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Original Article

Interventions to Improve Neonatal Health and Later Survival: An Overview of Systematic Reviews

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ABSTRACT

Background: Evidence-based interventions and strategies are needed to improve child survival in countries with a high burden of neonatal and child mortality. An overview of systematic reviews can focus implementation on the most effective ways to increase child survival.
Methods: In this overview we included published Cochrane and other systematic reviews of experimental and observational studies on antenatal, childbirth, postnatal and child health interventions aiming to prevent perinatal/neonatal and child mortality using the WHO list of essential interventions. We assessed the methodological quality of the reviews using the AMSTAR criteria and assessed the quality of the outcomes using the GRADE approach. Based on the findings from GRADE criteria, interventions were summarized as effective, promising or ineffective.
Findings: The overview identified 148 Cochrane and other systematic reviews on 61 reproductive, maternal, newborn and child health interventions. Of these, only 57 reviews reported mortality outcomes. Using the GRADE approach, antenatal corticosteroids for preventing neonatal respiratory distress syndrome in preterm infants; early initiation of breastfeeding; hygienic cord care; kangaroo care for preterm infants; provision and promotion of use of insecticide treated bed nets (ITNs) for children; and vitamin A supplementation for infants from six months of age, were identified as clearly effective interventions for reducing neonatal, infant or child mortality. Antenatal care, tetanus immunization in pregnancy, prophylactic antimalarials during pregnancy, induction of labour for prolonged pregnancy, case management of neonatal sepsis, meningitis and pneumonia, prophylactic and therapeutic use of surfactant, continuous positive airway pressure for neonatal resuscitation, case management of childhood malaria and pneumonia, vitamin A as part of treatment for measles associated pneumonia for children above 6 months, and home visits across the continuum of care, were identified as promising interventions for reducing neonatal, infant, child or perinatal mortality.
Interpretation: Comprehensive adoption of the above six effective and 11 promising interventions can improve neonatal and child survival around the world. Choice of intervention and degree of implementation currently depends on resources available and policies in individual countries and geographical settings.
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1. Introduction

The global burden of neonatal and child mortality is alarmingly high in low and middle income countries (LMICs). There has been a sharp decline in mortality rates in children under five years of age between 1990 and 2013 (from 90 mortalities per 1000 down to 46 mortalities per 1000 live births between 1990 and 2013). This rate needs to further decrease, to just 30 mortalities per 1000 live births, in order to meet the Millennium Development Goals (MDGs) 2015 target (You et al., 2013).

Despite all the progress made in the last decade, it is very unlikely that the MDG targets will be met in many LMICs, where 99% of global deaths occur (You et al., 2013). In countries with a high burden of neonatal and child mortality, a variety of interventions could substantially reduce deaths and improve maternal and perinatal outcomes. Interventions and care primarily employed during different periods from antenatal to the later childhood period can facilitate reductions in neonatal and later mortality. However, a major obstacle in meeting the proposed reduction is that most neonatal and child health programs do not reach to those who need it the most. Therefore, effective

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interventions and care-based strategies need to be widely deployed to all and be delivered across the continuum of reproductive, maternal, neonatal and child health (RMNCH) care.

As we approach the deadline for the target of the MDGs and begin the journey towards achieving sustainable development goals (SDGs) we must focus efforts on programs and interventions shown to work. Several systematic reviews have evaluated the role of individual antenatal, natal, postnatal and child health interventions and their potential role at improving morbidity and mortality, however, there has been no overview on these interventions. Such an overview of systematic reviews of interventions to prevent neonatal and child mortality would facilitate the development of a definitive framework for preventing neonatal and child mortality in LMICs.

2. Methodology

In this overview of reviews, we have included all published Cochrane and the most recent (most latest on the given subject) other systematic reviews of randomized, non-randomized controlled trials of interventions and observational studies aiming to prevent perinatal (stillbirths + early neonatal mortality) or neonatal or child mortality (or stillbirths where either of these were not reported). We included interventions considered for improving neonatal and child survival and provided during pre-pregnancy, antenatal, childbirth and postnatal periods to mothers or the infant or child included in a set of 61 RMNCH interventions reported as essential interventions for reproductive, maternal, newborn and child health by the World Health Organization (WHO) (Panel 1) (Pmnch, 2011). We considered reviews that included women of reproductive age, including pregnant women at any stage of gestation, their newborns and children up to five years of age. This overview considered reviews on interventions which were compared against no placebo or treatment or control group (unless otherwise indicated).

All available recent non-Cochrane and updated or most recent Cochrane systematic reviews were identified from the Cochrane Library and PubMed using the search strategy devised for each intervention separately during Nov 2012 to Jan 2013 (Supplementary Table 1). The search terms were limited to title, abstract, or keywords. The methodology for data collection and analysis is based on the Cochrane Handbook of Systematic Reviews of Interventions (Higgins and Green, 2011). The outcomes of interest for this overview of reviews were perinatal mortality, neonatal mortality, infant mortality and under-five mortality reported as primary or secondary outcomes in included reviews.

The protocol for this overview is registered with PROSPERO 2014: CRD42014007091 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007091#.U75a1RCLMiw). Two review authors (ZSL and PM) independently assessed the inclusion of all the potential systematic reviews and extracted information using a predefined form (intervention, comparison, mortality outcome, type of studies included — Characteristics of included reviews Supplementary Table 2). Any disagreement was resolved through discussion or, where required, we consulted a third person. We addressed two different quality assessments in this overview: the quality of evidence in the included reviews (Table 1) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008; Oxman and Group, 2004) and the methodological quality of the systematic reviews using the 'assessment of multiple systematic reviews' (AMSTAR) measurement tool (Shea et al., 2007) (Supplementary Table 3). We did not update individual reviews. Where reviews did not prepare and report mortality outcomes using GRADE-pro software (Brozek et al., 2008), we formulated 'summary of findings' tables. The following criteria were taken into account to grade the evidence: study limitations (risk of bias for the outcome of interest), consistency of effect, imprecision,

Panel 1
List of interventions reviewed.

