### **Neonatology**

Neonatology 2018;114:93–102 DOI: 10.1159/000488310 Received: March 5, 2018 Accepted: March 11, 2018 Published online: May 16, 2018

# Opportunities and Challenges in Global Perinatal Research

Jessica Duby<sup>a</sup> Renee Sharma<sup>b</sup> Zulfigar A. Bhutta<sup>b</sup>

<sup>a</sup>Division of Neonatology, University of Toronto, Toronto, ON, Canada; <sup>b</sup>Centre for Global Child Health, The Hospital for Sick Children, Toronto, ON, Canada

#### Keywords

Global health  $\cdot$  Neonatal mortality  $\cdot$  Stillbirth  $\cdot$  Research prioritization

#### **Abstract**

**Background:** The global plight of stillbirths and neonatal mortality is concentrated in low- and middle-income countries. The ambitious targets introduced by the World Health Organization in the Every Newborn Action Plan demand a commitment to research that promotes equitable perinatal outcomes. Objectives: The aim of this review was to understand the opportunities for global perinatal research and the accompanying challenges. Methods: We conducted a literature search to identify research prioritization exercises from 2014 to 2018 pertaining to global perinatal health. The top 50 questions with the highest research prioritization scores were extracted and analyzed. Results: The greatest priorities centered on community-based, implementation research targeting major causes of stillbirth and neonatal mortality in low-resource settings. The priorities are saddled with prerequisite conditions, design obstacles, and ethical considerations that require attention. Conclusions: While the challenges are undeniable, the need to make the perinatal period healthier for babies worldwide has never been clearer.

© 2018 S. Karger AG, Basel

#### Introduction

Every year 2.6 million newborns die [1], with an additional 2.6 million stillbirths occurring annually [2]. While progress has been made in reducing the global neonatal mortality and the stillbirth rate, the pace has been much slower than improvements in childhood survival [1]. Because of this disparity in progress, neonatal deaths now account for nearly half of all deaths under the age of 5 years.

Neonatal deaths and stillbirths are not evenly distributed across the globe. The majority of neonatal deaths and stillbirths occur in low- and middle-income countries (LMICs), with half of all neonatal deaths concentrated in just 5 countries: India, Pakistan, Nigeria, the Democratic Republic of the Congo, and Ethiopia. Even within countries that have a high neonatal mortality rate, poor perinatal outcomes disproportionately affect families with certain risk factors, such as relative poverty, low maternal education, and rural residence [3, 4].

To combat the tide of neonatal deaths and stillbirths, the World Health Organization and UNICEF endorsed

This paper is part of the special series "Research Methods in Neonatal Medicine" (Guest Editor: Bill McGuire, York, UK).

the Every Newborn Action Plan (ENAP) in 2014 [5]. ENAP commits to the ambitious goals of reducing the global neonatal mortality rate to 10 deaths per 1,000 live births and the global stillbirth rate to 10 stillbirths per 1,000 total births by 2035. To put these goals into perspective, it is important to remember that countries like Iceland already register only 1 neonatal death for every 1,000 live births, while countries like Pakistan currently have 46 deaths for every 1,000 live births [1]. ENAP targets, therefore, can be understood as a call for equity in perinatal care and perinatal outcomes.

#### **Prioritizing Research Agendas**

Global health research plays a vital role in attaining the goals set forth by ENAP. However, the landscape of research ideas to improve global neonatal health is as diverse as the numerous public and private sector stakeholders that partake in such research [6]. As a result, there has been a push in the past decade to prioritize global health research aims using standardized and transparent methodologies, the most ubiquitous being the Child Health and Nutrition Research Initiative (CHNRI) exercise [7].

The CHNRI method is a multistep process of democratic and transparent research prioritization [8]. First, a small management team defines the context for research priorities, including the health issue, the affected population, the timeframe for investment returns, the type of investment, and the expected return from investment. Second, the management team crowdsources research ideas from technical experts using the proposed context. To classify the myriad of potential research idea, the CHNRI uses a "4D framework," in which research questions are classified as either "description," "discovery," "development," or "delivery" questions. Next, researchers score all proposed research questions against priority-setting criteria on a scale of 0-100. The predetermined criteria often include answerability, effectiveness, deliverability, reduction of disease burden, and impact on equity. In the final step, external stakeholders can set different values for each of the priority-setting criteria based on the needs of the community to produce an overall research prioritization score (RPS).

