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A systematic review to identify proxy-indicators to quantify the impact of eHealth tools on maternal and neonatal health outcomes in low and middle-income countries - including Delphi consensus.

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Abstract

Background

E-Health can provide cost-efficient continuing education and specialized advice to isolated health care professionals in remote areas, therefore improving quality and access to health services. Often these applications are not being adopted on a significant scale, possibly due to the absence of robust and general supportive scientific evidence of their impact. The main difficulty of evaluating the impact remains in the limited identification of measurable and reliable indicators.

Objective

To identify interventions that could serve as reliable proxy-indicators to measure eHealth impact on maternal and neonatal outcomes.

Design

Systematic review and Delphi study.

Methods

We searched Pubmed, Embase, and Cochrane from January 1990 until May 2016 for studies and reviews that evaluated interventions aiming at improving maternal/neonatal health and reducing mortality. Interventions, which are not low and middle-income context appropriate, and that cannot currently be diagnosed or managed via telemedicine, or impacted via elearning were excluded. We used the Cochrane risk of bias, ROBINS-I, and ROBIS tool to assess risk of bias. A Delphi consensus was added to identify additional proxy-indicators and to prioritize the results.

Results

We included 44 studies and reviews for inclusion. These led to the identification of 40 potential proxy-indicators with a positive impact on maternal/neonatal outcomes. The Delphi experts completed and prioritized these, resulting in a list of 77 potential proxy-indicators.

Conclusions

The proxy-indicators propose relevant outcome measures to evaluate if eHealth tools directly affect

maternal/neonatal outcomes. Some of these need to be mapped to the local context, practices, and available resources. The local mapping facilitates the utilisation of the proxy-indicators in various contexts, while allowing systematically collecting data from different projects and programs. Based on the mapping the same proxy-indicator can be used for different contexts, measuring what is locally and temporally relevant, and is therefore sustainable.

Prospero registration number

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Strength and limitations of this study

- *Strength*: A review of this kind, aiming at identifying proxy-indicators that could be used to measure the impact of eHealth interventions on maternal and neonatal health outcomes, particularly in low and middle-income countries has not yet been attempted.
- *Limitation:* Some proxy-indicators may not have been identified in the systematic review due to a very low GRADE quality, or as they are standard of care. They may also have been overlooked as unforeseen, disruptive uses of eHealth may emerge and offer unexpected ways to improve practices.
- *Strength*: to address the limitation of not being able to address all potential proxy-indicators due to e.g. ethical reasons the results went through an expert Delphi consensus process with a group of international experts.

Introduction

Since 1990 maternal and child mortality have approximately halved, but still most of the remaining death are preventable.[1] Child mortality decreased disproportionate for older children and neonatal deaths account now for 45% of under 5-mortality.[2] Uneven progress between countries and within countries, with pro-rich and pro-urban inequalities, leaves women and children in rural areas with insufficient access to quality health care services.[1]

Information and communication technologies (ICTs) provide innovative approaches for alleviating inequalities, particularly in rural areas and isolated settings, by overcoming geographical barriers, increasing access to healthcare services, providing continuing education and enabling collaborative healthcare in remote locations.[3-13] The World Health Organization (WHO) defines eHealth as the cost-effective and secure use of ICTs for health and health-related fields. The potential of eHealth on positive therapeutic and clinical outcomes has been repeatedly postulated, but strong evidence is scarce. Although scientific literature offers an increasing number of publications studying the impact of eHealth tools on the quality, safety and cost-effectiveness of health care, there is still a significant gap between the postulated and empirically demonstrated benefits, including therapeutic and clinical outcomes.[14-19] It is essential to not only devote more effort to evaluation, but to ensure that the methodology adopted is multidisciplinary and thus capable of disentangling the often complex web of factors that may influence the results. It is equally important that existing activities are subject to rigorous, multidisciplinary, and independent

assessment. Even though low-cost telemedicine applications have proven to be feasible, clinically useful, sustainable, and scalable in such settings and underserved communities, these applications are not being adopted on a significant scale due to a variety of barriers, and possibly due to the absence of robust and general supportive scientific evidence of their impact.[14-16,20 21]

The need for evaluating eHealth impact on patient outcomes has been strongly emphasized.[18 19 21-27] The main barrier remains in the limited identification of measurable and reliable indicators. The relevance of these indicators may be context-dependent and their extrapolation considerably restricted. Availability of outcome indicators (direct and proxy) will facilitate consistent outcome measurements and comparability of studies.

The objective of this review is to identify proxy-indicators that can be utilized in future studies aiming at measuring the impact of eHealth interventions on maternal/neonatal health outcomes in low and middle-income countries (LMIC). The review question is: Which interventions that can be impacted by eHealth applications have results that can be clearly linked to maternal and neonatal health outcomes in LMIC countries and could therefore serve as reliable proxy-indicators?

Methods

The review methodology has been described in detail and registered in PROSPERO beforehand.[28] In short, the review identified interventions, which have an alleged impact on maternal/neonatal health, and are suitable for delivery in LMICs, to serve as proxy-indicators. In this article, previous reviews are included according to the recommendations for integrating existing systematic reviews into new reviews by Robinson et al.[29]

Searching

To identify studies and reviews that evaluated the effect of interventions on maternal and neonatal health a comprehensive search of Pubmed, EMBASE, and the Cochrane Library was carried out using a combination of text words and controlled vocabulary terms related to the interventions and possible outcome measures. The search strategy was adapted for each database. Studies with an abstract published in English from 1990 to May 2016 were considered for inclusion.

Inclusion/exclusion criteria

Randomized controlled trials, quasi-experimental studies, observational studies, systematic reviews, and inter-governmental and non-governmental agency reports were considered for this review.

Population: Pregnant women at any gestation age, postpartum women up to 6 weeks after giving birth, and newborns (up to 28 days after birth).

Intervention: We included any intervention at health system level aiming at improving maternal/neonatal health and reducing maternal/neonatal mortality.

Type of outcome measures: neonatal outcomes (e.g. neonatal mortality, stillbirth, low birth weight, preterm birth), and maternal outcomes (e.g. maternal mortality, preeclampsia, gestational hypertension).

Studies were excluded if they are not LMIC context appropriate or, if the interventions cannot currently be

diagnosed, managed, or impacted by eHealth interventions.

Study selection

One author conducted an initial screening to exclude duplicates and articles whose titles were obviously irrelevant. After the initial screening, two reviewers independently rated the title and abstract of each search result based on relevance to the study objectives. The third reviewer resolved discrepancies in the rating. It was verified that single studies were not already included in the systematic reviews and if so they were excluded. Figure 1 summarizes the study selection.

Data abstraction, quality assessment, and data synthesis and analysis

Study design, setting, study population characteristics, description of the intervention, outcomes measured and effects of studies, which were assessed as eligible, were abstracted by one author into a standardized spreadsheet and were thoroughly checked by the second reviewer. Disagreements were resolved by discussion and, if necessary, by arbitration involving the third reviewer. The risk of bias was assessed for all included studies and reviews. Randomized trials were assessed with the Cochrane risk of bias, non-randomized studies with the Cochrane ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions), and systematic reviews with the ROBIS (Tool to assess risk of bias in systematic reviews) tool.[30-32] The evidence of studies and reviews that met our inclusion criteria was summarized by outcome (proxy-indicators) including a quality assessment in a tabular form. For each proxy-indicator, the summary of findings (SOF) table includes the number of studies, a summary of the intervention effect, and a measure of the quality of evidence for each outcome according to GRADE.[33-35] Existing GRADE assessments of systematic reviews have been included after verification and are marked with a * in the SOF Table.

Delphi consensus

The results went through an expert Delphi consensus in a group of international experts, with the objective to complete and prioritize the provisional list of proxy-indicators. Indeed, some proxy-indicators may have been missed due to e.g. very low GRADE quality, as some interventions could not be conducted as randomized studies for ethical reasons.

The team of international experts completed the list of indicators and assessed each, as proxy-indicator identified intervention according to 1) their potential to reduce maternal and newborn morbidity and mortality, 2) whether they should be considered an 'essential' intervention, and 3) the appropriate level of care (primary, referral or both). An essential intervention was defined as an essential medical intervention, or ‘signal function,’ that treat the major causes of maternal/newborn morbidity and mortality. An essential intervention should be prioritized. Primary level care was defined as: may be provided by a nurse, family physician or other type of health worker. For example, a rural health center in Africa would be considered as primary level. Referral level care was defined as: this level of delivery refers to hospitals in general (district or referral), the health care providers at this level are professionals.

In round 1 of the Delphi consensus the experts added potential proxy-indicators to the provisional list

(Table 1). The results were grouped and drafted for circulation to all participants in a questionnaire. In round 2 the experts ranked their agreement with each statement. The rankings were summarized using the median and the interquartile range, and included in a repeat version of the questionnaire. In Round 3, the experts re-ranked their agreement with each statement, with the opportunity to change their score in view of the group's response. The re-rankings were summarized and assessed for degree of consensus using interquartile ranges for continuous numerical scales, and were accepted when the interquartile range was 2 or less.

The results of the Delphi consensus are summarized in Table 2 and are rated as low (+) if the median was between 0-3, medium (++) if the median was between 4-6, and high (+++) if the median was between 7-9.

Results of the systematic review

Our initial search identified 1725 publications, 44 additional records were identified through hand searching. The title and abstract scan resulted in 141 publications that underwent full-text review. Forty-four articles met our selection criteria after the full-text review. The results of the review are 40 potential proxy-indicators that are summarized in the SOF Table (Table 1).

