of pregnancy complications responsible for maternal deaths. The Microlife CRADLE is a semi-automated device that was used in the CLIP Trial for detection of hypertension. The device is now being tested in rural Africa and within India by the JNMC and King's College, London collaborative research team to further develop the device as an accurate and low-cost means to improve antenatal detection of pre-eclampsia as well as hypotension associated with postpartum hemorrhage and sepsis.¹⁷ Further adaptation of existing tools for blood pressure measurement will help ensure proper use by frontline health care providers working in communities and at first-level clinics. Wider use of dependable and easy-to-use devices in low and middle-income countries will increase the availability of blood pressure measurements and facilitate referrals of high-risk women to facilities capable of providing higher level care, thereby improving pregnancy outcomes for both the mother and infant.

The CRADLE Trial in India is co-funded by the United Kingdom's Medical Research Council and the Government of India, Department of Biotechnology. Notably, the India trial received the Newton Prize for excellent research and innovation. The Newton Prize is an annual £1 million fund designed to incentivize researchers and innovators to participate in the Newton Fund as

partners with the UK, and to work on the most important global challenges facing Newton Fund associated countries.

Maternal Nutrition

Among those concerned with maternal and child health, it is common to hear the phrase “*Healthy mothers, healthy babies.*” Thus, the Global Network partnership between the University of Colorado/Denver and Guatemala developed a trial to assess the benefits to the offspring of ensuring optimal maternal nutrition using micro and macro nutrient supplementation prior to conception compared to initiating the same supplementation beginning at 13 weeks of pregnancy and to providing pregnant women only standard of care without nutritional intervention; a second study phase is now active and designed to assess growth and development of offspring at various age intervals to 24 months. Four Global Network sites (Belagavi, India; Guatemala; the Democratic Republic of the Congo; and Pakistan) have been participating in this study funded by the Bill & Melinda Gates Foundation. Data collection for the maternal nutrition phase of the study is complete and currently being analyzed for the primary outcome of the study—infant length at birth. Not all infants born to mothers in one of the three study arms have yet reached 24 months of age; thus, the study is ongoing.

Studies Designed to Combat Asphyxia and to Help Babies Breathe

Between 2005 and 2008, the *First Breath Trial* used the World Health Organization’s *Essential Newborn Care* (ENC) program to train almost 4,000 birth attendants from 100 Global Network communities with more than 150 deliveries. To date, this is the largest trial for the training of community-based birth attendants, including traditional birth attendants, in neonatal resuscitation using bag and mask ventilation. Following ENC training, birth attendants participated in *Neonatal Resuscitation Program* (NRP) training in clusters randomized to this intervention (based upon the American Academy of Pediatrics’ training program). Although ENC training did not result in significant reduction from baseline in the rate of neonatal death from all causes in the 7 days after birth or in the rate of perinatal death, there was a significant reduction in the rate of stillbirth. Likewise, the additional training in the Neonatal Resuscitation Program failed to significantly affect the neonatal, perinatal, or stillbirth rates.¹⁸ However, when data for the Belagavi, India site was analyzed, this site demonstrated significant reduction in early neonatal mortality and in stillbirth and perinatal mortality rates.¹⁹

A sub-group of asphyxiated and resuscitated babies (from India, Pakistan and Zambia) were randomized to a parent-provided early developmental intervention (EDI) or a control group and compared with normal infants not requiring resuscitation at birth and randomized to the EDI or control group. At 12 months, there was no evidence of a significant difference between the resuscitated infants and the non-resuscitated infants based upon Mental Development Index (MDI) scores (using Bayley Scales of Infant Development-II) and other neurodevelopmental outcomes.²⁰ But importantly, assessments at 24 and 36 months provided evidence of a positive EDI effect regardless of whether children were exposed to birth asphyxia, preterm birth, or an essentially healthy birth, or different maternal age or education, child gender, or country.²¹

JNMC was one of the five sites selected by AAP for field testing the *Helping Babies Breathe* (HBB) curriculum. Subsequently, HBB was incorporated into the neonatal resuscitation training curriculum of the basic newborn care and resuscitation program of the Government of India called “Navjaat Shishu Suraksha Karyakram” (basic newborn care and resuscitation). Further,