To understand the research priorities that can facilitate ENAP targets of reducing stillbirths and neonatal mortality, we undertook a literature review of relevant CHNRI exercises. Special attention was given to priorities

with a high score of impacting equity given that ENAP focuses on equitable perinatal outcomes. An analysis of these research priorities will lead to an understanding of both the opportunities and challenges that face the global perinatal research community.

#### Methods

Perinatal CHNRI exercises were identified in Medline and EM-BASE using the following keyword search strategy: CHNRI OR "Child Health and Nutrition Research Initiative" OR "research priorit\*" AND (perinat\* OR maternat\* OR neonat\* OR newborn\* OR stillb\*). The publication year was limited to 2014–2018 inclusive, given that ENAP targets were formerly endorsed in 2014. The top 50 research questions with an RPS greater than or equal to 80 were extracted and analyzed.

#### **Summary of Findings**

Seven CHNRI exercises related to global perinatal health were identified [9–15]. Five of the exercises addressed comprehensive perinatal research priorities [10–14]. One exercise focused exclusively on complex humanitarian emergencies [9], while another exercise focused exclusively on integrating early childhood development with other perinatal research priorities [15].

Altogether, 1,700 research priorities were proposed and subsequently paired down to 675 scored questions [9–15]. The number of scored research questions in each CHNRI exercise ranged from 30 to 205 questions. The number of participants involved, either through question submission or question scoring, ranged from 24 to 339 stakeholders in each study.

The RPS for the top 50 questions ranged from 80 to 95 (Table 1). Five of the CHNRI exercises incorporated impact on equity scores which ranged from 66 to 93 for the included questions [9, 10, 13–15].

#### What Types of Research Are a Priority?

Thirty-five of the eligible CHNRI questions (70%) can be classified as "delivery" ideas that study how best to implement existing health interventions. Nine questions (18%) are "development" projects which focus on improving existing health interventions to increase their efficacy or suitability for a specific population. Six questions (12%) were epidemiological in nature and therefore fell into the "description" category. None of the

**Table 1.** Top 50 global perinatal research priorities

Research priority	RPS	Equity score	CHNRI		
Evaluate the effectiveness and costs of strategies to improve the quality and utilization of maternity services (e.g., maternity waiting homes, improved communication via mobile phones, community awareness strategies) to improve early detection and management of antenatal and intrapartum complications	95.00	90.00	Souza [10], 2014		
Develop and evaluate strategies for locally appropriate transport, communication, and referral systems for obstetric and newborn emergencies	94.00	93.00	Souza [10], 2014		
Evaluate the effectiveness and cost of strategies to prevent, detect, and treat causes of anemia in pregnancy (e.g., malaria, occult bleeding disorders, nutritional deficiencies)	92.00	Souza [10], 2014			
How can interventions and packages to reduce neonatal mortality be expanded to include ECD and stimulation interventions?	93.00	Sharma [15], 2017			
Evaluate the effectiveness and cost of training interventions for frontline healthcare workers (paramedics, doctors, CHWs, midwives, nurses) to diagnose, manage, and refer women with obstetric hemorrhage	90.00	Souza [10], 2014			
Evaluate the effectiveness and cost of a package of community-level interventions for preterm babies (e.g., implementing and providing guidelines for kangaroo mother care, home visits by CHWs, infection prevention strategies)	92.00	94.00	Souza [10], 2014		
How can sensory stimulation best be integrated with nutrition interventions for small for gestational age infants to significantly improve their developmental outcomes over the long-term?	90.04	90.00	Sharma [15], 2017		
Can a simplified neonatal resuscitation program delivered by trained health workers reduce neonatal deaths due to perinatal asphyxia?	90.00	92.00	Yoshida [13], 2016		
Evaluate the effectiveness and cost of training frontline healthcare workers, including nurses, midwives, and CHWs, to detect and treat neonatal sepsis (or to provide prereferral treatment only)	92.00	Souza [10], 2014			
Evaluate the effectiveness of midwife-led care when compared to other models of care across various settings, particularly on rates of fetal and infant death, preterm birth, and low birthweight	89.80	-	Kennedy [12], 2016		
Determine which indicators are most valuable in assessing quality maternal and newborn care 89.70 -					
Identify and describe aspects of care that optimize, and those that disturb, the biological/ physiological processes for healthy childbearing women and fetuses/newborn infants and those who experience complications					
Evaluate the effectiveness of midwifery care in providing culturally appropriate information, education, and health promotion (e.g., nutrition, substance use, domestic violence, and mental health)					
Identify and describe enabling factors from examples of successful implementation of evidence-based maternal and newborn care across a variety of settings	89.00	-,	Kennedy [12], 2016		
Describe and evaluate the effectiveness of midwives working with others (such as health professionals, CHWs, and traditional birth attendants) in achieving quality maternal and newborn care including, but not limited to: timely transfer of women to appropriate level/site of care; management of emergency situations; maximal use of skills and competencies; shared decision-making and accountability					
Assess the views and preferences of women and families across a variety of settings about their experiences of maternal and newborn care including, but not limited to, care providers and sites of care (e.g., place of birth, antenatal care)					
Develop setting-specific benchmarks to assess measurable progress on implementation of quality maternal and newborn care	88.30	_	Kennedy [12], 2016		