Outcome group	Outcome	Effect	Studies	Quality of the Evidence (GRADE)
PRECONCEPTION				
Birth spacing: inter-pregnancy-interval (IPI) between 6 months and under 60 months [36]				
Neonatal outcome	Preterm birth with short IPI (<6months)	OR 1.40, 95% CI [1.24, 1.58]	8	HIGH*
Neonatal outcome	Low birth weight with short IPI (<6months)	OR 1.61, 95% CI [1.39, 1.86]	4	HIGH*
Neonatal outcome	Birth outcome: preterm birth with long IPI (>60 months)	OR 1.20, 95% CI [1.17, 1.24]	7	HIGH*
Neonatal outcome	Birth outcome: low birth weight with long IPI (>60 months)	OR 1.43, 95% CI [1.27, 1.62]	4	HIGH*
Folic acid supplementation and fortification [37]				
Neonatal outcome	Primary prevention of neural tube defect	RR 0.38, 95% CI [0.29, 0.51]	4	MODERATE*
PREGNANCY				
Multiple micronutrient supplementation (with Iron and folic acid) [38]				
Neonatal outcome	Low birth weight	RR 0.88, 95% CI [0.85, 0.90]	15	HIGH*
Neonatal outcome	Stillbirth	RR 0.92, 95% CI [0.86, 0.99]	15	HIGH*
Administration / advice of folic acid to women with history of baby of Neural Tube Defect (NTD) [39]				
Neonatal outcome	Secondary NTD reduction	RR 0.30, 95% CI [0.14, 0.65]	3	HIGH
Diet supplementation (high energy biscuits) for chronically undernourished women [40]				
Neonatal outcome	Stillbirth	OR 0.47, 95% CI [0.23, 0.99]	1	LOW
Neonatal outcome	Mortality within 7 days	OR 0.54, 95% CI [0.35, 0.85]	1	LOW
Tetanus Toxoid immunization (at least 2 vaccinations) [41 42]				

Neonatal outcome	Tetanus specific neonatal mortality	RR 0.06, 95% CI [0.02, 0.20]	2	MODERATE*
Neonatal outcome	Preventing neonatal tetanus against neonatal death	RR 0.02, 95% CI [0.00, 0.30]	1	MODERATE*
Syphilis screening with treatment [43]				
Neonatal outcome	Stillbirth	RR 0.18, 95% CI [0.10, 0.33]	8	LOW*
Neonatal outcome	Neonatal mortality	RR 0.20, 95% CI [0.13, 0.32]	5	LOW*
Routine drug administration to prevent malaria and its consequences in pregnant women in areas of moderate to high malaria transmission [44]				
Maternal outcome	Severe anemia (during the third trimester)	RR 0.60, 95% CI [0.47, 0.75]	5	HIGH*
Maternal outcome	Antenatal parasitemia	RR 0.39, 95% CI [0.26, 0.58]	8	HIGH*
Intermittent preventive treatment of malaria in pregnancy (IPTp) [42]				
Maternal outcome	Maternal death	RR 0.79, 95% CI [0.29, 2.20]	2	MODERATE*
Neonatal outcome	Neonatal mortality	RR 0.69, 95% CI [0.49, 0.98]	6	HIGH*
Neonatal outcome	Low birth weight	RR 0.71, 95% CI [0.57, 0.89]	9	MODERATE*
Smoking cessation during pregnancy (psychosocial interventions) [45]				
Neonatal outcome	Preterm birth	RR 0.82, 95% CI [0.70, 0.96]	14	MODERATE*
Neonatal outcome	Low birth weight	RR 0.82, 95% CI [0.71, 0.94]	14	MODERATE*
Prevention and Management of HIV and Prevention of Mother to Child Transmission in Pregnancy				
Rapid HIV testing [46]				
Maternal outcome	HIV-testing uptake	RR 2.95, 95% CI [1.69, 5.16]	13	MODERATE*
Antiretroviral therapy e.g. Zidovudine (ZDV) given to mothers from 36 weeks gestation, during labor [47]				
Neonatal outcome	Reduced HIV infection at 4-8 weeks	Efficacy 43.78%, 95% CI [9.05, 60.05]	6	HIGH
Adherence to Antiretroviral medication; mobile phone messages [48]				
Maternal outcome	Viral load suppression at 52 weeks	RR 0.83, 95% CI [0.69, 0.99]	1	HIGH*
Maternal outcome	ART adherence at 48-52 weeks	RR 0.82, 95% CI [0.72, 0.94]	2	HIGH*
Management of pre-labor rupture of membranes and preterm labor				
Calcium Channel Blockers for women in preterm labor [49]				
Neonatal outcome	Reduction in birth less than 48 hours after trial entry	RR 0.30, 95% CI [0.21, 0.43]	2	LOW*
Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth [50]				
Neonatal outcome	Neonatal mortality	RR 0.69, 95% CI [0.58, 0.81]	18	HIGH*
External cephalic version for breech presentation at term (Spinning babies) [51]				
Neonatal outcome	Perinatal death	RR 0.39, 95% CI [0.09, 1.64]	8	LOW*
Prevention and Management of Hypertension in Pregnancy				
Ultrasound for detection of pre-eclampsia [52 53]				
Maternal outcome	Abnormal Doppler US developing preeclampsia	OR 2.93, 95% CI [1.20, 7.30]	1	LOW
Maternal outcome	Increased pulsatility index with notching (low risk patients)	PLR 7.5, 95% CI [5.40, 10.20]	1	LOW
Maternal outcome	Increased pulsatility index with notching (high	PLR 21, 95% CI [5.50, 80.50]	1	LOW

	risk patients)			
Maternal Calcium Supplementation [54 55]				
Maternal outcome	Severe preeclampsia	RR 0.75, 95% CI [0.57, 0.98]	5	MODERATE*
Maternal outcome	Gestational hypertension	RR 0.65, 95% CI [0.53, 0.81]	12	MODERATE*
Maternal outcome	Preeclampsia	RR 0.45, 95% CI [0.31, 0.65]	13	HIGH*
Neonatal outcome	Preterm birth	RR 0.76, 95% CI [0.60, 0.97]	11	HIGH*
Antiplatelets for pre-eclampsia (low dose aspirin) [56]				
Maternal outcome	Preeclampsia	RR 0.83, 95% CI [0.77, 0.89]	43	MODERATE*
Magnesium sulfate [57 58]				
Maternal outcome	Eclampsia	RR 0.41, 95% CI [0.29, 0.58]	6	HIGH*
Maternal outcome	Case fatality rate of severe preeclampsia and Eclampsia	RR 0.11, 95% CI [0.07, 0.16]	1	LOW
Early administration of magnesium sulfate (at home before referral) [59]				
Maternal outcome	Case fatality rate of severe preeclampsia and eclampsia	RR 0.21, 95% CI [0.06, 0.72]	1	LOW
Management of unintended pregnancy				
Combination of contraceptive-promoting and educational intervention [60]				
Maternal outcome	Unintended pregnancy among adolescents	RR 0.66 95% CI [0.50, 0.87]	4	MODERATE*
Medications for induced abortion (mifepristone, misoprostol) [61]				
Maternal outcome	No difference in complete abortion rates between medication and clinics group	OR 0.80, 95% CI [0.50, 1.50]	9	MODERATE
CHILDBIRTH				
Induction of labor for prolonged pregnancy (uterotonics: oxytocin, misoprostol) [62]				
Neonatal outcome	Perinatal mortality	RR 0.31, 95% CI [0.11, 0.88]	19	MODERATE*
Clean birth and postnatal practices at facility [63]				
Neonatal outcome	Neonatal mortality from sepsis	RR 0.73, 95% CI [0.64, 0.76]	DELPHI	LOW*
Neonatal outcome	Neonatal mortality from sepsis	RR 0.85, 95% CI [0.80, 0.90]	DELPHI	LOW*
Birth attendant hand washing before birth [63]				
Neonatal outcome	Cord infection	RR 0.70, 95% CI [0.61, 0.80]	2	MODERATE*
Management of postpartum hemorrhage				
Active management of third stage of labor (AMTSL) [64]				
Maternal outcome	Maternal Hb <9 g/dl 24 to 72 hours postpartum	RR 0.50, 95% CI [0.3, 0.83]	2	LOW*
Controlled cord traction (as part of AMTSL) [65]				
Maternal outcome	Blood loss > 500ml	RR 1.07, 95% CI [1.00, 1.14]	2	HIGH*
Preventive uterotonic drugs in the absence of active management of labor				
Oxytocin (when available) [66]				

Maternal outcome	Active bleeding controlled within 20 min	RR 0.94, 95% CI [0.91, 0.98]	1	HIGH
Oral misoprostol in preventing postpartum hemorrhage (when injectable uterotonics not available) [67]				
Maternal outcome	Blood loss >1000 ml	RR 0.66, 95% CI [0.45, 0.98]	1	HIGH
Uterine balloon tamponade (condom catheter) [68 69 70]				
Maternal outcome	UBT successfully treated PPH	97% [234 out of 241 cases]	13	LOW
Maternal outcome	All cause survival	95% [90 out of 201 cases]	1	LOW
Maternal outcome	Successful treatment of PPH	97% [223 out of 229 cases]	1	MODERATE
NEONATAL CARE				
Umbilical cord antiseptics in community and primary care settings [63 71]				
Neonatal outcome	Neonatal mortality	RR 0.81, 95% CI [0.71, 0.92]	3	HIGH*
Neonatal outcome	Omphalitis/infections	RR 0.77, 95% CI [0.63, 0.94]	3	HIGH*
Early skin to skin contact [72]				
Neonatal outcome	Breastfeeding 0–4 months post birth	RR 1.27, 95% CI [1.06, 1.53]	13	MODERATE
Delaying bathing until the second day of life [73]				
Neonatal outcome	Hypothermic newborn, rectal temperature	OR 2.90, 95% CI [1.69, 5.05]	1	MODERATE
Neonatal outcome	Hypothermic newborn, tympanic temperature	OR 4.67, 95% CI [2.62, 8.38]	1	MODERATE
Early initiation of breastfeeding (within the first 24 hours) [74]				
Neonatal outcome	Neonatal mortality	RR 0.56, 95% CI [0.40, 0.79]	3	MODERATE*
Exclusive breastfeeding in the first month of life [75]				
Neonatal outcome	Neonatal mortality exclusive vs. partial breastfeeding	OR 0.27, 95% CI [0.15, 0.49]	2	MODERATE*
Prophylactic vitamin K for vitamin K deficiency bleeding in neonates [76]				
Neonatal outcome	Any moderate to severe bleeding	RR 0.19, 95% CI [0.08, 0.46]	1	LOW*
Interventions for small and ill babies				
Kangaroo mother care for preterm and for < 2000g babies [28 77]				
Neonatal outcome	Neonatal mortality at discharge	RR 0.60, 95% CI [0.39, 0.92]	8	HIGH
Neonatal outcome	Neonatal mortality at latest follow up	RR 0.67, 95% CI [0.48, 0.95]	11	HIGH
Neonatal resuscitation and immediate newborn assessment at facility [78]				
Neonatal outcome	Early neonatal deaths	RR 0.62, 95% CI [0.41, 0.94]	3	MODERATE*
Danger signs predicting severe newborn illness to be assessed during postnatal contacts (predictive for need for hospitalization) [79]				
Neonatal outcome	History of difficulty feeding	OR 10.00, 95% CI [6.90, 14.50]	2	LOW
Neonatal outcome	Movement only when stimulated	OR 6.90, 95% CI [3.00, 15.50]	2	LOW
Neonatal outcome	Temperature <35.5	OR 9.20, 95% CI [4.60, 8.60]	2	LOW
Neonatal outcome	Temperature >/= 37.5	OR 3.40, 95% CI [2.40, 4.90]	2	LOW
Neonatal outcome	Respiratory rate >/=60	OR 2.70, 95% CI [1.90, 3.80]	2	LOW
Neonatal outcome	Severe chest in drawing	OR 8.90, 95% CI [4.00, 20.01]	2	LOW

Neonatal outcome	History of convulsions	OR 15.40, 95% CI [6.40, 37.20]	2	LOW

TABLE 1: Summary of Findings Table

1. Preconception

The preconception interventions reviewed included birth spacing and micronutrient supplementation.