JNMC and two other Global Network partnerships (Nagpur, India and Kenya) participated in a study known as *Evaluation of HELPING BABIES BREATHE in Belgaum, Kenya and Nagpur: Does Implementation of HELPING BABIES BREATHE Save Lives? Helping Babies Breathe (HBB) and Essential Newborn Care (ENC) trainings occurred in 71 facilities in the Global Network research areas. The pre-post evaluation study was designed to test the impact of HBB on perinatal mortality (fresh stillbirths or early neonatal deaths) among births >1500 grams. The trainings were not associated with consistent improvements in mortality among all neonates \geq 1500 grams; however, differential improvements in survival of infants <2500 grams occurred within the Site 8 (Belagavi) site.²² This study suggested the need for careful implementation of HBB training with attention to the target population, data collection, and ongoing quality monitoring activities. Since the conclusion of the Global Network HBB study in 2013, improvements have been made in the curriculum and the AAP issued *Helping Babies Breathe 2nd Edition*, which includes scientific updates, expanded educational advice, strengthened implementation guidance and new quality improvement resources. Qualitative and quantitative data generated by the Global Network HBB study and other related studies informed the 2nd edition updates.*

Studies Designed to Reduce Preterm Births

All research sites active in the Global Network in 2011 implemented the *Trial of the Use of Antenatal Corticosteroids in Developing Countries (ACT Trial)* between October 2011 and March 2014. The trial was designed as an 18-month, cluster randomized study but sites began and ended the study at variable times within the indicated period. The study's purpose was to assess the feasibility, effectiveness, and safety of a multifaceted intervention designed to increase the use of antenatal corticosteroids among women at risk for preterm birth at all levels of health care in low-income and middle-income countries. Although it was expected that the intervention would reduce neonatal mortality associated with prematurity, the study had both disappointing and unexpected results. A Network total of 2,520 infants <5th percentile birthweight (used as a proxy for preterm birth) from 51 intervention clusters and 2,258 such infants from 50 control clusters were assessed; despite increased use of antenatal corticosteroids in low-birthweight infants in the intervention group, neonatal mortality did not decrease in this group, and increased in the population overall; for every 1,000 women exposed to this strategy, an excess of 3·5 neonatal deaths occurred, and the risk of maternal infection increased.²³

Issuance of findings from the Global Network's ACT Trial resulted in questioning whether there was enough evidence to support antenatal corticosteroid use in the late preterm period and whether the results from other studies suggesting benefits of antenatal corticosteroids were generalizable to use in low-resource settings. Recognition that more research was needed led to a decision by the Bill & Melinda Gates Foundation to support two trials—*WHO ACTION-I and ACTION-II (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns) Trials*.²⁴ The Belagavi, Site 8 Research Unit is an implementing partner for both trials and serves as the coordinating center for three participating hospitals in India. ACTION-I aims to determine whether antenatal corticosteroids are safe and efficacious for women and newborns when given in hospitals in resource-limited settings to women with a live fetus/es at risk for imminent, early preterm birth (26 weeks 0 days - 33 weeks 6 days gestation). Besides the three hospitals in India, hospitals in Bangladesh, Kenya, Nigeria, and Pakistan are participating in ACTION-I. ACTION-II has the same objective of assessing safety and efficacy of antenatal corticosteroid but when

given in hospitals to women with a fetus/es at risk for imminent, preterm birth (34 weeks 0 days to 36 weeks 0 days gestation).

The Belagavi site also implemented a randomized placebo-controlled study, *Clindamycin to Reduce Preterm Birth in a Low Resource Setting*, which was funded by the Thrasher Research Fund to assess if pregnant women with high vaginal pH levels and treated with clindamycin were less likely to deliver preterm infants than pregnant women, also having high pH levels, who received a placebo. Publication of findings is pending for this study.