**Table 1** (continued)

Research priority	RPS	Equity score	CHNRI			
How can the health worker's skills in preventing and managing asphyxia be scaled up?	88.00	86.00	Yoshida [13], 2016			
Evaluate the effectiveness and cost of a package of interventions for the prevention, early 88.00 80.00 detection, and treatment of puerperal sepsis (e.g., sterile birth kits, access to antibiotics, automated thermometers)						
Identify and describe aspects of maternal and newborn care that strengthen or weaken women's psychosocial wellbeing and mental health	88.00	-	Kennedy [12], 2016			
Assess whether new measures of morbidity are needed to more effectively evaluate outcomes of maternal and newborn care						
Evaluate the effectiveness and cost of training interventions for skilled birth attendants to gain and 88.00 82.00 maintain competence in the management of obstructed labor, and assisted delivery techniques						
Evaluate the effectiveness and cost of training skilled birth attendants in intrapartum fetal monitoring 88.00 78.00 and neonatal resuscitation for reducing stillbirths and deaths/disability due to perinatal asphyxia						
Evaluate the effectiveness and cost of a package of mobile service interventions delivered at the community level, including mobile clinics and home-based care, on maternal and perinatal health outcomes 92.00						
Develop and evaluate the effectiveness and cost of strategies to improve access of women with obstetric hemorrhage to blood and blood replacement products in settings without transport capabilities  87.00 87.00						
Develop and evaluate the effectiveness of strategies to increase access of women to misoprostol at the community level where oxytocin is not available/feasible, by dispensing it antenatally as part of a birthing kit, or at the time of delivery via the attending CHW or nurse/midwife, to prevent and treat postpartum hemorrhage						
Can simple clinical algorithms used by the CHW identify and refer neonates with signs of infection and consequently reduce newborn mortality?	86.00	88.00	Yoshida [13], 2016			
How can exclusive breastfeeding in low-resource contexts be promoted to reduce neonatal 85.00 86.00 infections and mortality?						
Develop and evaluate strategies to increase appropriate use of the partograph, including decision- 85.00 76.00 making and action, to improve maternal and perinatal health outcomes						
Assess the effectiveness and cost of implementing a package of screening and treating syphilis and 85.00 82.00 HIV in women of reproductive age to improve maternal and perinatal health outcomes						
What strategies are effective in increasing demand for and use of skilled attendance? 84.60 85.20						
How can smart phone integrated community case management apps be implemented to accurately identify newborns and children under 5 years old requiring referral from their communities to a health facility?						
What is the feasibility, effectiveness, and cost of approaches to increase coverage of clean delivery 84.10 90.80 practices in facilities and in homes?						
What is the additional burden of neonatal mortality in different emergency situations (e.g., 83.30 85.80 conflict, acute vs. protracted, natural disaster)?						
Develop and evaluate a health systems package for effective task shifting for the management of 83.00 87.00 obstetric emergencies, including protocols, supervisory systems, and metrics						
Can simplified pregnancy surveillance at the community level be used to measure neonatal mortality?	83.00	86.70	Morof [9], 2014			

Table 1 (continued)