Higher risk for preterm birth, and low birth-weight (LBW) are associated to short inter-pregnancy-intervals (IPI) (less than 6 months) as well as long IPIs (60 months or more after birth), compared to an IPI of 18 to 23 months.[36] Therefore, especially in a LMIC context, birth spacing may be considered as an intervention to prevent these adverse outcomes.[39]

Folic acid supplementation and fortification are effective in reducing neonatal mortality, therefore women in reproductive age planning a pregnancy should be advised to take folic acid supplements pre-conceptually.[37]

2. Pregnancy

The antenatal interventions reviewed included micronutrient and diet supplementation, maternal immunization, screening and management of infections (syphilis, HIV/AIDS, malaria), prevention and management of pregnancy-induced disorders (notably arterial hypertension), management of pre-labor rupture of membranes and preterm labor, drug misuse, and management of unintended pregnancy.

Multiple micronutrient (MMN) supplementation (iron and folic acid) is improving birth outcomes.[38] Such supplementation is recommended, especially for pregnant women in LMIC where MMN deficiencies are common among women of reproductive age, and to woman with a history of baby with neural tube defect (NTD), as folic acid reduces recurrence by 70%, 95% CI [35, 86].[39]

Low birth weight (LBW) is a major contributor to neonatal mortality and over 95% of LBW babies are born in developing countries.[80] While there has been controversy about whether dietary supplementation (e.g. high energy biscuits for chronically undernourished women) in pregnancy can increase birth weight, [81-84] the 5-year prospective randomized controlled trial in 28 rural Gambian villages by Ceesay et al. concludes that supplementation significantly reduces perinatal mortality in at risk mothers (stillbirth OR 0.47, 95% CI [0.23, 0.99]).[40]

Major progress has been made for neonatal tetanus but it remains a significant preventable cause of neonatal mortality globally.[2] Immunization of pregnant women or women of reproductive age with at least two doses of tetanus toxoid is estimated to reduce mortality from neonatal tetanus by 94%, RR 0.06, 95% CI [80, 98].[42]

Infection is a well-acknowledged cause of stillbirth and accounts for an estimated half of all stillbirth, particularly in LMICs.[85] Syphilis screening and treatment with penicillin reduces syphilis related stillbirth by 82% RR 0.18, 95% CI [0.10, 0.33] and syphilis-specific neonatal death by 80% RR 0.20, 95% CI [0.13, 0.32].[43] The effect in all studies was large and there is a clear biological mechanism, but as only few of the included studies were adjusted for potential confounding factors, quality of the evidence was graded low.[43,86]

Intermittent preventive treatment of malaria in pregnancy (IPTp) is a routine drug administration to prevent malaria and its consequences in pregnant women in areas of moderate to high malaria transmission**.** Routine chemoprevention for malaria and its consequences have been extensively tested in RCTs, with clinically important benefits on anemia RR 0.60, 95% CI [0.47, 0.75] and parasitemia RR 0.39, 95% CI [0.26, 0.58] in the mother, and on birth weight in infants.[44] Bhutta et al. conclude similarly with reduced neonatal mortality RR 0.69, 95% CI [0.49, 0.98].[42]

The majority of HIV-infected children acquired their infections as a result of mother-to-child transmission during pregnancy, labor, or breastfeeding. In areas with lower health services infrastructure infections may stay undetected, which is problematic as early diagnosis and treatment demonstrated improved clinical outcomes.[87 88] About 50% of people living with HIV are unaware of their diagnosis.[46 89] Reliable point-of-care HIV diagnostic tests, administering antiretroviral drugs to the HIV-infected mother and/or to her child during pregnancy, labor, or breastfeeding, and adherence to antiretroviral medication are essential to prevent vertical transmission.[47,48,90]

Preterm birth is a major contributor to perinatal mortality and morbidity. Calcium channel blockers (CCBs) for women in preterm labor have benefits over placebo or no treatment in terms of postponement of birth RR 0.30, 95% CI [0.21, 0.43] and were shown to have benefits over beta-mimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects.[49] Corticosteroid therapy used to accelerate fetal lung maturation for women at risk of preterm birth is relatively inexpensive and feasible to implement at primary level in a LMIC context if skilled health-care providers are available to identify women at risk of preterm birth and administer intramuscular injections.[50, 91]

Gestational hypertensive diseases, including pregnancy-induced hypertension, pre-eclampsia, and eclampsia are a leading causes of maternal and infant morbidity and mortality.[92] Early detection is crucial for monitoring and prevention. Preeclampsia is related to a lack of placental invasion and its complications on the pregnancy can be detected by Ultrasound.[52,53,93] Gestational calcium supplementation is associated with a reduction in hypertensive disorders in pregnancy, especially for women with a low calcium intake.[54 94 95] It reduces gestational hypertension RR 0.65, 95% CI [0.53, 0.81], severe preeclampsia RR 0.75, 95% CI [0.57, 0.98], and preeclampsia RR 0.45, 95% CI [0.31, 0.65].[54,55]Antiplatelets (e.g. low dose aspirin) are used to prevent preeclampsia as it affects blood clotting, and should be administered to pregnant women at high risk of preeclampsia or those with gestational hypertension.[39 56] Magnesium sulfate is one of the most effective anticonvulsivant to protect women from severe preeclampsia and eclampsia, and, if administered timely, reduces the risk of seizure repetition and reduces case fatality rate of severe preeclampsia and eclampsia.[96-98] Magnesium sulfate more than halves the risk of eclampsia RR 0.41, 95% CI [0.29, 0.58].[57,58] For the women who received a magnesium sulfate injection before referral, case fatality rate of severe preeclampsia and eclampsia reduced by 79% RR 0.21, 95% CI [0.06 , 0.72].[59] Even though the effect was strong, due to a small sample size, the evidence was graded low. WHO recommends that women with severe preeclampsia should be transferred to a secondary or tertiary level of health care and that magnesium sulfate should be administered to these women prior to referral.[99]

A combination of contraceptive promoting and educational interventions reduce unintended pregnancy RR 0.66, 95% CI [0.50, 0.87], while only contraceptive-promoting interventions showed little or no difference in the risk of unintended first pregnancy RR 1.01, 95% CI [0.81, 1.26].[60]

Medical abortion uses drugs (Mifepristone, Misoprostol) to terminate a pregnancy and is an important alternative to surgical methods of pregnancy termination, especially in areas (e.g. rural setting in a low-income country) where access to surgical termination is non-existent or very challenging.[61,100]

3. Childbirth

Interventions during and close to childbirth include clean birth and postnatal practices, the management of postpartum hemorrhage, and preventive uterotonic drugs in the absence of active management of labor.

Clean birth practices include: hand washing, clean perineum, clean birth surface, cutting of the umbilical cord using a clean implement, and clean cord tying.[63] Clean postnatal practices include: chlorhexidine, other antimicrobial applications to the cord, avoidance of harmful cord applications, skin applications and emollients, and hand washing.[63] They are estimated to reduce neonatal mortality in a facility RR 0.73, 95% CI [0.64, 0.76] and home setting RR 0.85, 95% CI [0.80, 0.90]. Even though the evidence quality is low or very low, as there is strong biological plausibility, the GRADE recommendation for these practices is strong. [42 63]

Active management of third stage of labor (AMTSL) is a package of three components or steps: 1) administration of an uterotonic, preferably oxytocin, immediately after birth of the baby; 2) controlled cord traction (CCT) to deliver the placenta, if skilled birth attendants are available; [65 101] and 3) massage of the uterine fundus after the placenta is delivered, with administration of an uterotonic as most important part.[64,101] The use of uterotonics for the prevention of postpartum hemorrhage (PPH) during the third stage of labor is recommended for all births.[101]

In the absence of AMTSL, a preventive uterotonic drug (oxytocin or misoprostol) should be administered by a health worker trained in its use for prevention of PPH.[66,101] If both, oxytocin and misoprostol are available, oxytocin is the preferred first-line treatment.[66 101] Oral or sublingual misoprostol compared with placebo is effective in reducing severe PPH RR 0.66, 95% CI [0.45, 0.98] and is a suitable first-line treatment alternative for PPH in settings where the use of ocytocin is not feasible. [66 67]

Uterine balloon tamponade (UBT) is a relatively simple approach and demonstrated to be an effective technique to treat PPH in developed countries, but is underutilized in developing countries due to the high cost of the balloon. A sterile rubber catheter fitted with a condom was developed as innovative low cost alternative in Bangladesh in 2001.[102] Three studies suggest that C-UBT is simple to use, inexpensive, safe, and may be used by any healthcare provider involved in delivery for controlling massive PPH.[68-70]

4. Neonatal Care

Interventions for all newborn babies include hygienic care, prevention of hypothermia, support for immediate breastfeeding, and prophylactic vitamin K.

Early initiation and exclusiveness of breastfeeding are generally recommended as essential newborn intervention.[42 74,103] Early skin-to-skin contact benefits breastfeeding outcomes at 0-4 months post birth RR 1.27, 95%CI [1.06, 1.53],[72] while early initiation of breastfeeding lowers all cause neonatal

mortality among live birth RR 0.56, 95% CI [0.40, 0.79].[74] Exclusive breastfeeding reduces the risk of neonatal mortality OR 0.27, 95% CI [0.15, 0.49] compared to partial breastfeeding.[75] Neonates are to benefit from this low-cost intervention, especially in LMICs.

Thermal care is recommended for all newborns to prevent hypothermia (immediate drying, warming, skin to skin, delayed bathing).[39] Bathing in warm water one hour after delivery was associated with a significant increase in hypothermia in both measurement methods, rectal OR 2.90, 95% CI 1.69, 5.05] and tympanic OR 4.67, 95% CI [2.62, 8.38].[73]

Neonatal chlorhexidine cord care reduces the incidence of omphalitis RR 0.77, 95 % CI [0.63, 0.94] and neonatal mortality RR 0.81, 95% CI [0.71, 0.92].[71]

A single dose of 1 mg of intramuscular vitamin K after birth is effective in the prevention of classic hemorrhagic disease of the newborn RR 0.19, 95% CI [0.08, 0.46].[76]

Interventions for small and ill newborn babies include neonatal resuscitation and immediate newborn assessment, prevention of hypothermia, and danger signs predicting severe newborn illness to be assessed during postnatal contacts.