An ongoing Global Network study directed at the problem of preterm births is known as *Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN)*.²⁵ All 7 Global Network partnerships are participating in this study which will achieve a subject total of 11,920 nulliparous, pregnant women. Consenting subjects meeting eligibility criteria will be randomized and take a daily tablet of low-dose (81 mg) aspirin or a placebo beginning in the first trimester of pregnancy and continuing to 36 weeks gestation to determine if subjects taking aspirin are less likely to deliver a preterm infant than the control group of women taking a placebo. Recruitment for this study will be completed during Summer 2018 and results will be available mid-year 2019. If the study achieves the desired outcome of a 20% reduction in preterm births in the intervention group and if the intervention is proven safe and generally without serious side effects, then the study will provide the basis for a recommendation that low-dose aspirin be used to decrease the risk of preterm delivery among nulliparous pregnant women who are at higher risk for a preterm birth than multiparous women.

Emergency Obstetrics and Neonatal Care (EmONC) Trial

EmONC is a Global Network, multi-site trial that was implemented during 2008-2011 as a cluster randomized controlled trial to evaluate an intervention package, including community mobilization, to establish and sustain mechanisms of transport and payment and to foster client-oriented emergency obstetrical and neonatal care. It was hypothesized that this complex study would reduce perinatal and neonatal mortality rates within participating Global Network research areas. However, EmONC did not achieve detectable impact on pregnancy outcomes and participating researchers concluded that achieving improvement in such outcomes will require substantially more infrastructure for obstetric and neonatal care than was available at facilities in study area.²⁶ However, a separate analysis of Site 8's data was completed. Compared to data for a baseline period, JNMC's data for the last 6 months of the study indicated that the neonatal mortality rate was lower in the intervention vs. control clusters as was the perinatal mortality rate. However, the differences associated with these rates did not achieve statistical significance.²⁷ Nevertheless, the findings associated with Site 8's findings suggest that longer-term implementation of the intervention package might have resulted in statistically significant improvement in outcomes.

Conclusions

Global Network partnerships have been very productive during nearly two decades of research designed to decrease adverse pregnancy outcomes and improve the health status of mothers, infants and young children. Not all studies have achieved the desired primary and secondary outcomes; however, every study has increased knowledge and an understanding about what works and what doesn't in low-resource settings. Often studies have suggested new hypotheses and stimulated additional research.

The opportunity to implement MCH research has provided the stimulus for Global Network research units, which are geographically based within the foreign partner's university or research institute, to develop strong alliances with local health care providers and stakeholders and to engage community participants in the initiatives to improve women's and children's health. Such interactions frequently result in benefits (e.g., improved health practices) beyond direct benefits resulting from the studies conducted. Further, the research infrastructures at the foreign sites have developed and grown over time, and the research teams based at these sites are well-regarded for the research skills and knowledge inherent in team members.

The Maternal Newborn Health Registry has been valuable for monitoring trends and causes of mortality, and it has been the source for numerous secondary analyses and publication of findings in journals focused on global health. The Registry has also facilitated the identification of priorities for future research. For example, Registry data was recently used to assess the prevalence and seriousness of anemia during pregnancy and to associate this problem with poorer pregnancy outcomes. As a result, the site 8 partnership is designing research to test a new treatment approach for reducing maternal anemia; and other Network sites may participate assuming resources are identified for study implementation. While the Global Network has a fair and equitable process for prioritizing studies for use of federal funds funneled through NIH (and specifically NICHD, the primary institute), it is likely that other financial sponsors will offset a substantial percentage of the research costs of future studies designed collaboratively by participating Network sites; and this is consistent with Global Network policy and intent.

No Network partnership has yet ended the MCH disparities discussed in this article. However, indicators of the burden of MCH mortality—e.g., MMRs and U5MR, are trending downward worldwide and generally in the countries participating in the Global Network for Women's and Children's Health Research. Likely, the research initiatives of Global Network partnerships have positively influenced the trends by advancing practical knowledge and linking the acquired knowledge to health care delivery and public health practice. For this reason, the authors of this article are optimistic that continuation of the Global Network will yield even greater future success.

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