Research priority	RPS	Equity score	CHNRI
Develop and evaluate the effectiveness and cost of learning tools to gain and maintain competence in performing simple obstetrics procedures (e.g., e-learning, simulation exercises, mannequins) for frontline healthcare providers to improve maternal and perinatal health outcomes	83.00	82.00	Souza [10], 2014
Can simplified verbal autopsy tools be adapted for use in emergency settings to capture the main causes of neonatal mortality?	82.80	87.20	Morof [9], 2014
What is the feasibility, impact, and costs of adding newborn care (including PNS, home visits, treatment of infection, and caring for the newborn and children in the community) to the iCCM package?	82.74	-	Wazny [11], 2014
Develop and validate strategies to identify preterm babies at the community level by CHWs and family members	82.60	85.50	Morof [9], 2014
How can the administration of injectable antibiotics at home and first level facilities to newborns with signs of sepsis be scaled up to reduce neonatal mortality?	82.00	84.00	Yoshida [13], 2016
Which risk factors for neonatal sepsis can be identified in emergency settings and can these mothers and babies be given extra support? e.g., low birth weight, short gestational age, unhygienic delivery, skin and umbilical cord care, hypothermia, poor feeding practices	81.80	86.80	Morof [9], 2014
Can pregnancy surveillance at the community level contribute to increased uptake of facility-based delivery?	81.60	79.30	Morof [9], 2014
Can a standardized newborn kit (simple bag/mask, clean blades/knives, and cord clamps) with appropriate education reduce newborn mortality and morbidity?	81.54	90.00	Sharma [14], 2017
What is the feasibility, effectiveness, and cost of different approaches to increase the coverage of syphilis screening in pregnancy, treatment, and partner treatment?	81.40	81.40	Morof [9], 2014
What is the feasibility, effectiveness, and cost of different approaches to promote handwashing among caregivers?	80.70	Morof [9], 2014	
What is the incidence of neonatal sepsis in emergency settings?	80.30	86.10	Morof [9], 2014
Can community-based initiation of kangaroo mother care reduce neonatal mortality of clinically stable preterm and low birth weight babies?	77.00	Yoshida [13], 2016	
How can facility-based initiation of kangaroo mother care or continuous skin-to-skin contact be scaled up?	80.00	81.00	Yoshida [13], 2016
How can chlorhexidine application to the cord be scaled up in facility births and in low neonatal mortality rate settings to reduce neonatal infections and neonatal mortality?	80.00	81.00	Yoshida [13], 2016

questions proposed "discovery" studies that would result in the generation of completely new health interventions.

It is no surprise that the majority of the research questions focus on how to deliver effective interventions. The opportunities for delivery research in the realm of perinatal health are abundant. A recent review for the Every Newborn series in *The Lancet* found more than 50 evidence-based interventions in the domains of: (1) in-

tegrated antenatal care; (2) quality care at birth; (3) essential newborn care, and (4) care of small and ill newborns, which have already been proven to reduce maternal mortality, stillbirths, and neonatal mortality [16]. If delivery of these interventions improved to 90% coverage, over 3 million lives could be saved at a cost of USD 1.15 per person.

#### Where Should the Research Occur?

Thirteen questions (26%) specifically focus on community-based research ideas. An additional 5 questions (10%) target the link between the community and health facilities.

Research ideas that focus on community-based delivery platforms have become a necessity given the paucity of highly skilled health workers and inaccessibility of medical facilities in LMICs [17]. Community health workers (CHWs), who are local workers with limited, targeted training on basic maternal and newborn care, have demonstrated the capacity to change neonatal outcomes if given the appropriate support [18]. Interventions, such as clean delivery kits, tetanus immunization, skin-to-skin care, and breastfeeding support, can be bundled into packages and delivered by CHWs. Such community-based packages have been shown to reduce stillbirths by 19% and neonatal mortality by 25% [19].

#### What Problems Should the Research Address?

Thirty-one (62%) of the research questions targeted one or more specific health conditions. Nineteen (38%) of the proposals concerned either birth asphyxia, prematurity, and/or infection. These 3 problems are known to be the leading causes of neonatal mortality and account for more than 80% of all neonatal deaths [20].

Eight questions (16%) dealt with obstetrical emergencies. Given that half of all stillbirths occur during the process of labor [2], ideas targeting obstetrical emergencies can be understood to facilitate a reduction in stillbirths.

#### What Research Prerequisites Need to Be Considered?

Researching how to deliver interventions that save newborn lives in low-resource settings is not without its challenges. Table 2 lists sample interventions from the eligible CHNRI along with specific prerequisites that should be met prior to engaging in implementation studies. A few challenges common to all of the eligible research questions deserve more detailed explanation, as outlined below.

Confirming Efficacy and Effectiveness in Low-Resource Settings

Prior to researching how a certain intervention can be delivered, it is crucial to confirm that the intervention

benefits the specific population of interest. Many health interventions implemented in LMICs have been adapted from therapies designed in high-income countries. A different context may lead to differing results. Low-resource settings require their own efficacy trials and effectiveness trials prior to establishing an intervention as recommended.