Every year an estimated 10 million babies require assistance to initiate breathing. Basic neonatal care (warming, drying, stimulation and resuscitation including bag-and-mask ventilation) would be sufficient to save most babies in need of resuscitation in low-resource settings.[104] Training of neonatal resuscitation in facilities could reduce 30% of intrapartum-related mortality RR 0.70, 95% CI [0.59, 0.84] and 38% of early neonatal mortality RR 0.62, 95% CI [0.41, 0.94].[78] The coverage of this intervention remains low in countries where most neonatal deaths occur, a missed opportunity to save lives.[78]

Kangaroo mother care (KMC), amongst other benefits, is associated with a reduction in the risk of mortality at discharge (or 40-41 weeks postmenstrual) RR 0.60, 95% CI [0.39, 0.92], and a mortality reduction at the latest follow up RR 0.67, 95% CI [0.48, 0.95]. [77] KMC in LBW infants is an alternative to conventional neonatal care.

The Young Infants Clinical Signs Study Group developed a single simple algorithm that can identify severe illness in infants aged 0–2 months who are brought to health facilities.[79] The algorithm was developed from a large prospectively collected dataset and consists of seven signs: 1) history of difficulty feeding, 2) history of convulsions, 3) movement only when stimulated, 4) respiratory rate of 60 breaths per minute or more, 5) severe chest in-drawing, 6) temperature of 37·5°C or more, 7) temperature below 35.5°C. Each of these signs is predictive for the need of hospitalization in infants of the age group 0-6 days and 7-59 days, and should be used to identify sick infants that need referral faster.[79]

Results of the Delphi consensus

The Delphi experts completed and prioritized the results of the systematic review, resulting in a table of 77 potential proxy-indicators (Table 2).

I. PRECONCEPTION	Mortality/ Morbidity	Essential	Primary	Referral
Family Planning				

Birth spacing: inter-pregnancy-interval (IPI) between 6 months and under 60 months	++	++	✓	✓
Combination of contraceptive-promoting and educational interventions to avoid unwanted pregnancy*	+++	+++	✓	-
Folic acid supplementation and fortification	++	+++	✓	✓
Administration / advice folic acid to women with history of baby of NTDs*	+++	+++	✓	✓
Advise for cessation of alcohol consumption*	+++	+++	✓	✓
Education (maternal age, physiology, nutritional status of mother: BMI, etc)*	+++	+++	✓	-
Weight reduction in overweight, obese and morbidly obese women*	+++	+++	✓	✓
Rubella screening*	++	++	✓	-
Hemoglobin level / anemia status before pregnancy*	+++	+++	✓	✓

II. PREGNANCY	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Iron and folic acid supplementation (multiple micronutrient)	+++	+++	✓	✓
Iron supplementation from second trimester to 3 months postnatal*	+++	+++	✓	✓
Nutritional status of mother: BMI*	+++	+++	✓	-
Diet supplementation (high energy biscuits) for chronically undernourished women	++	++	✓	✓
Tetanus toxoid immunization (at least 2 vaccinations)	+++	+++	✓	✓
Whooping cough immunization at T2 or T3*	+++	+++	✓	✓
Syphilis screening with treatment	++	+++	✓	✓
Intermittent preventive treatment of malaria in pregnancy (IPTp)	+++	+++	✓	✓
Identification of bacteriuria and treatment (Urine culture and antibiotic treatment of bacteriuria)*	+++	+++	✓	✓
Palpation of uterus and measurement of fundus height (for detecting problems with fetal growth)*	++	++	✓	-
Advise for cessation of alcohol consumption (adverse effect of alcohol)*	+++	+++	✓	✓
Smoking cessation during pregnancy (psychosocial interventions)	+++	+++	✓	✓
Management of unintended Pregnancy: Medications for induced abortion (Mifepristone, Misoprostol)	+++	+++	✓	✓
Thyroxine for euthyroid women with positive antithyroid antibodies & recurrent miscarriages*	++	++	-	✓
Kegel exercises to reduce stress incontinence*	+	+	✓	✓
Fasting Blood Sugar checking for high risk population for Gestational diabetes mellitus*	+++	+++	✓	✓
Availability of ultrasound	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Fetal echography screening: abnormalities, malformations, growth retardation, Macrosomia*	++	++	-	✓
Prevention and management of HIV and prevention of mother to child transmission in pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Rapid HIV testing	+++	+++	✓	✓
Antiretroviral therapy	+++	+++	✓	✓
Adherence to Antiretroviral medication; mobile phone messages	+++	+++	✓	✓
Management of pre-labor rupture of membranes and preterm labor	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Calcium Channel Blockers for women in preterm labor	++	+++	✓	✓
Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth	+++	+++	✓	✓
Antenatal transfer to higher level of neonatal care*	+++	+++	✓	✓
Magnesium sulfate in preterm delivery before 34 weeks for neuro-protection*	+++	+++	-	✓
Antibiotics in management of preterm pre-labor rupture of membranes*	+++	+++	✓	✓
Prevention and management of hypertension in pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Early detection of pre-eclampsia by signs and symptoms*	+++	+++	✓	✓
(Better) implementation/adherence to protocols for pregnancy-induced hypertension (PIH)*	+++	+++	✓	✓
Antihypertensive drugs to treat pregnancy-induced hypertension (PIH)*	+++	+++	✓	✓
Maternal calcium supplementation (in areas with poor calcium diet)	+++	+++	✓	✓
Antiplatelet drugs for pre-eclampsia (low dose aspirin)	+++	+++	✓	✓

Use of magnesium sulfate	+++	+++	✓	✓
Early administration of magnesium sulfate (before referral)	+++	+++	✓	✓

III. CHILDBIRTH	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
External cephalic version (ECV) for breech presentation at term	+++	+++	-	✓
Clean birth and postnatal practices at facility	+++	+++	✓	✓
Birth attendant hand washing before birth	+++	+++	✓	✓
Fetal heart (intermittent) auscultation*	+++	+++	✓	✓
Early referral if prolonged labor*	+++	+++	✓	-
Instrumental vaginal delivery (e.g. Kiwi vacuum extractor)*	+++	+++	✓	✓
Delivery of baby to mother's abdomen*	+++	+++	✓	✓
Antibiotic prophylaxis against streptococcus B*	+++	+++	✓	✓
Induction of prolonged pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Induction of labor for prolonged pregnancy with uterotonics (oxytocin, misoprostol)	+++	+++	-	✓
Induction with Foley catheter*	+++	+++	-	✓
Management of postpartum hemorrhage	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Active management of third stage of labor (AMTSL)	+++	+++	✓	✓
Use of uterotonics for PPH prevention: oxytocin preferred (if available), oral misoprostol 2nd choice (when injectable uterotonics not available)	+++	+++	✓	✓
Uterine balloon tamponade (UBT) (condom catheter)	+++	+++	✓	✓
Measurement of blood loss (Blood collection bag, blood collection sheets)*	+++	+++	✓	✓
Recombinant Factor VII in massive PPH*	++	++	✓	✓
Tranexamic acid in post-partum hemorrhage (PPH)*	+++	+++	✓	✓
Uterine massage and emptying the bladder*	+++	+++	✓	✓

IV. NEONATAL CARE	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Umbilical cord antiseptics in community and primary care settings	+++	+++	✓	✓
Early skin to skin contact	+++	+++	✓	✓
Avoidance of hypothermia (delaying bathing until the second day of life, temperature monitoring)	+++	+++	✓	✓
Early initiation of breastfeeding within 1 hour of life	+++	+++	✓	✓
Exclusive breastfeeding in the first months of life	+++	+++	✓	✓
Prophylactic vitamin K for vitamin K deficiency bleeding in neonates	+++	+++	✓	✓
Antibiotic prophylaxis for newborns at risk of bacterial infection*	+++	+++	✓	✓
BCG vaccination before discharge (In areas where tuberculosis is common)*	+++	+++	✓	✓
Congenital cardiac disease screening*	++	++	-	✓
Advise and teach mother to wash hands after change of nappy (infection prevention)*	+++	+++	✓	✓
Interventions for small and ill babies	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Parents Kangaroo care for preterm and for < 2000g babies	+++	+++	✓	✓
Umbilical cord milking for pre-term babies*	++	++	✓	✓
Nasal continuous positive airway pressure for newborns with respiratory distress syndrome*	+++	+++	-	✓
Antibiotics for sepsis*	+++	+++	✓	✓
Prevention of hypoglycemia for small for gestational age and preterm babies (monitor glycemia and early feeding/glucose)*	+++	+++	✓	✓
Neonatal resuscitation and immediate newborn assessment at facility	+++	+++	✓	✓
Danger signs predicting severe newborn illness to be assessed during postnatal contacts (predictive for need for hospitalization)	+++	+++	✓	✓

V. POSTPARTUM*	Mortality/ Morbidity	Essential	Primary	Referral
Precautions to avoid endometritis*	+++	+++	✓	✓
Contraception to avoid unwanted pregnancy*	+++	+++	✓	✓

TABLE 2: Delphi-consensus summary table

Discussion

Health outcomes research established as a mean to evaluate the effectiveness of healthcare interventions and an approach to inform resource allocation.[105 106] Obstacles for the outcomes evaluation of eHealth tools are the absence of methodologies and indicators. The identification of indicators is complex as the timespan between intervention and potential outcome (reduction in maternal / neonatal mortality) is long. Due to this duration the outcome might be influenced by various confounding factors and it is difficult to attribute the outcome to the eHealth intervention. The use of proxy-indicators helps addressing this issue by measuring changes closer to the intervention.

This systematic review identified a set of proxy-indicators to evaluate the impact of eHealth tools in low resource settings with a clear focus on healthcare impact and health outcomes of maternal and neonatal health.

In practice, proxy-indicators related to the eHealth intervention are identified from the list (Table 2). Before measurement some of the indicators need to be mapped to the local context, practices, and available resources. For example 'the use of uterotonics for PPH prevention': oxytocin is the preferred choice when available, while oral misoprostol should be the second choice, when injectable uterotonics are not available. The proxy-indicators can detect and attest changes in behaviour and may explain changes in mortality, even if causality cannot be formally demonstrated.

The local mapping enables the utilisation of the proxy-indicators in various contexts, while the 'high level' of the indicators allows systemically collecting data from different projects and programs (collective data/evidence). Because of the mapping it is the same proxy-indicator for different context, measuring what is locally and temporally relevant, and therefore sustainable.