- Pre pregnancy interventions
  - Family planning
  - Prevention and management of sexually transmitted infections including HIV
  - Folic acid fortification and/or supplementation
- Pregnancy interventions
  - Antenatal care
  - Iron and folic acid supplementation during pregnancy
  - Tetanus immunization in pregnancy
  - Prophylactic antimalarial and insecticide treated bednets for preventing malaria in pregnancy
  - Interventions for smoking cessation during pregnancy
  - Screening and treatment of syphilis
  - Prevention and management of HIV and prevention of mother to child transmission in pregnancy
  - Calcium supplementation in pregnancy
  - Low-dose aspirin for the prevention of pre-eclampsia
  - Use of antihypertensive drugs for treating severe hypertension in pregnancy
  - Prevention and treatment of eclampsia
  - Reduce mal presentation at term using external cephalic version (>36 weeks)
  - Induction of labour for management of premature rupture of membranes at term.
  - Antibiotics for management of preterm rupture of membranes
- Childbirth interventions
  - Corticosteroids for preventing neonatal respiratory distress syndrome
  - Management of unintended pregnancy
  - Social support during childbirth
  - Prophylactic antibiotic for caesarean-section
  - Prevention of postpartum haemorrhage: prophylactic uterotonic to prevent postpartum haemorrhage
  - Active management of third stage of labour to prevent postpartum haemorrhage
  - Induction of labour for prolonged pregnancy
  - C-section for absolute maternal indication (e.g. obstructed labour and central placenta previa)
  - Management of post-partum haemorrhage e.g. uterine massage
  - Uterotonics
- Postpartum interventions
  - Advice and provision of family planning
  - Prevent, measure and treat maternal anaemia
  - Detection and management of postpartum sepsis
  - Screening and initiation or continuation of ARV therapy for HIV
- Neonatal interventions
  - Promotion and provision of thermal care for all newborns to prevent hypothermia
  - Promotion and support for early initiation and exclusive breastfeeding (within the first hour)
  - Promotion and provision of hygienic cord and skin care
  - Neonatal resuscitation with bag and mask for babies who do not breath at birth
  - Newborn immunization
  - Presumptive antibiotic therapy for the newborns at risk of bacterial infection
  - Case management of neonatal sepsis, meningitis and pneumonia
  - Kangaroo mother care for low birth babies
  - Extra support for feeding the small and preterm baby
  - Prophylactic and therapeutic use of surfactant to prevent respiratory distress syndrome in pre-term babies
  - Continuous positive airway pressure (CPAP) to manage pre-term babies with respiratory distress syndrome
  - Management of newborns with jaundice
- Infant and child health interventions
  - Promotion and support for exclusive breastfeeding for 6 months
  - Continued breastfeeding up to 2 years and beyond
  - Appropriate complementary feeding starting at 6 months
  - Provision and promotion of use of insecticide treated bed nets for children
  - Case management of childhood malaria
  - Comprehensive care of children infected or exposed to HIV infection
  - Promote and provide routine immunization plus *H. Influenza*, meningococcal, pneumococcal, and rotavirus vaccines
  - Vitamin A supplementation from 6 months of age in Vitamin A deficient populations
  - Management of severe acute malnutrition
  - Case management of childhood pneumonia
  - Vitamin A as part of treatment for measles-associated pneumonia for children above 6 months
  - Vitamin A as part of treatment for non-measles-associated pneumonia for children above 6 months
  - Case management of diarrhoea: Acute watery diarrhoea
  - Dysentery
- Cross cutting intervention
  - Home visits across the continuum of care women's groups

indirectness, and publication bias. We summarised the main results of the included reviews into following categories.

- What works?

Effective interventions: indicating that the review found high quality evidence with the effect likely to be similar to research findings.

- What might work?

Promising interventions (more evidence needed): indicating that the review found moderate quality evidence with the effect expected to be similar to research findings, but with a possibility that it will be substantially different in the future.

- Insufficient evidence to make judgement

Ineffective or probably ineffective interventions: indicating that the review found low or very low quality evidence of effectiveness or lack of effectiveness for an intervention.

For low quality of evidence, it is likely that the effect will be substantially different from research findings, but that these will indicate what might be expected.

For very low quality of evidence, the anticipated effect is very uncertain and the research does not provide a reliable indication of what might be expected.

3. Funders and Their Role

This review was part of doctoral thesis which was funded by University of Adelaide, Australia. The funders had no role in the study design, study conduct, data analysis, data interpretation, or writing of the report. All authors take responsibility for the integrity and the accuracy of the data. The corresponding author had final responsibility to submit the report for publication.

4. Results

The overview included 61 reproductive (n = 3), maternal (pregnancy: n = 15; childbirth: n = 11; postpartum: n = 4), newborn (n = 12) and child (n = 16) health interventions to assess their impact on neonatal and child survival (Panel 1). A total of 148 systematic reviews were identified for these 61 RMNCH interventions, of which 92 were Cochrane reviews, 55 were non-Cochrane reviews and one was a WHO guideline on management of unintended pregnancy. Of these 148 reviews, only 57 reviews reported mortality outcomes (Panel 2).

Using the GRADE approach, we identified six interventions to be clearly effective in reducing neonatal, infant or child mortality (corticosteroids for preventing neonatal respiratory distress syndrome in preterm infants; early initiation of breastfeeding; hygienic cord care; kangaroo care for preterm infants; provision and promotion of use of insecticide treated bed nets (ITNs) for children; and vitamin A supplementation for infants from six months of age).

We identified 11 promising interventions for reducing neonatal, infant, child or perinatal mortality (antenatal care; tetanus immunization in pregnancy; prophylactic antimalarial during pregnancy; induction of labour for prolonged pregnancy; case management of neonatal sepsis, meningitis and pneumonia; prophylactic and therapeutic use of surfactant; continuous positive airway pressure; case management of childhood malaria; case management of childhood pneumonia; vitamin A as part of treatment for measles associated pneumonia for children above 6 months; and home visits across the continuum of care) and a further four interventions were rated as promising for reducing stillbirths (prophylactic antimalarial during pregnancy; provision and promotion of ITNs during pregnancy; induction of labour for prolonged pregnancy; and home visits across the continuum of care). Eighteen interventions showed insufficient evidence of benefit in one or more of the mortality categories (Table 1).

4.1. Effective Interventions

4.1.1. Corticosteroids for Preventing Neonatal Respiratory Distress Syndrome (RDS)

This overview identified three reviews (Mwansa-Kambafwile et al., 2010; Roberts and Dalziel, 2006; Brownfoot et al., 2013), of which two (Mwansa-Kambafwile et al., 2010; Roberts and Dalziel, 2006) reviewed the impact of antenatal corticosteroids on the mother before anticipated preterm birth (with additional analysis for women in LMICs) (Mwansa-Kambafwile et al., 2010). Brownfoot and colleagues (Brownfoot et al., 2013) assessed different corticosteroid regimens. Two reviews reported the impact of corticosteroids on neonatal mortality (Mwansa-Kambafwile et al., 2010; Roberts and Dalziel, 2006). Roberts and Dalziel pooled 18 trials on 3956 women at risk of preterm birth and found a 31% (Risk Ratio (RR) 0.69; 95% Confidence Interval (CI): 0.58, 0.81) reduction in neonatal mortality (high GRADE rating) in women who were given antenatal corticosteroids compared to women who were not given any corticosteroids or given placebo (Roberts and Dalziel, 2006). Mwansa-Kambafwile and colleagues (Mwansa-Kambafwile et al., 2010) reported a 31% (RR 0.69; 95% CI: 0.58, 0.81) reduction (high GRADE rating) in preterm-specific mortality on pooling 18 trials on 3956 women mostly from high-income countries and 53% (RR 0.47; 95% CI: 0.35, 0.64) reduction in preterm-specific mortality on pooling a subset of four trials on 672 women from middle-income countries who were given antenatal corticosteroids.

4.1.2. Early Initiation of Breastfeeding

The overview identified six reviews (Dyson et al., 2005; Lewin et al., 2010; Lassi et al., 2010; Imdad et al., 2011a; Debes et al., 2013; Lumbiganon et al., 2012) that reported the impact of different interventions on improving early initiation of breastfeeding. Lewin and colleagues (Lewin et al., 2010) and Lassi and colleagues (Lassi et al., 2010) assessed the impact of interventions delivered through lay health workers and in the form of packages, respectively, on improving breastfeeding rates. These reviews reported reductions in mortality; however, reduction in deaths may have been achieved by other parts of the intervention package and therefore the reduction does not necessarily reflect the impact of a breastfeeding intervention alone. Dyson and colleagues (Dyson et al., 2005), Imdad and colleagues (Imdad et al., 2011a), and Lumbiganon and colleagues (Lumbiganon et al., 2012) did not report outcomes on mortality. The review by Debes and colleagues (Debes et al., 2013) identified 18 studies, of which three prospective cohort studies (including 44,249 newborns) with moderate GRADE quality showed neonatal mortality was reduced by 44% (RR 0.56; 95% CI: 0.40, 0.79) with early initiation of breastfeeding (within less than 24 h of birth).