The importance of this prerequisite has recently been highlighted with the controversy surrounding the use of antenatal corticosteroids in LMICs. Antenatal corticosteroids have significantly reduced mortality and morbidities associated with preterm birth in high-income countries. In 2013, the WHO added dexamethasone for women at risk of preterm delivery to its list of essential medicine despite the fact that all trials up to that point had occurred only in high-income countries [21]. In 2015, Althabe et al. [22] published results from the Antenatal Corticosteroids Trial (ACT), the first cluster randomized controlled trial to study the effects of antenatal corticosteroids for women at risk of preterm delivery in 6 LMICs. Shockingly, the study showed a statistical increase in maternal infection, neonatal mortality, and stillbirths in the intervention cluster.

The reason for the poor results in low-resource settings is likely multifactorial but may be related to the inability to accurately date gestational age, higher level of baseline maternal and neonatal infection, and less skilled obstetrical care in LMICs. Such contextual considerations may demand modification of how this therapy is used across the globe [23]. As a result of ACT, the WHO in partnership with the Bill and Melinda Gates Foundation has announced a multicountry double-blind place-bo-controlled randomized controlled trial to determine whether antenatal corticosteroids are safe and efficacious when prescribed in facilities in low-resource settings [24].

#### Accurate Outcome Measurement

The study of any health intervention demands the ability to measure the change in relevant outcomes. For implementation research aimed at reducing the stillbirth rate or neonatal mortality rate, a basic count of all births and all deaths during the first month of life in the population of interest is a prerequisite. Nevertheless, the countries with the highest neonatal mortality and morbidity have the poorest vital registration coverage [20].

Currently, most high-burden countries rely on household survey data collected every 2–5 years to measure births and deaths. Given the time-lag and accuracy concerns, this methodology is less than ideal from a research

**Table 2.** Prerequisites for sample health interventions

Health intervention		Prerequisites
Emergency obstetric care	1. 2. 3.	Understand how mobile technology can facilitate emergency preparedness  Develop protocols for identifying and task shifting emergency obstetric care  Develop locally appropriate referral and transport systems
Clean birth practices at home	1. 2. 3.	Ensure early distribution of supplies and birth preparation Develop accountable cohort of skilled birth attendants Understand how clean birth practices can be incorporated into local cultural birth practices
Neonatal resuscitation at home	1. 2. 3. 4.	Establish accurate pregnancy surveillance Determine the minimum criteria for CHWs to be competent in neonatal resuscitation Train and support CHWs Develop a referral system for postresuscitative care
Kangaroo mother care (KMC) for preterm infants		
Community-based antibiotics for neonatal sepsis	1. 2. 3.	Map communities with and without access to healthcare facilities Understand local care-seeking behavior and openness to referral Study whether CHWs are equipped with the time and resources to diagnosis and treat suspected neonatal sepsis

perspective. An ENAP objective is to count every newborn with the ultimate goal of establishing a minimum perinatal dataset that allows for the comparison of consistent outcome metrics across high-burden regions [5].

More than 70% of the included CHNRI research ideas target specific health conditions which require the ability to measure cause-of-death. In low-resource settings, the majority of stillbirths and neonatal deaths occur at home. Without medical certification, defining cause-of-death becomes an additional obstacle. For the past decade, the WHO verbal autopsy tool, a lengthy, structured interview with the next of kin, has become the primary method for ascertaining cause-of-death [25]. When compared to hospital data, verbal autopsy has been shown to have a specificity above 90% and a sensitivity greater than 75% for the top 3 causes of neonatal death [26]. Therefore, any implementation research aimed at reducing a specific cause-of-death must allocate sufficient resources and time to both collect and interpret verbal autopsies.

#### Ensuring the Ability to Scale-Up

Scaling-up the implementation of health interventions remains the greatest challenge for delivery research. To

scale-up an effective intervention, stakeholders must be engaged, knowledge must be disseminated, and barriers must be found and addressed. These steps are all the more complicated in LMICs where cultural practices are diverse, infrastructure is underdeveloped, and resources are limited.

The challenge of scale-up is currently being played out with community-based management of neonatal infections. Researchers have developed a simplified antibiotic regimen for suspected neonatal sepsis that can be delivered in the home or outpatient setting when hospital referral is not possible. Randomized trials of ill neonates in sub-Saharan Africa and South Asia have demonstrated similar outcomes between these regimens and the standard combination of parental penicillin/ampicillin with gentamicin [27–29]. As a result, in 2015, the WHO published guidelines for how CHWs can identify and treat possible serious bacterial infections in neonates with amoxicillin and gentamicin in the community [30].