Limitations

The proxy-indicators are probably more suitable to evaluate programs or components of a program generally targeting maternal and neonatal care. For specific programs or projects, additional indicators might be identifiable (e.g. vertical transmission of HIV/AIDS).

Some proxy-indicators may not have been identified in the systematic review due to a very low GRADE quality, or as they are standard of care. They may also have been overlooked as unforeseen, disruptive uses of eHealth may emerge and offer unexpected ways to improve practices.

Delphi Consensus

The Delphi consensus identified additional indicators like e.g. 'Whooping cough immunization at T2 or T3', reorganized the list, and also added proxy-indicators on postpartum care.

Some of the additional proxy-indicators were not identified in the systematic review, as these are not directly linked to outcomes. The experts added these as they provide essential information for a better case management that may lead to improved outcomes, e.g. measurement of blood loss (Blood collection bag, blood collection sheets), or nutritional status of mother (BMI). Systematically collecting information on blood loss does not prevent PPH, but early detection of excess bleeding may allow for fast and efficient treatment.

Some additional proxy-indicators measure if cases are managed better, which is assumed to improve outcomes, e.g. early referral if prolonged labor, antenatal transfer to higher level of neonatal care, or implementation/adherence to protocols for pregnancy-induced hypertension (PIH). These are proxy-indicators that need to be mapped to the local context, as the appropriate time to refer in case of e.g. prolonged labor varies depending on the location and context of the facility.

The experts added 'Antihypertensive drugs to treat pregnancy-induced hypertension (PIH)' as a general indicator, in addition to more specific ones, like e.g. antiplatelet drugs for pre-eclampsia (low dose aspirin), that were identified through the systematic review.

The Delphi consensus identified 'Tranexamic acid in post-partum hemorrhage', a potential proxy-indicator that has not been detected by the systematic review due to in-conclusive literature, or poor quality evidence at the time of the systematic review, but was recently published in a new randomised, double blind, placebo-controlled trial concluding that tranexamic acid reduces PPH death of clinically diagnosed women, and that early treatment seems to optimize benefits.[107]

Table 2 could also serve as checklist when implementing a project, as a basis for the baseline questionnaire, and for creating the didactic contents.

Conclusion

The identified proxy-indicators provide a workable approach to measuring the impact of eHealth interventions on maternal and neonatal health. Their validation and calibration in various settings with different methodologies is still required.

The availability of indicators (direct and proxy) facilitates consistent outcome measurements and comparability of studies, and this methodology could be applied to other domains, e.g. chronic diseases.
This implementation research aims at creating evidence to supports decision-makers to answer questions like "why should we invest in eHealth rather than medical staff, immunization or medications?" and to identify and implement solutions with the greatest potential impact on health. Availability of indicators, and the ability to measure and demonstrate scientific evidence for medical benefits that is based on reliable indicators will accelerate decision-makers to institutionalize eHealth activities and to commit strategically at the regional and national level.

Contributors

CP designed the work with input from AG. CP designed the protocol with input of AG and LH. CP did the initial screening of studies. CP and LH rated the studies, AG solved discrepancies in the ratings. CP extracted the data, which was thoroughly checked and verified by LH. CP drafted the article. AG and LH made a critical revision of the article. CP, AG and LH gave their final approval of the version to be published.

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Competing Interest Statement

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Figure Legend

Figure 1: Flow chart of study selection for inclusion in the systematic review.

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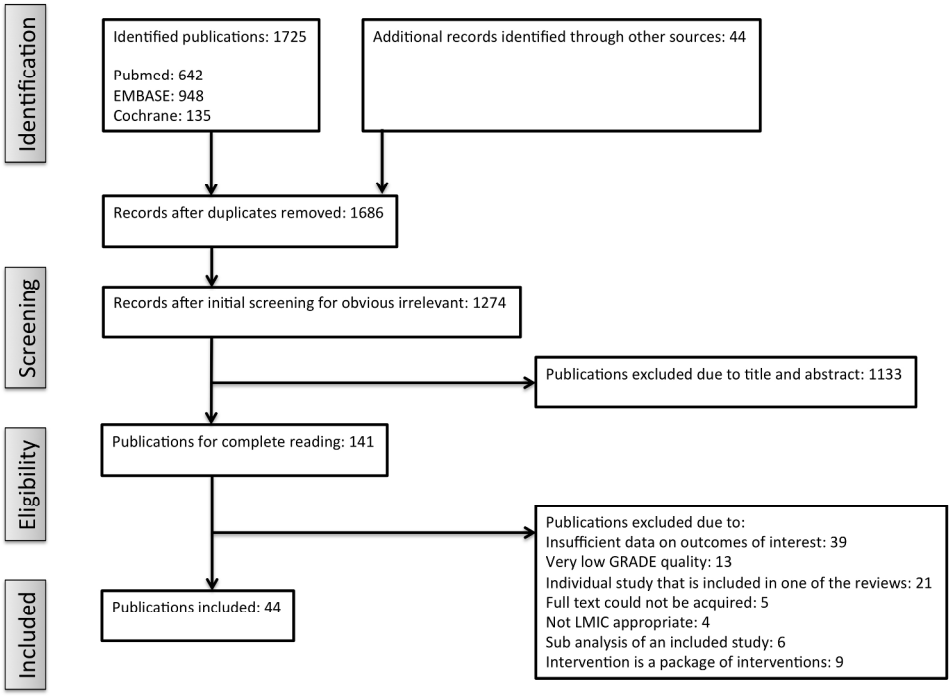

Figure 1: Flow chart of study selection for inclusion in the systematic review

1057x793mm (72 x 72 DPI)

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("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields]) OR ("infection"[MeSH Terms] OR "infection"[All Fields] OR "infections"[All Fields]) OR ("eclampsia"[MeSH Terms] OR "eclampsia"[All Fields]) OR ("pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[All Fields] OR ("pre"[All Fields] AND "eclampsia"[All Fields]) OR "pre eclampsia"[All Fields]) OR obstructed[All Fields] AND ("labour complications"[All Fields] OR "obstetric labor complications"[MeSH Terms] OR ("obstetric"[All Fields] AND "labor"[All Fields] AND "complications"[All Fields]) OR "obstetric labor complications"[All Fields] OR ("labor"[All Fields] AND "complications"[All Fields]) OR "labor complications"[All Fields]) AND ("delivery, obstetric"[MeSH Terms] OR ("delivery"[All Fields] AND "obstetric"[All Fields]) OR "obstetric delivery"[All Fields] OR "delivery"[All Fields]) OR ("premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR ("pre"[All Fields] AND "term"[All Fields]) OR "pre term"[All Fields]) OR ("asphyxia neonatorum"[MeSH Terms] OR ("asphyxia"[All Fields] AND "neonatorum"[All Fields]) OR "asphyxia neonatorum"[All Fields] OR ("birth"[All Fields] AND "asphyxia"[All Fields]) OR "birth asphyxia"[All Fields]) AND ("maternal mortality"[MeSH Terms] OR ("maternal"[All Fields] AND "mortality"[All Fields]) OR "maternal mortality"[All Fields]) OR ("infant mortality"[MeSH Terms] OR ("infant"[All Fields] AND "mortality"[All Fields]) OR "infant mortality"[All Fields] OR ("neonatal"[All Fields] AND "mortality"[All Fields]) OR "neonatal mortality"[All Fields]) AND reduction[All Fields] AND "intervention"[All Fields] OR (essential[All Fields] AND interventions[All Fields] AND ("maternal mortality"[MeSH Terms] OR ("maternal"[All Fields] AND "mortality"[All Fields]) OR "maternal mortality"[All Fields]) AND ("infant mortality"[MeSH Terms] OR ("infant"[All Fields] AND "mortality"[All Fields]) OR "infant mortality"[All Fields] OR ("neonatal"[All Fields] AND "mortality"[All Fields]) OR "neonatal mortality"[All Fields]) AND "humans"[MeSH Terms] AND English[lang]) AND ("1990/01/01"[PDAT] : "2015/10/23"[PDAT])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See supplementary file search strategy PM
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

A systematic review to identify proxy-indicators to quantify the impact of eHealth tools on maternal and neonatal health outcomes in low and middle-income countries - including Delphi consensus.

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A systematic review to identify proxy-indicators to quantify the impact of eHealth tools on maternal and neonatal health outcomes in low and middle-income countries - including Delphi consensus.

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Word count: 4106

Abstract

Objective

To identify interventions that could serve as reliable proxy-indicators to measure eHealth impact on maternal and neonatal outcomes.

Design

Systematic review and Delphi study.

Methods

We searched Pubmed, Embase, and Cochrane from January 1990 until May 2016 for studies and reviews that evaluated interventions aimed at improving maternal/neonatal health and reducing mortality. Interventions, which are not low and middle-income context appropriate, and that cannot currently be diagnosed, managed, or impacted by eHealth (e.g. via telemedicine distance diagnostic, or e-learning) were excluded. We used the Cochrane risk of bias, ROBINS-I, and ROBIS tool to assess the risk of bias. A three-step modified Delphi method was added to identify additional proxy-indicators and prioritize the results, involving a panel of thirteen experts from different regions, representing obstetricians and neonatologists.

Results

We included 44 studies and reviews, identifying 40 potential proxy-indicators with a positive impact on maternal/neonatal outcomes. The Delphi experts completed and prioritized these, resulting in a list of 77 potential proxy-indicators.

Conclusions

The proxy-indicators propose relevant outcome measures to evaluate if eHealth tools directly affect maternal/neonatal outcomes. Some proxy-indicators require mapping to the local context, practices, and available resources. The local mapping facilitates the utilisation of the proxy-indicators in various contexts, while allowing the systematic collection of data from different projects and programs. Based on the mapping the same proxy-indicator can be used for different contexts, allowing it to measure what is

locally and temporally relevant, making the proxy-indicator sustainable.

Prospero registration number

CRD42015027351

Strength and limitations of this study

- *Limitation:* Some potential proxy-indicators may not have been identified in the systematic review for two possible reasons 1) due to e.g. a very low GRADE quality, as for some interventions based on ethical reasons it is not possible to conduct high quality randomized studies, or 2) no studies have investigated these as they are standard of care.. They may also have been overlooked as unforeseen, for example disruptive uses of eHealth may emerge and offer unexpected ways to improve practices.
- *Strength*: to address the limitation of potentially overlooked proxy-indicators the results were assessed and completed in a Delphi consensus process with a group of international experts.
- *Strength*: A review of this kind, aiming at identifying proxy-indicators that could be used to measure the impact of eHealth interventions on maternal and neonatal health outcomes, particularly in low and middle-income countries has not yet been conducted.