4.1.3. Hygienic Cord Care

The overview identified two reviews, of which Zupan and colleagues assessed topical cord care (Zupan et al., 2004) and the other two by Imdad and colleagues assessed chlorhexidine application alone and other application for cord care and included almost similar studies (Imdad et al., 2013a,b). The latter two reported neonatal mortality (Imdad et al., 2013a,b). Pooled analysis of three studies (n = 54,561) found a moderate GRADE quality and significant 23% (RR 0.77; 955 CI: 0.63, 0.94) reduction in neonatal mortality with the application of chlorhexidine when compared with no application to the umbilical cord (dry cord care) (Imdad et al., 2013a,b). However the Cochrane review by Imdad and colleagues also compared washing the cord with dry care, reporting no difference in all-cause mortality (RR 1.00; 95% CI: 0.76, 1.32, moderate GRADE quality) (Imdad et al., 2013b).

4.1.4. Kangaroo Mother Care for Preterm Infants

The overview identified two reviews (Lawn et al., 2010; Conde-Agudelo and Díaz-Rossello, 2014) that assessed the impact of kangaroo

Panel 2
GRADE interventions according to outcomes.

What works	What might work	Insufficient evidence
Mortality (neonatal or infant or child)		
Corticosteroid for prevention of neonatal respiratory distress syndrome	Tetanus immunization in pregnancy (tetanus toxoid vs. placebo)	Family planning
Early initiation of breastfeeding	Prophylactic antimalarial during pregnancy	Periconceptional folic acid supplementation
Hygienic cord care	Induction of labour for prolonged pregnancy	Folic acid supplementation during pregnancy*
Kangaroo mother care for low birth weight babies	Case management of neonatal sepsis, meningitis and pneumonia	Iron supplementation during pregnancy
Provision and promotion of use of insecticide treated bed nets for children	Prophylactic and therapeutic use of surfactant	Tetanus immunization in pregnancy (TT vs. diphtheria and influenza)
Vitamin A supplementation from 6 months of age	Continuous positive airway pressure (CPAP)	Smoking cessation during pregnancy
	Case management of childhood malaria	Prevention and treatment of eclampsia
	Case management of childhood pneumonia	Active management for third stage of labour
	Vitamin A as part of treatment for measles associated pneumonia for children above 6 months	Induction of labour for PROM
	Home visits across the continuum of care women's groups	Antibiotic for PROM
		Thermal care for all newborns
		Neonatal resuscitation with bag and mask
		Presumptive antibiotic therapy for newborns
		Case management of childhood malaria (monthly sulfadoxine pyrimethamine (SP) compared to standard 2-dose SP)
		Comprehensive care of children infected or exposed to HIV infection
		Vitamin A as part of treatment for non-measles-associated pneumonia for children above 6 months
		Case management of diarrhoea
Perinatal mortality		
	Antenatal care	Periconceptional folic acid supplementation vs. placebo
	Prophylactic antimalarial during pregnancy	Smoking cessation during pregnancy
	Induction of labour for prolonged pregnancy	Calcium supplementation
	Home visits across the continuum of care women's groups	Prevention and treatment of eclampsia (MgSO4 vs. none or other)
		External cephalic version
		Induction of labour for PROM
		Antibiotic for PROM**
		Corticosteroid for prevention of neonatal RDS (dexamethasone versus betamethasone)
Stillbirths		
	Provision and promotion of ITNs***	Periconceptional folic acid supplementation vs. no treatment/placebo
	Prophylactic antimalarial during pregnancy	Folic acid supplementation during pregnancy*
	Induction of labour for prolonged pregnancy	Smoking cessation during pregnancy
	Home visits across the continuum of care women's groups	

Interventions in bold indicate that the outcomes estimates were statistically significant.
* Stillbirths + neonatal mortality.
** Perinatal mortality or death before discharge.
*** Foetal loss (miscarriage and stillbirths).

mother care (KMC) on preterm and low birth weight infants (<2000 g) and reported mortality outcome. Pooled analysis of 11 studies from 2167 infants reported a significant 33% reduction in mortality (moderate GRADE quality) at the latest follow up (RR 0.67; 95% CI: 0.48, 0.95) (Conde-Agudelo and Díaz-Rossello, 2014). The meta-analysis of three randomized controlled trials (RCTs) (n = 1075) — a subset of those pooled in the latest Cochrane review (Conde-Agudelo and Díaz-Rossello, 2014) — that provided KMC to infants in the first week of life showed a significant 51% reduction in neonatal mortality (RR 0.49; 95% CI: 0.29, 0.82 — high GRADE quality) when compared to standard care (Lawn et al., 2010). This review also pooled three observational studies and found a similar beneficial impact on neonatal mortality (RR 0.68; 95% CI: 0.58, 0.79) (Lawn et al., 2010).

4.1.5. Provision and Promotion of use of ITNs for Children

The overview identified one review that pooled five studies on 149,221 children and compared ITNs with control and found a significant 18% reduction in child mortality (RR 0.82; 95% CI: 0.76, 0.89 — moderate GRADE quality) (Lengeler, 2004).

4.1.6. Vitamin A Supplementation From 6 Completed Months of age

The overview identified three reviews from the same review authors who assessed the impact of vitamin A supplementation from six months of age, and reported neonatal mortality (Imdad et al., 2010, 2011b; Mayo-Wilson et al., 2011). In the latest of these, pooling of 17 trials including 194,795 children found that vitamin A supplementation is effective in reducing all-cause mortality by 24% (RR 0.76; 95% CI: 0.69, 0.83) when compared with no treatment or placebo (Imdad et al., 2010). The quality was high on GRADE analysis.

4.2. Promising Interventions

4.2.1. Antenatal Care

The overview identified two reviews (Dowswell et al., 2010; Carroli et al., 2001) assessing the impact of fewer than usual antenatal care visits. This review of five trials including 108,002 pregnant women identified that reduced number of antenatal care visits (ranged 4–9) was associated with 14% higher risk of perinatal mortality (RR 1.14; 95% CI: 1.00, 1.31) when compared with standard antenatal care visits (ranged

Table 1
Grading analysis of mortality outcomes from included reviews.

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
Pre-pregnancy interventions									
Family planning	Less than 18 months of interval compared to 36–<60 months (Kozuki 2013)[68]	Neonatal mortality OR 1.49 (95% CI: 0.93, 2.37) 5 studies, n = 19240	Observational	Serious	Serious	Serious	Serious	Dose response relationship	Low ⊕⊕⊖⊖
	>60 months compared to 36–60 months of interval (Kozuki 2013)[68]	Neonatal mortality OR 1.01 (95% CI: 0.68, 1.49) 5 studies, n = 19240	Observational	Serious	Serious	Serious	Serious	Dose response relationship	Low ⊕⊕⊖⊖
Folic acid supplementation	Folic acid versus placebo (Blencowe 2010)[69]	**Neonatal mortality RR 0.43 (95% CI: 0.27, 0.67) 1 study, n = 360994**	Before/after study	Not serious	Very serious	Very serious	Not serious	-	Very low ⊕⊖⊖⊖
		Perinatal mortality RR 0.34 (95% CI: 0.25, 0.47) 1 study, n = 321,711	Before/after study	Not serious	Not serious	Very serious	Not serious	-	Low ⊕⊕⊖⊖
	Folic acid versus no treatment/other micronutrients/placebo (De Regil 2010)[70]	Stillbirths RR 0.96 (95% CI: 0.51, 1.83) 4 studies, n = 5994	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	Folic acid alone versus no treatment/placebo (De Regil 2010)[70]	Stillbirths RR 0.13 (95% CI: 0.01, 2.46) 1 study, n = 188	Experimental	Not serious	Not serious	Very serious	Serious	-	Very low ⊕⊖⊖⊖
Pregnancy interventions									
Antenatal care	Reduced number of antenatal care visits/goal oriented versus standard antenatal care visits (Dowswell 2010)[26]	Perinatal mortality RR 1.14 (95% CI: 1.00, 1.31) 5 studies, n = 108002	Experimental	Serious	Not serious	Not serious	Not serious	Certain confounding factors	Moderate ⊕⊕⊕⊖
Iron and folic acid supplementation	Folic acid versus no folic acid (Lassi 2013)[71]	Stillbirths/neonatal mortality RR 1.33 (95% CI: 0.96, 1.85) 3 studies, n = 3110	Experimental	Very serious	Serious	Not serious	Not serious	Certain confounding factors	Very low ⊕⊖⊖⊖
	Supplements containing iron versus same supplements without iron/no iron or placebo (Penna Rosas 2012)[72]	Neonatal mortality RR 0.90 (95% CI: 0.68, 1.19) 4 studies, n = 7465	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Tetanus immunization in pregnancy	TT versus influenza vaccine (Demicheli 2013)[29]	Neonatal mortality RR 0.12 (95% CI: 0.00, 7.88) 1 study , n = 1182	Experimental	Not serious	Very serious	Very serious	Not serious	-	Very low ⊕⊖⊖⊖
	tetanus-diptheria toxoid vs with cholera toxoid (Demicheli 2013)[29]	**Neonatal mortality RR 0.68 (95% CI 0.56, 0.82) 1 study**	Experimental	Not serious	Very serious	Very serious	Not serious	-	Very low ⊕⊖⊖⊖