However, the ability to train large swaths of CHWs, adapt to local conditions, and provide adequate coverage of this therapy in LMICs remains uncertain. A recent

cluster randomized controlled trial in rural Pakistan suggested that busy public sector CHWs may not be able to cope with the additional duties of diagnosing and treating infections [31]. Therefore, the WHO in collaboration with multiple other stakeholders has designed a multicountry trial to study the implementation, monitoring, and evaluation of its 2015 guidelines [32]. This study will be essential in deconstructing the barriers to sustained coverage of community-based management for neonatal infections

## **Ethical Considerations for Global Perinatal Health Research**

Perinatal health research in LMICs raises unique ethical challenges that may not be present with research in high-income countries [33]. Since 1982, the Council for International Organizations for Medical Sciences (CIOMS), under the auspices of the WHO and UNESCO, has published internationally vetted guidelines for ethical research [34]. The guidelines, most recently updated in 2016, pay particular attention to the ethical issues of research in LMICs.

The controversy surrounding HIV treatment trials in low-resource countries highlights the unique ethical issues facing global health research. At the end of the 20th century, a variety of interventions to prevent perinatal HIV transmission were studied in comparison to control groups that were denied any treatment, despite the proven effectiveness of zidovudine [35]. International organizations and high-income countries sponsoring these placebo-controlled trials defended their decision to withhold treatment from women in the control arms by arguing that the zidovudine regimen was not a standard-of-care in low-income countries.

Yet, it was obvious that similar trials would never have stood ethical muster in high-income countries. The double standard in low- versus high-income countries raised outcries over postcolonial exploitation and has changed the global health community's approach to research ethics [36]. While interventions must be tailored to the local context, lack of access to an effective intervention is no longer sufficient justification for designing placebo-controlled trials [34].

Addressed for the first time in the 2016 CIOMS guidelines is the need for community engagement in the design and implementation of research in LMICs. While many LMICs have started to build their own research agendas, the vast majority of global health research remains funded and spearheaded by governments or organizations based in high-income countries [37]. This postcolonial imbalance necessitates the participation of local communities both to ensure that the research is responsive to the community's needs and to guarantee respect for the community norms [33]. Community engagement is especially important in the planning and execution of informed consent so that the process is grounded in participants' understanding rather than the legal protection of the researchers [38].

#### Conclusion

Engaging in global perinatal health research is essential for reducing stillbirths and neonatal deaths. Research in LMICs must be prioritized given the unequitable distribution of preventable stillbirths and neonatal deaths across the globe. However, research in low-resource settings comes with unique opportunities and challenges that need to be addressed. Prior to engaging in perinatal health research in LMICs, investigators should consider the following questions:

- How does the proposed research promote equity in perinatal health outcomes?
- Will the proposed research align with established CHNRI research priorities?
- Does the proposed research consider the unique context of low-resource settings?
- Are the outcomes clear and measurable in low-resource settings?
- Will the results be generalizable across low-resource settings?
- Does the proposed research meet international ethical standards?

By addressing this checklist, researchers have the potential to meet the ambitious goals of ENAP and improve the lives of newborns across the globe.

#### **Disclosure Statement**

None of the authors have a conflict of interest to declare for the purposes of this article.