Introduction

Since 1990 maternal and child mortality have approximately halved, however most of the remaining deaths are preventable.[1] Child mortality decreased disproportionately for older children and neonatal deaths account now for 45% of under 5-mortality.[2] Uneven progress between countries and within countries, with pro-rich and pro-urban inequalities, leaves women and children in rural areas with insufficient access to quality health care services.[1]

Information and Communication Technologies (ICTs) can provide innovative approaches for alleviating these inequalities, particularly in rural and isolated settings. They do so by overcoming geographical barriers, increasing access to healthcare services, providing continuing education and enabling collaborative healthcare in remote locations.[3-13] The World Health Organization (WHO) defines eHealth as the cost-effective and secure use of ICTs for health and health-related fields.[14] The potential of eHealth on positive therapeutic and clinical outcomes has been repeatedly postulated, but strong evidence is scarce. Although scientific literature offers an increasing number of publications studying the impact of eHealth tools on the quality, safety and cost-effectiveness of health care, there is still a significant gap between the postulated and empirically demonstrated benefits, including therapeutic and clinical outcomes.[15-20] It is essential to not only devote more effort to evaluation, but to also ensure that the methodology adopted is multidisciplinary and thus capable of disentangling the often complex web of factors that may influence the results. It is equally important that existing activities are subject to rigorous, multidisciplinary, and independent assessment. Even though low-cost telemedicine applications have proven to be feasible, clinically useful, sustainable, and scalable, they are not being adopted on a

significant scale due to a variety of barriers, including the absence of robust and general supportive scientific evidence of their impact.[15-17,21 22]

The need for evaluating eHealth impact on patient outcomes has been strongly emphasized.[19 20 22-28] The main barrier remains in the limited identification of measurable and reliable indicators.[29] The relevance of these indicators may be context-dependent and their extrapolation considerably restricted. Availability of outcome indicators (direct and proxy) will facilitate consistent outcome measurements and comparability of studies.[29]

Health outcomes research established as a mean to evaluate the effectiveness of healthcare interventions and an approach to inform resource allocation.[30 31] Obstacles for the outcomes evaluation of eHealth tools include the absence of methodologies and indicators.[29] The identification of indicators is complex as the timespan between intervention and potential outcome (reduction in maternal / neonatal mortality) is long. Due to this duration the outcome might be influenced by various confounding factors and it is difficult to attribute the outcome to the eHealth intervention. The use of proxy-indicators helps addressing this issue by measuring changes closer to the intervention.

The objective of this review is to identify proxy-indicators that can be utilized in future studies aiming at measuring the impact of eHealth interventions on maternal/neonatal health outcomes in low and middle-income countries (LMIC). The review question is: Which interventions that can be impacted by eHealth applications have results that can be clearly linked to maternal and neonatal health outcomes in LMIC countries and could therefore serve as reliable proxy-indicators?

Methods

The review was conducted and reported in line with the standards of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). [32] The review protocol is registered in PROSPERO, the detailed description can be accessed on the platform.[33] In short, the review identified interventions, which have an alleged impact on maternal/neonatal health, and are suitable for delivery in LMICs, to serve as proxy-indicators. In this article, previous reviews are included according to the recommendations for integrating existing systematic reviews into new reviews by Robinson et al.[34]

Searching

To identify studies and reviews that evaluated the effect of interventions on maternal and neonatal health, a comprehensive search of Pubmed, EMBASE, and the Cochrane Library was carried out using a combination of text words and controlled vocabulary terms related to the interventions and possible outcome measures. The search strategy was adapted for each database. Studies with an abstract published in English from 1990 to May 2016 were considered for inclusion. The third phase consisted of searching databases of multi-lateral organizations, and Google Scholar.

Inclusion/exclusion criteria

Randomized controlled trials, quasi-experimental studies, observational studies, systematic reviews, and inter-governmental and non-governmental agency reports were considered for this review.

Population: Pregnant women at any gestation age, postpartum women up to 6 weeks after giving birth, and neonates (up to 28 days after birth).

Intervention: We included any intervention at health system level aiming at improving maternal/neonatal health and reducing maternal/neonatal mortality.

Type of outcome measures: neonatal outcomes (e.g. neonatal mortality, stillbirth, low birth weight, preterm birth), and maternal outcomes (e.g. maternal mortality, preeclampsia, gestational hypertension).

Studies were excluded if they were not LMIC context appropriate or, if the interventions cannot currently be diagnosed, managed, or impacted by eHealth interventions, such as telemedicine distance diagnostics or e-learning, as well as qualitative studies and opinion pieces.

Study selection

One author conducted an initial screening to exclude articles whose titles were obviously irrelevant. Subsequently, two reviewers independently rated titles and abstracts based on relevance to the study objectives. The third reviewer resolved discrepancies in the rating. All studies that were rated potentially relevant or definitely relevant underwent full-text review. For each included study, the authors verified that these were not comprised in the included systematic reviews and if so they were excluded. Figure 1 summarizes the study selection.

Data abstraction, quality assessment, and data synthesis and analysis

Study design, setting, study population characteristics, description of the intervention, outcomes measured and effects of studies, which were assessed as eligible, were abstracted by one author into a standardized spreadsheet and were thoroughly checked by the second reviewer. Disagreements were resolved by discussion and, if necessary, by arbitration involving the third reviewer. The risk of bias was assessed for all included studies and reviews. Randomized trials were assessed with the Cochrane risk of bias, non-randomized studies with the Cochrane ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions), and systematic reviews with the ROBIS (Tool to assess risk of bias in systematic reviews) tool.[35-37] The level of evidence of studies and reviews that met the inclusion criteria were summarized by outcome (proxy-indicators) including a quality assessment in a tabular form. For each proxy-indicator, the summary of findings (SOF) table includes the number of studies, a summary of the intervention effect, and a measure of the quality of evidence for each outcome according to GRADE.[38-40] Existing GRADE assessments of systematic reviews have been included after verification and are marked with a * in the SOF Table.

Delphi consensus

A three-step modified Delphi method was used to add additional proxy-indicators and to establish consensus on the interventions' (proxy-indicators) potential to reduce morbidity and mortality, if they should be considered an 'essential' intervention, and the appropriate level of care.

Thirteen international experts, with backgrounds in obstetrics and neonatal care, from different regions were approached. All of them agreed to participate and all completed the three rounds.

In round 1 the experts added potential proxy-indicators to the provisional list (Table 1). Some proxy-

indicators may have been missed in the systematic review due to e.g. very low GRADE quality, as some interventions could not be conducted as randomized studies for ethical reasons.

In round 2 the completed the list of indicators was circulated to the experts and they were asked to assessed each, as proxy-indicator identified intervention according to 1) their potential to reduce maternal and neonatal morbidity and mortality, 2) whether they should be considered an 'essential' intervention, and 3) the appropriate level of care (primary, referral or both). An essential intervention was defined as an essential medical intervention, or 'signal function,' that treat the major causes of maternal/neonatal morbidity and mortality, and that should be prioritized. Primary level care was defined as care provided by a nurse, family physician or other type of health worker. For example, a rural health centre in Africa would be considered as primary level. Referral level care was defined as care provided in hospitals in general (district or referral); the health care providers at this level are professionals.

The rankings were summarized using the median and the interquartile range, and included in a repeat version of the questionnaire.

In Round 3, the experts re-ranked their agreement with each statement, with the opportunity to change their score in view of the group's response. The re-rankings were summarized and assessed for degree of consensus using interquartile ranges for continuous numerical scales, and were accepted when the interquartile range was 2 or less.

The results of the Delphi consensus are summarized in Table 2 and are rated as low (+) if the median was between 0-3, medium (++) if the median was between 4-6, and high (+++) if the median was between 7-9.

Patient involvement

Patients were not involved in setting the research question, the outcome measures, the design or the implementation of the study. No patients were asked to advise on interpretation or writing up of results. No patients were advised on dissemination of the present study and its main results.

Results of the systematic review

Our initial search identified 1725 publications, 44 additional records were identified through hand searching. The title and abstract scan resulted in 141 publications that underwent full-text review. Forty-four articles met our selection criteria after the full-text review. The results of the review are 40 potential proxy-indicators that are summarized in the SOF Table (Table 1).

Outcome group	Outcome	Effect	Studies	Quality of the Evidence (GRADE)
PRECONCEPTION				
Birth spacing: inter-pregnancy-interval (IPI) between 6 months and under 60 months [41]				
Neonatal outcome	Preterm birth with short IPI (<6months)	OR 1.40, 95% CI [1.24, 1.58]	8	HIGH*
Neonatal outcome	Low birth weight with short IPI (<6months)	OR 1.61, 95% CI [1.39, 1.86]	4	HIGH*
Neonatal outcome	Birth outcome: preterm birth with long IPI (>60 months)	OR 1.20, 95% CI [1.17, 1.24]	7	HIGH*
Neonatal outcome	Birth outcome: low birth weight with long IPI (>60 months)	OR 1.43, 95% CI [1.27, 1.62]	4	HIGH*