(continued on next page)

Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
	TT immunization versus none (Blencowe 2010)[30]	**Neonatal mortality from tetanus RR 0.06 (95% CI: 0.02, 0.20) 2 studies, n = 2146**	Experimental and observational	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Antimalarials during Pregnancy	Any antimalarial drug versus no drug (Radeva-Petrova 2014)[32]	Stillbirth RR 1.01 (95% CI: 0.79, 1.28) 7 studies, n = 9833	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
		Perinatal mortality RR 0.99 (95% CI: 0.81, 1.22) 6 studies, n = 6836	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
		Neonatal mortality RR 0.93 (95% CI: 0.76, 1.14) 9 studies, n = 10,486	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	IpTp versus none (Eisele 2010)[31]	Neonatal mortality RR 0.62 (95% CI: 0.37, 1.05) 2 studies, n = 2091	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Perinatal mortality RR 0.83 (95% CI: 0.52, 1.20) 1 study, n = 904	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Provision and promotion of ITNs	ITNs versus none (Gamble 2007)[33]	**Fetal loss (miscarriage/stillbirth) RR 0.68 (95% CI: 0.48, 0.89) 3 studies, n = 4457**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	ITNs versus none (Gamble 2007)[34]	**Fetal loss (miscarriage/stillbirth) RR 0.68 (95% CI: 0.48, 0.98) 5 studies**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Smoking cessation during pregnancy	Nicotine replacement therapy versus control (Coleman 2012)[73]	Neonatal mortality RR 0.28 (95% CI: 0.06, 1.41) 3 studies, n = 1386	Experimental	Not Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	Smoking cessation interventions: counselling vs usual care (Chamberlain 2013)[74]	Perinatal mortality RR 1.10 (95% CI: 0.52, 2.31) 1 study, n = 935	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
		Stillbirths RR 1.08 (95% CI: 0.51, 2.30) 4 studies, n = 2212	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
		Neonatal mortality 2.06 (95% CI: 0.61, 6.92) 3 studies, n = 2095	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖

Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
Calcium supplementation	Calcium supplementation versus none (Jabeen 2011)[75]	Perinatal mortality RR 0.86 (95% CI: 0.70, 1.07) 4 studies, n = 333	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	Calcium supplementation versus none (Hofmeyr 2014)[76]	5 Stillbirth or death before discharge from hospital RR 0.90 [95% CI: 0.74, 1.09]11 studies, n = 15665	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
Prevention and treatment of eclampsia	Magnesium sulphate versus phenytoin (Duley 2010)[77]	Neonatal mortality RR 0.95 (95% CI: 0.59, 1.53) 2 studies, n = 665	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Magnesium sulphate verses none or other	Neonatal mortality RR 1.16 (95% CI: 0.94, 1.42) 1 study, n = 8260 (Duley 2010)[78]	Experimental	Not Serious	Very serious	Very serious	Not serious	-	Very low ⊕⊖⊖⊖
		Perinatal mortality RR 0.98 (95% CI: 0.88, 1.10) 2 studies, n = 1079 (Jabeen 2011)[75]	Experimental	Not Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Magnesium sulphate versus lytic cocktail (Duley 2010)[79]	Neonatal mortality RR 0.37 (95% CI: 0.14, 1.00) 2 studies, n = 153	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	Magnesium sulphate versus diazepam (Duley 2010)[80]	Neonatal mortality RR 1.18 (95% CI: 0.75, 1.84) 4 studies, n = 759	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
		Stillbirths RR 0.97 (95% CI: 0.70, 1.34) 5 studies, n = 799	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
External cephalic version	Tocolytic drugs vs placebo Cluver 2012[81]	Perinatal mortality RR 0.0 (95% CI: 0.0, 0.0) 1 study, n = 310	Experimental	Not Serious	Very serious	Very serious	Serious	-	Very low ⊕⊖⊖⊖
	Planned caesarean section for term breech presentation (Hofmeyr 2003)[82]	**Perinatal/neonatal death or severe neonatal morbidity RR 0.33 (95% CI: 0.19, 0.56) 1 study, n = 2078**	Experimental	Not Serious	Very serious	Very serious	Not serious	-	Very low ⊕⊖⊖⊖
	External cephalic version at term (Hofmeyr 2012)[83]	Perinatal death RR 0.34 (95% CI: 0.05, 2.12) 6 studies, n = 1053	Experimental	Serious	serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
	External cephalic version before term versus no ECV (Hutton 2006)[84]	Perinatal mortality RR 0.35 (95% CI: 0.04, 3.22) 1 study, n = 102	Experimental	Not Serious	Very serious	Very serious	Serious	-	Very low ⊕⊖⊖⊖

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Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
Induction of labor for PROM	Any planned versus expectant management (Buchanan 2010) [85]	Perinatal mortality RR 0·98 (95% CI: 0·41, 2·36) 7 studies, n=692	Experimental	Serious	serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
		Neonatal mortality RR 1·59 (95% CI: 0·61, 4·16) 7 studies, n=692	Experimental	Serious	serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
Antibiotic for PROM	Any antibiotic versus placebo	Perinatal mortality /death before discharge RR 0·93 (95% CI: 0·76, 1·14) 12 studies, n=6301 (Kenyon 2013) [86]	Experimental	Serious	serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
		Neonatal mortality RR 0·90 (95% CI: 0·72, 1·12) 15 trials, n=4269 (Cousens 2010) [87]	Experimental	Serious	serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
Childbirth interventions									
Corticosteroid for prevention of neonatal RDS	Dexamethasone versus betamethasone (Brownfoot 2013) [10]	Perinatal mortality RR 1·41 (95% CI: 0·54, 3·67) 4 studies, n=596	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
	Antenatal steroids (Mwansa Kambafwile 2010) [8]	**Neonatal mortality** All countries **RR 0·69 (95% CI: 0·58, 0·81) 18 studies, n= 3956** Subset of middle income countries **RR 0·47 (95% CI: 0·35, 0·64) 4 studies, n=672**	Experimental	Not Serious	Not serious	Not serious	Not serious	-	High ⊕⊕⊕⊕
	Corticosteroids versus placebo or no treatment (Roberts 2006) [9]	**Neonatal mortality RR 0·69(95% CI: 0·58, 0·81) 18 studies, n=3956**	Experimental	Not serious	Not serious	Not serious	Not serious	-	High ⊕⊕⊕⊕
Active management for third stage of labor	Early versus late cord clamping (McDonald 2013) [88]	Neonatal mortality RR 0·37 (95% CI: 0·04, 3·41) 2 studies, n=381	Experimental	Serious	Not serious	Not serious	Serious	-	Moderate ⊕⊕⊕⊖
Induction of labor for prolonged pregnancy	Labour induction versus expectant management by cervical status	**Perinatal mortality RR 0·31 (95% CI: 0·12, 0·81) 17 studies, n=7407 (Gulmezoglu 2012) [35]**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Stillbirth RR 0·30 (95% CI: 0·08, 1·08) 17 studies, n=7407 (Gulmezoglu 2012) [35]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Newborn death within 7 days RR 0·37 (95% CI: 0·10, 1·38) 17 studies, n=7407 (Gulmezoglu 2012) [35]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Perinatal mortality RR 0·31 (95% CI: 0·11, 0·88) 14 studies, n=6597 (Hussain 2011) [36]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖

Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
		Stillbirths RR 0·29 (95% CI: 0·06, 1·38) 14 studies, n=6597 (Hussain 2011) [36]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Newborn interventions									
Thermal care for all newborns	Plastic wrap versus routine care (McCall 2010) [89]	Death within hospital stay RR 0·66 (95% CI: 0·35, 1·24) 4 studies, n=266	Experimental	Serious	Not serious	Not serious	serious	-	Low ⊕⊕⊖⊖
	Plastic cap versus routine care (McCall 2010) [89]	Death within hospital stay RR 1·5 (95% CI: 0·27, 8·38) 1 study, n=64	Experimental	Serious	Not serious	Not serious	serious	-	Low ⊕⊕⊖⊖
Early initiation of breastfeeding	Early versus none (Debes 2013) [15]	**Neonatal mortality** **RR 0·56 (95% CI: 0·40, 0·79)** **3 studies, n=44249**	Observational	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Hygienic cord care	Cord care versus none/standard (Imdad 2013) [18]	**Neonatal mortality** **RR 0·77 (95% CI: 0·63, 0·94)** **3 studies, n=54651**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Cord care versus none/standard (Imdad 2013) [19]	**Neonatal mortality** **RR 0·77 (95% CI: 0·63, 0·94)** **3 studies, n=54651**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Washing cord vs· dry/placebo (Imdad 2013) [19]	Neonatal mortality RR 1·00 (95% CI: 0·76, 1·32) 1 study, n=10189	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Neonatal resuscitation with bag and mask	Training on resuscitation (lee 2011) [90]	**Deaths among babies "not breathing at birth"** **RR 0·70 (95% CI: 0·59, 0·84)** **3 studies, n=197061**	Before/after studies	Serious	Not serious	Not serious	serious	-	Low ⊕⊕⊖⊖
Presumptive antibiotic therapy	Prophylactic versus selective antibiotics (Ungrerer 2004) [91]	Neonatal mortality Risk Ratio: Non estimable 2 studies, n=116	Experimental	Not Serious	Not serious	Not serious	Very Serious	-	Very Low ⊕⊖⊖⊖
Case management of neonatal sepsis, meningitis and pneumonia	Community-based management versus none	**all-cause neonatal mortality** **RR 0·73 (95% CI: 0·65, 0·82)** **(Bhutta 2009)** [40]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Pneumonia-specific mortality, **RR 0·58 (95% CI: 0·43, 0·78)** **(Bhutta 2009)** [40]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		All-cause mortality **RR 0·75 (95% CI: 0·64, 0·89)** **(Zaidi 2011)** [39]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖

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Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
		Pneumonia specific mortality RR 0·58 (95% CI: 0·41- 0·82) 4 studies, n=11080 (Zaidi 2011) [39]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Kangaroo mother care for preterm	KMC versus conventional neonatal care (Conde-Agudelo 2014) [21]	**Mortality at latest follow-up RR 0·67; 95% CI: 0·48, 0·95) 11 studies, n=2167**	Experimental	Serious	Not serious	Not serious	Not serious		Moderate ⊕⊕⊕⊖
	KMC versus none/standard (Lawn 2010) [20]	**Neonatal mortality RR 0·49 (955 CI: 0·29, 0·82) 3 studies, n=1075**	Experimental	Not Serious	Not serious	Not serious	Not serious	-	High ⊕⊕⊕⊕
Prophylactic and therapeutic use of surfactant	Synthetic surfactant vs placebo (Soll 1998) [42]	**Mortality RR 0·73 (95% CI: 0·61, 0·98) 6 studies, n=2352**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Multiple vs single dose surfactant for severe RDS (Soll 2009) [41]	**Mortality RR 0·59 (95% CI: 0·44, 0·78) 3 studies, n=1220**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Early vs delayed selective surfactant treatment (Bahadue 2012) [43]	**Neonatal mortality RR 0·84 (95% CI: 0·74, 0·95) 6 studies, n=3577**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Continuous positive airway pressure (CPAP)	HFPPV vs CMV (Greenough 2008) [44]	Mortality RR 0·80 (95% CI: 0·62, 1·03) 3 studies, n=585	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	CDP vs standard care (Ho 2002) [46]	**Mortality RR 0·52 (95% CI: 0·32, 0·87) 6 studies, n=355**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	Prophlactic CPAP vs· control (Subramaniam 2005) [47]	Neonatal mortality RR 1·29 (95% CI: 0·45, 3·67) 2 studies, n=312	Experimental	Serious	Not serious	Not serious	Serious	-	Low ⊕⊕⊖⊖
Infancy and child health interventions									
Provision and promotion of use of ITNs for children	ITNs versus all controls (Lengeler 2004) [22]	**Child mortality from all causes RR 0·82 (95% CI: 0·76, 0·89) 5 studies, n= 149221**	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Case management of childhood malaria	Case management of malaria versus placebo (Thwing 2011) [49]	**Malaria mortality in children 1-23 months RR 0·01 (95% CI: 0·00, 0·06)**	Observational	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Malaria mortality in children 24-59 months RR 0·03 (95% CI: 0·01, 0·14)	Observational	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
	IPTc versus placebo or no IPTc (Meremikwu 2012) [48]	Death from any cause RR 0·66 (95% CI: 0·31, 1·39) 6 studies, n=9533	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖

Table 1 (*continued*)

Intervention	Comparison	Outcomes	Study design	ROB	Inconsistency	Indirectness	Imprecision	Other consideration	Overall quality
Comprehensive care of children infected or exposed to HIV infection	Cotrimoxazole versus control (Grimwade 2009) [92]	**Mortality RR 0·67 (95% CI: 0·53, 0·85) 1 study, n=534**	Experimental	Not Serious	Very serious	Very serious	Not serious	-	Very Low ⊕⊖⊖⊖
Vitamin A supplementation from 6 months of age	Vitamin A versus no treatment (Imdad 2010) [23]	**Mortality (all-cause) RR 0·76 (95% CI: 0·69, 0·83) 17 studies, n=194795**	Experimental	Not Serious	Not serious	Not serious	Not serious	-	High ⊕⊕⊕⊕
Case management of childhood pneumonia	Case management versus standard	**Acute Lower Respiratory Infections (ALRI) mortality RR 0·65 (95% CI: 0·52, 0·82) 9 studies (Theodaratu 2010)** [50]	Concurrent Before/after	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		All-cause mortality RR 0·79 (95% CI: 0·70, 0·82) 9 studies (Theodaratu 2010) [50]	Concurrent Before/after	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		ALRI specific mortality RR 0·65 (95% CI: 0·52, 0·82) (Das 2013) [53]	Experimental and before/after	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		pneumonia specific mortality RR 0·68 (95% CI: 0·53, 0·86) 11 studies (Das 2013) [53]	Experimental and before/after	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
Vitamin A as part of treatment for measles-associated pneumonia for children above 6 months	Vitamin A versus control (Fawzi 1993) [54]	**Overall mortality OR 0·70 (95% CI: 0·56, 0·87) 8 studies, n=135609**	Experimental	Serious	serious	Not serious	Serious	-	Moderate ⊕⊕⊕⊖
Vitamin A as part of treatment for non-measles-associated pneumonia for children above 6 months	Vitamin A versus control (Wu 2005) [93]	Mortality during hospitalisation OR 1·29 (95% CI: 0·63, 2·66) 3 studies, n=1446	Experimental	Serious	Not serious	Not serious	serious	-	Low ⊕⊕⊖⊖
Case management of diarrhoea	Preventive zinc supplementation (Yakoob 2011) [94]	All-cause mortality RR 0·91 (95% CI: 0·82, 1·01) 10 studies	Experimental	Serious	Serious	Not serious	Not Serious	-	Low ⊕⊕⊖⊖
Home visits across the continuum of care women's groups	Community-based intervention versus control	**Neonatal mortality RR 0·78 (95% CI: 0·67, 0·92) 5 studies, n=56878 (Lassi 2010)** [13]	Experimental	Not serious	Serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Perinatal mortality RR 0·72 (95% CI: 0·61, 0·85) 3 studies, n=45835 (Lassi 2010) [13]		Not serious	Serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Stillbirths RR 0·73 (95% CI: 0·67, 0·81) 3 studies, n=45835 (Lassi 2010) [13]		Not serious	Serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖
		Neonatal mortality RR 0·62 (95% CI: 0·44 0·87) 5 studies (Gogia and Sachdev 2010) [58]	Experimental	Serious	Not serious	Not serious	Not serious	-	Moderate ⊕⊕⊕⊖