#### References

- 1 UN IGME: Levels and Trends in Child Mortality. New York, UNICEF, WHO, The World Bank, United Nations, 2017.
- 2 Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Frøen JF, Qureshi ZU, Calderwood C, Shiekh S, Jassir FB, You D, McClure EM, Mathai M, Cousens S: Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;387:587–603.
- 3 McKinnon B, Harper S, Kaufman JS, Bergevin Y: Socioeconomic inequality in neonatal mortality in countries of low and middle income: a multicountry analysis. Lancet Glob Health 2014;2:e165–e173.
- 4 Helova A, Hearld KR, Budhwani H: Associates of neonatal, infant and child mortality in the Islamic Republic of Pakistan: a multilevel analysis using the 2012–2013 demographic and health surveys. Matern Child Health J 2017;21:367–375.
- 5 WHO, UNICEF: Every Newborn: An Action Plan to End Preventable Deaths. Geneva, WHO. 2014.
- 6 Rudan I, Sridhar D: Structure, function and five basic needs of the global health research system. J Glob Health 2016;6:010505.
- 7 Yoshida S: Approaches, tools and methods used for setting priorities in health research in the 21st century. J Glob Health 2016;6:010507.
- 8 Rudan I, Gibson JL, Ameratunga S, El Arifeen S, Bhutta ZA, Black M, Black RE, Brown KH, Campbell H, Carneiro I, Chan KY, Chandramohan D, Chopra M, Cousens S, Darmstadt GL, Meeks Gardner J, Hess SY, Hyder AA, Kapiriri L, Kosek M, Lanata CF, Lansang MA, Lawn J, Tomlinson M, Tsai AC, Webster J; Child Health and Nutrition Initiative: Setting priorities in global child health research investments: guidelines for implementation of CHNRI method. Croat Med J 2008;49:720– 733.
- 9 Morof DF, Kerber K, Tomczyk B, Lawn J, Blanton C, Sami S, Amsalu R: Neonatal survival in complex humanitarian emergencies: setting an evidence-based research agenda. Confl Health 2014;8:8.
- 10 Souza JP, Widmer M, Gülmezoglu AM, Lawrie TA, Adejuyigbe EA, Carroli G, Crowther C, Currie SM, Dowswell T, Hofmeyr J, Lavender T, Lawn J, Mader S, Martinez FE, Mugerwa K, Qureshi Z, Silvestre MA, Soltani H, Torloni MR, Tsigas EZ, Vowles Z, Ouedraogo L, Serruya S, Al-Raiby J, Awin N, Obara H, Mathai M, Bahl R, Martines J, Ganatra B, Phillips SJ, Johnson BR, Vogel JP, Oladapo OT, Temmerman M: Maternal and perinatal health research priorities beyond 2015: an international survey and prioritization exercise. Reprod Health 2014;11:61.

- 11 Wazny K, Sadruddin S, Zipursky A, Hamer DH, Jacobs T, Kallander K, Pagnoni F, Peterson S, Qazi S, Raharison S, Ross K, Young M, Marsh DR: Setting global research priorities for integrated community case management (iCCM): results from a CHNRI (Child Health and Nutrition Research Initiative) exercise. J Glob Health 2014;4:020413.
- 12 Kennedy HP, Yoshida S, Costello A, Declercq E, Dias MA, Duff E, Gherissi A, Kaufman K, McConville F, McFadden A, Michel-Schuldt M, Moyo NT, Schuiling K, Speciale AM, Renfrew MJ: Asking different questions: research priorities to improve the quality of care for every woman, every child. Lancet Glob Health 2016;4:e777–e779.
- 13 Yoshida S, Martines J, Lawn JE, Wall S, Souza JP, Rudan I, et al: Setting research priorities to improve global newborn health and prevent stillbirths by 2025. J Glob Health 2016;6: 010508
- 14 Sharma R, Buccioni M, Gaffey MF, Mansoor O, Scott H, Bhutta ZA; Canadian Expert Group on Maternal, Newborn, Child and Adolescent Health: Setting an implementation research agenda for Canadian investments in global maternal, newborn, child and adolescent health: a research prioritization exercise. CMAJ Open 2017;5:E82–E89.
- 15 Sharma R, Gaffey MF, Alderman H, Bassani DG, Bogard K, Darmstadt GL, Das JK, de Graft-Johnson JE, Hamadani JD, Horton S, Huicho L, Hussein J, Lye S, Pérez-Escamilla R, Proulx K, Marfo K, Mathews-Hanna V, Mclean MS, Rahman A, Silver KL, Singla DR, Webb P, Bhutta ZA: Prioritizing research for integrated implementation of early childhood development and maternal, newborn, child and adolescent health and nutrition platforms. J Glob Health 2017;7:011002.
- 16 Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, Sankar MJ, Sankar JM, Blencowe H, Rizvi A, Chou VB, Walker N; Lancet Newborn Interventions Review Group, Lancet Every Newborn Study Group: Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? Lancet 2014;384:347–370.
- 17 Haines A, Sanders D, Lehmann U, Rowe AK, Lawn JE, Jan S, Walker DG, Bhutta Z: Achieving child survival goals: potential contribution of community health workers. Lancet 2007;369:2121–2131.
- 18 Bhutta Z, Lassi Z, Pariyo G, Huicho L: Global Experience of Community Health Workers for Delivery of Health Related Millennium Development Goals: A Systematic Review, Country Case Studies, and Recommendations for Integration into National Health Systems. Geneva, WHO Global Health Workforce Alliance, 2010.