Folic acid supplementation and fortification [42]				
Neonatal outcome	Primary prevention of neural tube defect	RR 0.38, 95% CI [0.29, 0.51]	4	MODERATE*
PREGNANCY				
Multiple micronutrient supplementation (with Iron and folic acid) [43]				
Neonatal outcome	Low birth weight	RR 0.88, 95% CI [0.85, 0.90]	15	HIGH*
Neonatal outcome	Stillbirth	RR 0.92, 95% CI [0.86, 0.99]	15	HIGH*
Administration / advice of folic acid to women with history of baby of Neural Tube Defect (NTD) [44]				
Neonatal outcome	Secondary NTD reduction	RR 0.30, 95% CI [0.14, 0.65]	3	HIGH
Diet supplementation (high energy biscuits) for chronically undernourished women [45]				
Neonatal outcome	Stillbirth	OR 0.47, 95% CI [0.23, 0.99]	1	LOW
Neonatal outcome	Mortality within 7 days	OR 0.54, 95% CI [0.35, 0.85]	1	LOW
Tetanus Toxoid immunization (at least 2 vaccinations) [46 47]				
Neonatal outcome	Tetanus specific neonatal mortality	RR 0.06, 95% CI [0.02, 0.20]	2	MODERATE*
Neonatal outcome	Preventing neonatal tetanus against neonatal death	RR 0.02, 95% CI [0.00, 0.30]	1	MODERATE*
Syphilis screening with treatment [48]				
Neonatal outcome	Stillbirth	RR 0.18, 95% CI [0.10, 0.33]	8	LOW*
Neonatal outcome	Neonatal mortality	RR 0.20, 95% CI [0.13, 0.32]	5	LOW*
Routine drug administration to prevent malaria and its consequences in pregnant women in areas of moderate to high malaria transmission [49]				
Maternal outcome	Severe anaemia (during the third trimester)	RR 0.60, 95% CI [0.47, 0.75]	5	HIGH*
Maternal outcome	Antenatal parasitaemia	RR 0.39, 95% CI [0.26, 0.58]	8	HIGH*
Intermittent preventive treatment of malaria in pregnancy (IPTp) [47]				
Maternal outcome	Maternal death	RR 0.79, 95% CI [0.29, 2.20]	2	MODERATE*
Neonatal outcome	Neonatal mortality	RR 0.69, 95% CI [0.49, 0.98]	6	HIGH*
Neonatal outcome	Low birth weight	RR 0.71, 95% CI [0.57, 0.89]	9	MODERATE*
Smoking cessation during pregnancy (psychosocial interventions) [50]				
Neonatal outcome	Preterm birth	RR 0.82, 95% CI [0.70, 0.96]	14	MODERATE*
Neonatal outcome	Low birth weight	RR 0.82, 95% CI [0.71, 0.94]	14	MODERATE*
Prevention and Management of HIV and Prevention of Mother to Child Transmission in Pregnancy				
Rapid HIV testing [51]				
Maternal outcome	HIV-testing uptake	RR 2.95, 95% CI [1.69, 5.16]	13	MODERATE*
Antiretroviral therapy e.g. Zidovudine (ZDV) given to mothers from 36 weeks gestation, during labour [52]				
Neonatal outcome	Reduced HIV infection at 4-8 weeks	Efficacy 43.78%, 95% CI [9.05, 60.05]	6	HIGH
Adherence to Antiretroviral medication; mobile phone messages [53]				
Maternal outcome	Viral load suppression at 52 weeks	RR 0.83, 95% CI [0.69, 0.99]	1	HIGH*

Maternal outcome	ART adherence at 48-52 weeks	RR 0.82, 95% CI [0.72, 0.94]	2	HIGH*
Management of pre-labour rupture of membranes and preterm labour				
Calcium Channel Blockers for women in preterm labour [54]				
Neonatal outcome	Reduction in birth less than 48 hours after trial entry	RR 0.30, 95% CI [0.21, 0.43]	2	LOW*
Antenatal corticosteroids for accelerating foetal lung maturation for women at risk of preterm birth [55]				
Neonatal outcome	Neonatal mortality	RR 0.69, 95% CI [0.58, 0.81]	18	HIGH*
External cephalic version for breech presentation at term (Spinning babies) [56]				
Neonatal outcome	Perinatal death	RR 0.39, 95% CI [0.09, 1.64]	8	LOW*
Prevention and Management of Hypertension in Pregnancy				
Ultrasound for detection of preeclampsia [57 58]				
Maternal outcome	Abnormal Doppler US developing preeclampsia	OR 2.93, 95% CI [1.20, 7.30]	1	LOW
Maternal outcome	Increased pulsatility index with notching (low risk patients)	PLR 7.5, 95% CI [5.40, 10.20]	1	LOW
Maternal outcome	Increased pulsatility index with notching (high risk patients)	PLR 21, 95% CI [5.50, 80.50]	1	LOW
Maternal Calcium Supplementation [59 60]				
Maternal outcome	Severe preeclampsia	RR 0.75, 95% CI [0.57, 0.98]	5	MODERATE*
Maternal outcome	Gestational hypertension	RR 0.65, 95% CI [0.53, 0.81]	12	MODERATE*
Maternal outcome	Preeclampsia	RR 0.45, 95% CI [0.31, 0.65]	13	HIGH*
Neonatal outcome	Preterm birth	RR 0.76, 95% CI [0.60, 0.97]	11	HIGH*
Antiplatelets for preeclampsia (low dose aspirin) [61]				
Maternal outcome	Preeclampsia	RR 0.83, 95% CI [0.77, 0.89]	43	MODERATE*
Magnesium sulfate [62 63]				
Maternal outcome	Eclampsia	RR 0.41, 95% CI [0.29, 0.58]	6	HIGH*
Maternal outcome	Case fatality rate of severe preeclampsia and Eclampsia	RR 0.11, 95% CI [0.07, 0.16]	1	LOW
Early administration of magnesium sulfate (at home before referral) [64]				
Maternal outcome	Case fatality rate of severe preeclampsia and eclampsia	RR 0.21, 95% CI [0.06, 0.72]	1	LOW
Management of unintended pregnancy				
Combination of contraceptive-promoting and educational intervention [65]				
Maternal outcome	Unintended pregnancy among adolescents	RR 0.66 95% CI [0.50, 0.87]	4	MODERATE*
Medications for induced abortion (mifepristone, misoprostol) [66]				
Maternal outcome	No difference in complete abortion rates between medication and clinics group	OR 0.80, 95% CI [0.50, 1.50]	9	MODERATE
CHILDBIRTH				
Induction of labour for prolonged pregnancy (uterotonics: oxytocin, misoprostol) [67]				
Neonatal outcome	Perinatal mortality	RR 0.31, 95% CI [0.11, 0.88]	19	MODERATE*

Clean birth and postnatal practices at facility [68]				
Neonatal outcome	Neonatal mortality from sepsis	RR 0.73, 95% CI [0.64, 0.76]	DELPHI	LOW*
Neonatal outcome	Neonatal mortality from sepsis	RR 0.85, 95% CI [0.80, 0.90]	DELPHI	LOW*
Birth attendant hand washing before birth [68]				
Neonatal outcome	Cord infection	RR 0.70, 95% CI [0.61, 0.80]	2	MODERATE*
Management of postpartum haemorrhage				
Active management of third stage of labour (AMTSL) [69]				
Maternal outcome	Maternal Hb <9 g/dl 24 to 72 hours postpartum	RR 0.50, 95% CI [0.3, 0.83]	2	LOW*
Controlled cord traction (as part of AMTSL) [70]				
Maternal outcome	Blood loss > 500ml	RR 1.07, 95% CI [1.00, 1.14]	2	HIGH*
Preventive uterotonic drugs in the absence of active management of labour				
Oxytocin (when available) [71]				
Maternal outcome	Active bleeding controlled within 20 min	RR 0.94, 95% CI [0.91, 0.98]	1	HIGH
Oral misoprostol in preventing postpartum haemorrhage (when injectable uterotonics not available) [72]				
Maternal outcome	Blood loss >1000 ml	RR 0.66, 95% CI [0.45, 0.98]	1	HIGH
Uterine balloon tamponade (condom catheter) [73 74 75]				
Maternal outcome	UBT successfully treated PPH	97% [234 out of 241 cases]	13	LOW
Maternal outcome	All cause survival	95% [90 out of 201 cases]	1	LOW
Maternal outcome	Successful treatment of PPH	97% [223 out of 229 cases]	1	MODERATE
NEONATAL CARE				
Umbilical cord antiseptics in community and primary care settings [68 76]				
Neonatal outcome	Neonatal mortality	RR 0.81, 95% CI [0.71, 0.92]	3	HIGH*
Neonatal outcome	Omphalitis/infections	RR 0.77, 95% CI [0.63, 0.94]	3	HIGH*
Early skin to skin contact [77]				
Neonatal outcome	Breastfeeding 0–4 months post birth	RR 1.27, 95% CI [1.06, 1.53]	13	MODERATE
Delaying bathing until the second day of life [78]				
Neonatal outcome	Hypothermic neonate, rectal temperature	OR 2.90, 95% CI [1.69, 5.05]	1	MODERATE
Neonatal outcome	Hypothermic neonate, tympanic temperature	OR 4.67, 95% CI [2.62, 8.38]	1	MODERATE
Early initiation of breastfeeding (within the first 24 hours) [79]				
Neonatal outcome	Neonatal mortality	RR 0.56, 95% CI [0.40, 0.79]	3	MODERATE*
Exclusive breastfeeding in the first month of life [80]				
Neonatal outcome	Neonatal mortality exclusive vs. partial breastfeeding	OR 0.27, 95% CI [0.15, 0.49]	2	MODERATE*
Prophylactic vitamin K for vitamin K deficiency bleeding in neonates [81]				

Neonatal outcome	Any moderate to severe bleeding	RR 0.19, 95% CI [0.08, 0.46]	1	LOW*
Interventions for small and ill babies				
Kangaroo mother care for preterm and for < 2000g babies [33 82]				
Neonatal outcome	Neonatal mortality at discharge	RR 0.60, 95% CI [0.39, 0.92]	8	HIGH
Neonatal outcome	Neonatal mortality at latest follow up	RR 0.67, 95% CI [0.48, 0.95]	11	HIGH
Neonatal resuscitation and immediate assessment at facility [83]				
Neonatal outcome	Early neonatal deaths	RR 0.62, 95% CI [0.41, 0.94]	3	MODERATE*
Danger signs predicting severe neonatal illness to be assessed during postnatal contacts (predictive for need for hospitalization) [84]				
Neonatal outcome	History of difficulty feeding	OR 10.00, 95% CI [6.90, 14.50]	2	LOW
Neonatal outcome	Movement only when stimulated	OR 6.90, 95% CI [3.00, 15.50]	2	LOW
Neonatal outcome	Temperature <35.5	OR 9.20, 95% CI [4.60, 8.60]	2	LOW
Neonatal outcome	Temperature >/= 37.5	OR 3.40, 95% CI [2.40, 4.90]	2	LOW
Neonatal outcome	Respiratory rate >/=60	OR 2.70, 95% CI [1.90, 3.80]	2	LOW
Neonatal outcome	Severe chest in drawing	OR 8.90, 95% CI [4.00, 20.01]	2	LOW
Neonatal outcome	History of convulsions	OR 15.40, 95% CI [6.40, 37.20]	2	LOW

TABLE 1: Summary of Findings Table

1. Preconception

The preconception interventions reviewed included birth spacing and micronutrient supplementation.

Higher risk for preterm birth, and low birth-weight (LBW) are associated to short inter-pregnancy-intervals (IPI) (less than 6 months) as well as long IPIs (60 months or more after birth), compared to an IPI of 18 to 23 months.[41]

Folic acid supplementation and fortification are effective in reducing neonatal mortality.[42]

2. Pregnancy

The antenatal interventions reviewed included micronutrient and diet supplementation, maternal immunization, screening and management of infections (syphilis, HIV/AIDS, malaria), prevention and management of pregnancy-induced disorders (notably arterial hypertension), management of pre-labour rupture of membranes and preterm labour, drug misuse, and management of unintended pregnancy.