12–14+) (Dowswell et al., 2010), indicating that fewer antenatal visits than the standard number may be harmful. Another review, comparing group with standard antenatal care did not detect significant differences in perinatal mortality (RR 0.59; 95% CI: 0.22, 1.52; 2 trials, n = 1315) (Homer et al., 2012).

4.2.2. Tetanus Immunization in Pregnancy

The overview identified two reviews on tetanus toxoid (TT) vaccination versus placebo: Demicheli and colleagues (Demicheli et al., 2013) compared TT vaccination with influenza and cholera vaccination, whereas Blencowe and colleagues (Blencowe et al., 2010a) compared TT immunization with no immunization. The comparison of TT with influenza and cholera was judged as low quality and therefore included in "insufficient evidence interventions" section. The meta-analyses from Blencowe and colleagues (Blencowe et al., 2010a) displayed a significant impact of TT immunization on reducing neonatal mortality when compared with no immunization (RR 0.06; 95% CI: 0.02, 0.20; two studies, n = 2146). This review pooled two studies, of which one was an experimental trial and the other was an observational study.

4.2.3. Prophylactic Antimalarials During Pregnancy

The overview identified four reviews on prophylactic antimalarial and intermittent preventive treatment (IPT) in pregnancy (Eisele et al., 2010; Radeva-Petrova et al., 2014). Two reviews reported outcomes on neonatal mortality and perinatal mortality (Eisele et al., 2010; Radeva-Petrova et al., 2014), whereas one reported stillbirths (Radeva-Petrova et al., 2014).

4.2.3.1. Neonatal Mortality. Radeva-Petrova and colleagues assessed antimalarial drug prophylaxis (e.g. chloroquine given weekly) or IPT (typically sulfadoxine-pyrimethamine given two to three times during pregnancy) with no regular or routine antimalarial or comparator IPT and found a non-significant 7% reduction in neonatal and infant mortality (RR 0.93; 95% CI: 0.76, 1.14 — low GRADE quality) on pooling nine trials including 10,486 women in their first or second pregnancy (Radeva-Petrova et al., 2014). The review by Eisele and colleagues compared IPT with control and found a non-significant 17% reduction in neonatal mortality (RR 0.83; 95% CI: 0.52, 1.20 — moderate GRADE quality) (Eisele et al., 2010).

4.2.3.2. Perinatal Mortality. Radeva-Petrova and colleagues pooled six trials on 6836 women in their first or second pregnancy and found a non-significant 1% reduction in perinatal mortality (RR 0.99; 95% CI: 0.81, 1.22 — low GRADE quality) (Radeva-Petrova et al., 2014). Eisele and colleagues found a non-significant 17% reduction in perinatal mortality (RR 0.83; 95% CI: 0.52, 1.20 — moderate GRADE quality) (Eisele et al., 2010).

4.2.3.3. Stillbirths. Radeva-Petrova and colleagues pooled seven trials on 9833 women in their first or second pregnancy and reported a non-significant increase in stillbirths (RR 1.01; 95% CI: 0.79, 1.28 — low GRADE quality) (Radeva-Petrova et al., 2014).

4.2.4. Provision and Promotion of ITNs During Pregnancy

The overview identified two reviews by Gamble and colleagues (Gamble et al., 2006, 2007) that studied the effect of ITN on pregnant women and reported moderate GRADE quality foetal loss. Pooled analysis of five trials reported a significant 32% reduction in foetal loss (miscarriage or stillbirths) (RR 0.68; 95% CI: 0.48, 0.98) (Gamble et al., 2006). A subset of those trials pooled in the Cochrane review reported a significant 32% reduction in foetal loss (miscarriage or stillbirths) (RR 0.68; 95% CI: 0.48, 0.89; three studies, n = 4557) (Gamble et al., 2007).

4.2.5. Induction of Labour for Prolonged Pregnancy

The overview identified two reviews that evaluated the benefits and harms of a policy of labour induction at term or post-term compared with awaiting spontaneous labour or later induction of labour (Gulmezoglu et al., 2012; Hussain et al., 2011). Both of the reviews included almost the same set of studies and reported outcomes on perinatal mortality and stillbirths (Gulmezoglu et al., 2012; Hussain et al., 2011), while only Gulmezoglu and colleagues reported neonatal mortality (Gulmezoglu et al., 2012).

4.2.5.1. Neonatal Mortality. The meta-analysis by Gulmezoglu and colleagues found a moderate GRADE quality non-significant 63% (RR 0.37; 95% CI: 0.10, 1.38; 17 studies, n.7407) reduction in neonatal deaths within seven days when compared with labour induction at term or post-term with awaiting spontaneous labour or later induction of labour (Gulmezoglu et al., 2012).

4.2.5.2. Perinatal Mortality. The meta-analysis of 17 studies on 7407 women by Gulmezoglu and colleagues found a significant 69% (RR 0.31; 95% CI: 0.12, 0.81 — moderate GRADE quality) (Gulmezoglu et al., 2012) and meta-analysis of 14 studies on 6597 women by Hussain and colleagues found a significant 69% (RR 0.31; 95% CI: 0.11, 0.88 — moderate GRADE) (Hussain et al., 2011) reduction in perinatal mortality with induced labour at term or post-term.

4.2.5.3. Stillbirths. The meta-analysis of 17 studies on 7407 women by Gulmezoglu and colleagues found a non-significant 70% (RR 0.30; 95% CI: 0.08, 1.08 — moderate GRADE quality) (Gulmezoglu et al., 2012) and meta-analysis of 14 studies on 6597 women by Hussain and colleagues found a 71% (RR 0.29; 95% CI: 0.06, 1.38 — moderate GRADE quality) (Hussain et al., 2011) reduction in stillbirths.