- 19 Lassi ZS, Bhutta ZA: Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. Cochrane Database Syst Rev 2015;CD007754.
- 20 Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, Mathers C, Cousens SN; Lancet Every Newborn Study Group: Every newborn: progress, priorities, and potential beyond survival. Lancet 2014;384:189–205.
- 21 WHO: WHO Model List of Essential Medicines. Geneva, World Health Organization, 2013
- 22 Althabe F, Belizán JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, et al: A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. Lancet 2015;385:629–639.
- 23 McClure EM, Goldenberg RL, Jobe AH, Miodovnik M, Koso-Thomas M, Buekens P, Belizan J, Althabe F: Reducing neonatal mortality associated with preterm birth: gaps in knowledge of the impact of antenatal corticosteroids on preterm birth outcomes in low-middle income countries. Reprod Health 2016;13:61.
- 24 Vogel JP, Oladapo OT, Pileggi-Castro C, Adejuyigbe EA, Althabe F, Ariff S, Ayede AI, Baqui AH, Costello A, Chikamata DM, Crowther C, Fawole B, Gibbons L, Jobe AH, Kapasa ML, Kinuthia J, Kriplani A, Kuti O, Neilson J, Patterson J, Piaggio G, Qureshi R, Qureshi Z, Sankar MJ, Stringer JSA, Temmerman M, Yunis K, Bahl R, Metin Gülmezoglu A: Antenatal corticosteroids for women at risk of imminent preterm birth in low-resource countries: the case for equipoise and the need for efficacy trials. BMJ Glob Health 2017;2:e000398.
- 25 WHO: Verbal Autopsy Standards: The 2016 WHO Verbal Autopsy Instrument. Geneva, World Health Organization, 2016.
- 26 Soofi SB, Ariff S, Khan U, Turab A, Khan GN, Habib A, Sadiq K, Suhag Z, Bhatti Z, Ahmed I, Bhal R, Bhutta ZA: Diagnostic accuracy of WHO verbal autopsy tool for ascertaining causes of neonatal deaths in the urban setting of Pakistan: a hospital-based prospective study. BMC Pediatr 2015;15:144.
- 27 Zaidi AK, Tikmani SS, Warraich HJ, Darmstadt GL, Bhutta ZA, Sultana S, Thaver D: Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens. Pediatr Infect Dis J 2012;31:667–672.

ownloaded by: INARI Syrian Arab Republic 58 232 240 120 - 8/2/2018 5:36:50 PM

- 28 Baqui AH, Saha SK, Ahmed AS, Shahidullah M, Quasem I, Roth DE, Samsuzzaman AK, Ahmed W, Tabib SM, Mitra DK, Begum N, Islam M, Mahmud A, Rahman MH, Moin MI, Mullany LC, Cousens S, El Arifeen S, Wall S, Brandes N, Santosham M, Black RE; Projahnmo Study Group in Bangladesh: Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial. Lancet Glob Health 2015;3:e279–e287.
- 29 Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S: Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. Lancet 2015;385:1767-1776.

- 30 WHO: Managing possible serious bacterial infection in young infants 0–59 days old when referral is not feasible. Geneva, WHO, 2015.
- 31 Soofi S, Cousens S, Turab A, Wasan Y, Mohammed S, Ariff S, Bhatti Z, Ahmed I, Wall S, Bhutta ZA: Effect of provision of home-based curative health services by public sector health-care providers on neonatal survival: a community-based cluster-randomised trial in rural Pakistan. Lancet Glob Health 2017; 5:e796–e806
- 32 Qazi SA: Implementation of an innovative approach to jump start simplified management of sick young infants with possible serious bacterial infection (PSBI) where referral is not feasible for potential scale-up. Australian New Zealand Clinical Trials Registry, ACTRN12617001373369. Geneva, WHO, 2017.
- 33 Bhutta ZA: Ethics in international health research: a perspective from the developing world. Bull World Health Organ 2002;80: 114–120.
- 34 Council for International Organizations of Medical Sciences: International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, CIOMS, 2016.
- 35 Lurie P, Wolfe SM: Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Engl J Med 1997;337:853–856.
- 36 Angell M: The ethics of clinical research in the Third World. N Engl J Med 1997;337:847–849.
- 37 McCoy D, Chand S, Sridhar D: Global health funding: how much, where it comes from and where it goes. Health Policy Plan 2009;24: 407–417.
- 38 Bhutta ZA: Beyond informed consent. Bull World Health Organ 2004;82:771–777.