4.2.6. Case Management of Neonatal Sepsis, Meningitis and Pneumonia

The overview identified four reviews that assessed the impact of case management of diagnosed sepsis, meningitis and pneumonia among neonates (Gordon and Jeffery, 2005; Sazawal and Black, 2003a; Zaidi et al., 2011; Bhutta et al., 2009a). Among these, two reviews reported an impact on mortality which was moderate on GRADE quality (Zaidi et al., 2011; Bhutta et al., 2009a). Case management of neonatal infectious diseases reported 27% (RR 0.73; 95% CI: 0.65, 0.82) (Bhutta et al., 2009a) and 25% (RR 0.75, 95% CI: 0.64, 0.89; 4 studies) (Zaidi et al., 2011) reduction in all-cause mortality. Similarly, the reviews also reported reduction in pneumonia specific mortality by 42% (RR 0.58; 95% CI: 0.43, 0.78) (Bhutta et al., 2009a) and (RR 0.58; 95% CI: 0.41, 0.82; 3 studies) (Zaidi et al., 2011).

4.2.7. Prophylactic and Therapeutic use of Surfactant

The overview identified three reviews on the impact of prophylactic and therapeutic use of surfactant and reported moderate quality GRADE outcomes on neonatal mortality (Soll and Ozek, 2009; Soll, 1998; Bahadue and Soll, 2012). Soll pooled six studies on 2352 newborns that compared synthetic surfactant with placebo and found a significant 27% reduction in neonatal mortality (RR 0.73; 95% CI: 0.61, 0.88) (Soll, 1998). Soll and Ozek assessed the impact of multiple doses of surfactant with single dose from three trials on 1220 newborns with severe RDS and found a significant 41% reduction in neonatal mortality (RR 0.59; 95% CI: 0.44, 0.78) (Soll and Ozek, 2009). Bahadue and Soll compared early versus delayed selective surfactant treatment for RDS from six studies (n = 3577) and found a significant 16% reduction in neonatal mortality (RR 0.84; 95% C: 0.74, 0.95) (Bahadue and Soll, 2012).

4.2.8. Continuous Positive Airway Pressure (CPAP)

The overview identified three reviews (Greenough et al., 2008; Lemyre et al., 2002; Ho et al., 2002; Subramaniam et al., 2005), of which two reported mortality as an outcome (Greenough et al., 2008; Ho et al., 2002; Subramaniam et al., 2005). Greenough 2008 compared high frequency positive pressure ventilation (HFPPV) with conventional ventilation (CMV) and reported a non-significant 20% reduction in neonatal mortality (RR 0.80; 95% CI: 0.62, 1.03; three studies, n =

585 — moderate GRADE) (Greenough et al., 2008). Ho and colleagues compared continuous distending pressure (CDP) with standard care and found a significant 48% reduction in neonatal mortality (RR 0.52; 95% CI: 0.32, 0.87; six studies, n = 355 — moderate GRADE) (Ho et al., 2002). Subramaniam and colleagues, compared prophylactic CPAP with control and reported an increase in neonatak deaths with prophylactic use (RR 1.29; 95% CI: 0.45, 3.67 — low GRADE) (Subramaniam et al., 2005).

4.2.9. Case Management of Childhood Malaria

The overview identified four reviews (Eisele et al., 2010; Meremikwu et al., 2012; Thwing et al., 2011), of which Thwing and colleagues reported a reduction in malaria mortality in children 1 to 23 months (RR 0.01; 95% CI: 0.00, 0.06) and in children 24 to 59 months of age (RR 0.03; 95% CI: 0.01, 0.14 — moderate GRADE quality) (Thwing et al., 2011). Meremikwu and colleagues compared IPT versus placebo or no IPT and reported a non-significant reduction in child mortality (RR 0.66; 95% CI: 0.31, 1.39; six studies, n = 9533 — moderate GRADE quality) (Meremikwu et al., 2012).

4.2.10. Case Management of Childhood Pneumonia

The overview identified four reviews (Theodoratou et al., 2010; Sazawal and Black, 2003b; Lamberti et al., 2013; Das et al., 2013), of which two reviews reported mortality as an outcome. Both of these reviews reported a significant reduction in acute lower respiratory tract infections (ALRI) specific mortality (RR 0.65; 95% CI: 0.52, 0.82; nine studies) (Theodoratou et al., 2010); (RR 0.65; 95% CI: 0.52, 0.82) (Das et al., 2013) and all-cause mortality (RR 0.79; 95% CI: 0.70, 0.82; nine studies);Theodoratou et al., 2010 (RR 0.68; 95% CI: 0.53, 0.86) (Das et al., 2013) with case management of pneumonia when compared to standard or no care. The evidence was moderate quality on GRADE analysis.

4.2.11. Vitamin A as Part of Treatment for Measles-Associated Pneumonia for Children Above 6 Months

The overview identified two reviews (Fawzi et al., 1993; Sudfeld et al., 2010), of which one reported mortality (Fawzi et al., 1993). This review pooled eight studies on 135,609 children and compared vitamin A supplementation with none for measles associated pneumonia and reported a significant 30% reduction in child mortality (RR 0.70; 95 CI: 0.56, 0.87 — moderate GRADE quality) (Fawzi et al., 1993).

4.2.12. Home Visits Across the Continuum of Care women's Groups

The overview identified four reviews (Lassi et al., 2010; Kidney et al., 2009; Bhutta et al., 2009b; Gogia and Sachdev, 2010). Only two reviews (Lassi et al., 2010; Gogia and Sachdev, 2010) assessed home visitation as part of delivery strategy. Both of these reviews reported outcome on neonatal mortality (Lassi et al., 2010; Gogia and Sachdev, 2010), whereas only one reported outcomes on perinatal mortality and stillbirths (Lassi et al., 2010).

4.2.12.1. Neonatal Mortality. The review by Lassi and colleagues reported a 22% reduction in neonatal mortality (RR 0.78; 95% CI: 0.67, 0.92 — moderate GRADE quality) on pooling five studies on 56,878 participants (Lassi et al., 2010). On the other hand, Gogia 2010 pooled five studies and reported a 38% reduction in neonatal mortality (RR 0.62; 95% CI: 0.44, 0.87 — moderate GRADE quality) (Gogia and Sachdev, 2010).

4.2.12.2. Perinatal Mortality. The review by Lassi and colleagues pooled three studies on 45,835 participants and reported a 28% reduction in perinatal mortality (RR 0.72; 95% CI: 0.61, 0.85 — moderate GRADE quality) (Lassi et al., 2010).

4.2.12.3. Stillbirths. The review by Lassi and colleagues pooled three studies on 45,835 participants and reported a 27% reduction in stillbirths (RR 0.73; 95% CI: 0.67, 0.81 — moderate GRADE quality) (Lassi et al., 2010).

4.3. Ineffective or probably ineffective interventions

Panel 2 reports the list of interventions which were low or very low on GRADE quality and thus were categorized as interventions with insufficient evidence. Some of those interventions reported their impact on stillbirths, perinatal or neonatal mortality and those includes family planning (Kozuki et al., 2013), periconceptional folic acid supplementation (Blencowe et al., 2010b, De-Regil et al., 2010), folic acid supplementation during pregnancy (Lassi et al., 2013b, Pena-Rosas et al., 2012), smoking cessation during pregnancy (Coleman et al., 2012, Chamberlain et al., 2013), calcium supplementation during pregnancy (Imdad et al., 2011c, Hofmeyr et al., 2014), magnesium sulphate compared to phenytoin for prevention and management of pre-eclampsia (Duley et al., 2010a, Duley et al., 2010b, Duley et al., 2010c, Duley et al., 2010d), external cephalic version (Cluver et al., 2012, Hofmeyr et al., 2003, Hofmeyr and Kulier, 2012, Hutton and Hofmeyr, 2006), induction of labor for PROM (Buchanan et al., 2010), antibiotics for PROM (Kenyon et al., 2013, Cousens et al., 2010), active management for third stage of labor (McDonald et al., 2013,), thermal care (McCall et al., 2010), neonatal resuscitation with bad and mask (Lee et al., 2011), presumptive antibiotic therapy for newborn (Ungerer et al., 2004,), Comprehensive care of children infected or exposed to HIV infection (Grimwade and Swingler, 2006), Vitamin A as part of treatment for non-measles-associated pneumonia for children above 6 months (Wu et al., 2005), and case management of diarrhea (Yakoob et al., 2011).

5. Discussion

There have been many great successes in reducing neonatal mortality as part of the MDGs, however, the current rates are still too high since each year 2.9 million newborns do not live to their first month of life (Berkley et al., 2014). In order to accelerate the progress towards reaching the targets set for 2015, this overview aimed to identify key interventions for neonatal and later survival. Review of all the recent Cochrane and other reviews on pre-pregnancy, pregnancy, neonatal and child health interventions which have reported perinatal or neonatal and child mortality identified six highly effective and 11 promising interventions which are likely to improve health and survival among babies. During the past decade, notable advances have been made in reviewing the evidence base for newborn interventions (Bhutta et al., 2013, 2014), especially in the context of essential interventions, packages of care and their interconnections (Lassi et al., 2013a).

The key effective interventions for improving the survival identified in this overview include antenatal corticosteroids for preventing neonatal RDS in preterm infants; early initiation of breastfeeding; hygienic cord care; KMC for preterm infants; provision and promotion of use of ITNs for children; and vitamin A supplementation for infants from six months of age. Among these, four are particularly effective for neonates, while two had clear implications for improving the survival among infants and children. Most of the interventions identified are very effective for premature infants, as deaths from preterm births complications are the leading cause for neonatal deaths (Bhutta et al., 2013). Every year, an estimated 15 million babies are born preterm. Of these over one million die. The common cause of neonatal mortality is RDS which is related to prematurity. The incidence of mortality due to prematurity is highest in LMIC (Blencowe et al., 2012) where even moderately preterm babies strive for survival. Preventing deaths from preterm births, is therefore of the utmost importance. Administration of antenatal corticosteroids to women at risk of preterm birth can prevent deaths among babies related to RDS. This overview further suggests that the risk of deaths among those who are born too soon can be halved (50%) by encouraging KMC which not only ensures skin-to-skin contact, but promotes breastfeeding and early recognition of danger signs and

illnesses in newborns. Similarly, the benefits of breastfeeding have been well documented; with studies suggesting much greater benefits of early vs. late feeding (Debes et al., 2013). Early initiation of breastfeeding can reduce neonatal deaths by 44%. At the same time hygienic cord care can further reduces mortality by 23%. For children under the age of five years, infections accounts for a large number of deaths. Prevention of malaria particularly in malaria endemic countries can ensure 18% reduction in mortality. Provision of vitamin A for children above 6 months of age, which decreases the susceptibility towards infection, can also improve survival and health.

Despite the clear evidence of these interventions, coverage is still low and therefore their impact to reduce mortality among newborns and children is very poor. The recent Lancet every newborn series (Bhutta et al., 2013, 2014) has clearly highlighted that approximately three-quarters of deaths under five years can be averted if countries implement interventions at a coverage of 70–90% by 2025 (Bhutta et al., 2013). Considering the example of TT immunization, it is quite evident that 60% increase in coverage in last 25 years has led to 90% reduction in tetanus mortality in babies (Blencowe et al., 2010a). However, the coverage for insecticide treated bed nets in 2011 is still low 35.3% (5.2%–75.5%) and countries should prioritize mechanisms to increase coverage (Hill et al., 2014). Moreover, effective interventions such as hygienic cord care, which includes chlorhexidine cord cleansing, and adopting antenatal corticosteroids for preventing neonatal respiratory distress syndrome in preterm infants have very low coverage according to surveys with less than a third of women and neonates in need receiving them (Mason et al., 2014). Therefore, integrating these interventions into existing neonatal and childhood programs whereby mothers may also receive interventions such TT immunization, ITNs and corticosteroids when at risk at the same time may be an effective way to increase coverage.

High coverage of available interventions by 2025 can prevent almost three-quarters of neonatal deaths, and can save around 2 million lives per year (Bhutta et al., 2014). Interventions delivered in packages, especially for the care of small and ill neonates have the potential to save 1.9 million newborn infants (Bhutta et al., 2014). Estimate suggests that available interventions can reduce neonatal deaths related to prematurity by 58%, intrapartum by 79% and infections by 84% among neonates (Bhutta et al., 2014). Therefore, the implementation of the interventions identified in this overview will be of paramount importance for improving neonatal and child survival especially in the countries with the highest burden of mortality. It is vital to understand that these interventions are central for LMIC where neonatal and child health indicators are still not up to a high standards and many lives are either lost or their quality compromised due to a dearth of simple and effective actions (Bhutta et al., 2005). These interventions need to be deployed to all and promoted from the very outset, including the preconception period, which is vital to ensuring that women of child bearing age understand the importance of these interventions for their babies' health and survival.

A step forward to seeing improvements in annual reductions in neonatal mortality rates would be to pay more attention to the target group for the interventions; funding and resources may need to be reallocated to include stillbirth prevention which has received very little attention so far (Frøen et al., 2011). High fertility rates may also be adding to the problem. Care and resources in LMICs may be inadequate to cover already existing newborns; and increasing numbers of neonates will lead to strains on existing health care systems. Improved access to family planning, contraceptive methods, awareness and education will decrease the disparity and help efforts to achieve decreased neonatal mortality rates (Bhutta et al., 2014).

Community-based delivery strategies to increase access to needed care must be foremost to bringing about a positive change in the LMICs because appropriate education and awareness needs to precede interventions. Empowerment of women, removing barriers to accessibility to health care services, increased education and awareness in communities, and shifting the focus to evidence based interventions may help in adopting healthy practices among mothers and improve child survival rates (Bhutta et al., 2014). Appropriate, culturally sensitive education and awareness provided to the communities, followed by timely implementation of discussed interventions which can be integrated with existing healthcare practices, will definitely bring the required improvement in child health and survival.

Several limitations do however need to be recognised. First, it is important to consider that many of the interventions assessed in this review demonstrated important reductions in morbidity but may have been underpowered to show differences in neonatal and later survival. Second, it is also important to be aware that some clearly effective interventions, such TT immunization during pregnancy for reducing tetanus related mortality in neonates do not rate highly on GRADE, due to the study designs required to address this issue. Third, it is not possible to account for all the biases involved in the individual primary studies during the conduct of an overview of systematic reviews, where only systematic reviews and not individual primary studies are included. In addition, the high level synthesis of an overview may not always capture important contextual factors, such as educational attainment, socio-economic status, and access to care.

6. Conclusion

The implementation of these interventions will help in achieving the targets set for MDGs 4 and 5. Adoption of effective interventions promises a much needed improvement in neonatal and child outcomes around the world, especially if selected depending on the clinical indications and keeping in mind the need for cost-effectiveness in view of the limited resources in LMICs.

Research in Context

The synthesis of findings from 148 reviews on interventions for mothers and babies showed that steroids for pregnant mothers at risk of delivering babies early, breastfeeding, cord care, kangaroo care for babies born early, treated bednets for children, and vitamin A for babies from six months of age, are effective interventions for improving survival among babies and children. Antenatal care, tetanus injection during pregnancy, drugs to prevent malaria during pregnancy, inducing labour during prolonged pregnancy, use of surfactant and resuscitation to improve breathing among babies, management of infections among babies and children, and home visits during pregnancy and postnatal period, are the promising interventions for their survival.

Author's Contribution

ZSL conceptualised the review in consultation with PM, CC, and ZAB and wrote the first draft of the paper with substantial inputs from PM. ZSL, PM contributed to the scientific literature search, screening, collection, and analysis of data for all the included interventions with close inputs from CC and ZAB. All authors saw successive drafts of the paper and provided input. ZSL, PM, CC and ZAB finalized the paper and ZSL is the overall guarantor.

Conflict of Interest

None.

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