Multiple micronutrient (MMN) supplementation (iron and folic acid) is improving birth outcomes.[43], For woman with a history of a baby with neural tube defect (NTD) folic acid reduces the recurrence by 70%,.[44]

Low birth weight (LBW) is a major contributor to neonatal mortality and over 95% of LBW babies are born in LMIC countries.[85] While there has been controversy about whether dietary supplementation (e.g. high energy biscuits for chronically undernourished women) in pregnancy can increase birth weight, [86-89] the 5-year prospective randomized controlled trial in 28 rural Gambian villages by Ceesay et al. concludes that supplementation significantly reduces perinatal mortality in at risk mothers.[45]

Major progress has been achieved for neonatal tetanus but it remains a significant preventable

cause of neonatal mortality globally.[2] Immunization of pregnant women or women of reproductive age with at least two doses of tetanus toxoid is estimated to reduce mortality from neonatal tetanus by 94%.[47]

Infection is a well-acknowledged cause of stillbirth and accounts for an estimated half of all stillbirth, particularly in LMICs.[90] Syphilis screening and treatment with penicillin reduces syphilis related stillbirth by 82% and syphilis-specific neonatal death by 80%.[48] The effect in all studies was large and there is a clear biological mechanism, but as only few of the included studies were adjusted for potential confounding factors, quality of the evidence was graded as low.[48,91]

Intermittent preventive treatment of malaria in pregnancy (IPTp) is a routine drug administration to prevent malaria and its consequences in pregnant women in areas of moderate to high malaria transmission**.** Routine chemoprevention for malaria and its consequences have been extensively tested in RCTs, with clinically important benefits on anaemia and parasitaemia in the mother,[49] and reduced neonatal mortality.[47]

The majority of HIV-infected children acquired their infections as a result of mother-to-child transmission during pregnancy, labour, or breastfeeding. In areas with lower health services infrastructure infections may stay undetected, which is problematic as early diagnosis and treatment demonstrated improved clinical outcomes.[92 93] About 50% of people living with HIV are unaware of their diagnosis.[51 94] Reliable point-of-care HIV diagnostic tests, administering antiretroviral drugs to the HIV-infected mother and/or to her child during pregnancy, labour, or breastfeeding, and adherence to antiretroviral medication are essential to prevent vertical transmission.[52,53,95]

Preterm birth is a major contributor to perinatal mortality and morbidity. Calcium channel blockers (CCBs) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth and were shown to have benefits over beta-mimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects.[54] Corticosteroid therapy used to accelerate foetal lung maturation for women at risk of preterm birth is relatively inexpensive and feasible to implement at primary level in a LMIC context if skilled health-care providers are available to identify women at risk of preterm birth and administer intramuscular injections.[55, 96]

Gestational hypertensive diseases, including pregnancy-induced hypertension, preeclampsia, and eclampsia are a leading causes of maternal and infant morbidity and mortality.[97] Early detection is crucial for monitoring and prevention. Preeclampsia is related to a lack of placental invasion and its complications on the pregnancy can be detected by ultrasound.[57,58,98] Gestational calcium supplementation is associated with a reduction in hypertensive disorders in pregnancy, especially for women with a low calcium intake, [59 99 100] and reduces gestational hypertension, severe preeclampsia, and preeclampsia.[59,60] Administration of antiplatelets (e.g. low dose aspirin) to pregnant women at high risk of preeclampsia or those with gestational hypertension prevents preeclampsia.[44 61] Magnesium sulfate is one of the most effective anticonvulsant to protect women from severe preeclampsia and eclampsia, and, if administered timely, reduces the risk of seizure repetition and reduces case fatality rate of severe preeclampsia and eclampsia.[101-103] Magnesium sulfate more than halves the risk of eclampsia.[62,63] For women who received a magnesium sulfate injection before referral, case fatality rate of severe preeclampsia and eclampsia reduced by 79%.[64] Even though the effect was strong, due to a small sample size, the evidence was graded

low. WHO recommends that magnesium sulfate is administered to women with severe preeclampsia before they are transferred to a secondary or tertiary level facility.[104]

A combination of contraceptive promoting and educational interventions reduce unintended pregnancy, while only contraceptive-promoting interventions showed little or no difference in the risk of unintended first pregnancy RR 1.01, 95% CI [0.81, 1.26].[65]

Medical abortion uses drugs (Mifepristone, Misoprostol) to terminate a pregnancy and is an important alternative to surgical methods of pregnancy termination, especially in areas where access to surgical termination is not available.[66,105]

3. Childbirth

Interventions during and close to childbirth include clean birth and postnatal practices, the management of postpartum haemorrhage, and preventive uterotonic drugs in the absence of active management of labour.

Clean birth practices include: hand washing, clean perineum, clean birth surface, cutting of the umbilical cord using a clean implement, and clean cord tying.[68] Clean postnatal practices include: chlorhexidine, other antimicrobial applications to the cord, avoidance of harmful cord applications, skin applications and emollients, and hand washing.[68] These are estimated to reduce neonatal mortality in a facility and home setting. Even though the evidence quality is low or very low, as there is strong biological plausibility, the GRADE recommendation for these practices is strong. [47 68]

Active management of third stage of labour (AMTSL) is a package of three components or steps: 1) administration of an uterotonic, preferably oxytocin, immediately after birth of the baby; 2) controlled cord traction (CCT) to deliver the placenta, if skilled birth attendants are available; [70 106] and 3) massage of the uterine fundus after the placenta is delivered, with administration of an uterotonic as most important part.[69,106] In the absence of AMTSL, a preventive uterotonic drug (oxytocin or misoprostol) should be administered by a health worker trained in its use for prevention of PPH.[71,106] If both, oxytocin and misoprostol are available, oxytocin is the preferred first-line treatment.[71 106] Oral or sublingual misoprostol compared with placebo is effective in reducing severe and is a suitable first-line treatment alternative for PPH in settings where the use of oxytocin is not feasible. [71 72]

Uterine balloon tamponade (UBT) is a relatively simple approach and demonstrated to be an effective technique to treat PPH in developed countries, but is underutilized in LMIC countries due to the high cost of the balloon. A sterile rubber catheter fitted with a condom was developed as innovative low cost alternative in Bangladesh in 2001.[107] Three studies suggest that C-UBT is simple to use, inexpensive, safe, and may be used by any healthcare provider involved in delivery for controlling massive PPH.[73-75]

4. Neonatal Care

Interventions for all neonates include hygienic care, prevention of hypothermia, support for immediate breastfeeding, and prophylactic vitamin K.

Early skin-to-skin contact benefits breastfeeding outcomes at 0-4 months post birth,[77] while early initiation of breastfeeding lowers all cause neonatal mortality among live birth.[79] Exclusive breastfeeding reduces the risk of neonatal mortality compared to partial breastfeeding.[80]

Thermal care (immediate drying, warming, skin to skin, delayed bathing) of neonates prevents hypothermia.[44] Bathing in warm water one hour after delivery is associated with a significant increase in hypothermia in both measurement methods, rectal and tympanic.[78]

Neonatal chlorhexidine cord care reduces the incidence of omphalitis and neonatal mortality.[76]

A single dose of 1 mg of intramuscular vitamin K after birth is effective in the prevention of classic haemorrhagic disease of the neonate.[81]

Interventions for small and ill neonates include neonatal resuscitation and immediate assessment, prevention of hypothermia, and danger signs predicting severe neonatal illness to be assessed during postnatal contacts.

Every year an estimated 10 million babies require assistance to initiate breathing. Basic neonatal care (warming, drying, stimulation and resuscitation including bag-and-mask ventilation) would be sufficient to save most babies in need of resuscitation in low-resource settings.[108] Training of neonatal resuscitation in facilities could reduce 30% of intrapartum-related mortality RR 0.70, 95% CI [0.59, 0.84] and 38% of early neonatal mortality.[83] The coverage of this intervention remains low in countries where most neonatal deaths occur, which presents a missed opportunity to save lives.[83]

Kangaroo mother care (KMC), amongst other benefits reduces neonatal mortality.. [82] KMC in LBW infants is an alternative to conventional neonatal care.

The Young Infants Clinical Signs Study Group developed a single simple algorithm that can identify severe illness in infants aged 0–2 months who are brought to health facilities.[84] The algorithm was developed from a large prospectively collected dataset and consists of seven signs: 1) history of difficulty feeding, 2) history of convulsions, 3) movement only when stimulated, 4) respiratory rate of 60 breaths per minute or more, 5) severe chest in-drawing, 6) temperature of 37·5°C or more, 7) temperature below 35.5°C. Each of these signs is predictive for the need of hospitalization in infants of the age group 0-6 days and 7-59 days, and should be used to identify sick infants that need referral faster.[84]

Results of the Delphi consensus

The Delphi experts completed and prioritized the results of the systematic review, resulting in a table of 77 proxy-indicators (Table 2). Indicators that were added or modified in the Delphi process are marked with a *.

I. PRECONCEPTION	Mortality/ Morbidity	Essential	Primary	Referral
Family Planning				
Birth spacing: inter-pregnancy-interval (IPI) between 6 months and under 60 months	++	++	✓	✓
Combination of contraceptive-promoting and educational interventions to avoid unwanted pregnancy*	+++	+++	✓	-
Folic acid supplementation and fortification	++	+++	✓	✓
Administration / advice folic acid to women with history of baby of NTDs*	+++	+++	✓	✓
Advise for cessation of alcohol consumption*	+++	+++	✓	✓
Education (maternal age, physiology, nutritional status of mother: BMI, etc)*	+++	+++	✓	-

Weight reduction in overweight, obese and morbidly obese women*	+++	+++	✓	✓
Rubella screening*	++	++	✓	-
Hemoglobin level / anaemia status before pregnancy*	+++	+++	✓	✓

II. PREGNANCY	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Iron and folic acid supplementation (multiple micronutrient)	+++	+++	✓	✓
Iron supplementation from second trimester to 3 months postnatal*	+++	+++	✓	✓
Nutritional status of mother: BMI*	+++	+++	✓	-
Diet supplementation (high energy biscuits) for chronically undernourished women	++	++	✓	✓
Tetanus toxoid immunization (at least 2 vaccinations)	+++	+++	✓	✓
Whooping cough immunization at T2 or T3*	+++	+++	✓	✓
Syphilis screening with treatment	++	+++	✓	✓
Intermittent preventive treatment of malaria in pregnancy (IPTp)	+++	+++	✓	✓
Identification of bacteriuria and treatment (Urine culture and antibiotic treatment of bacteriuria)*	+++	+++	✓	✓
Palpation of uterus and measurement of fundus height (for detecting problems with foetal growth)*	++	++	✓	-
Advise for cessation of alcohol consumption (adverse effect of alcohol)*	+++	+++	✓	✓
Smoking cessation during pregnancy (psychosocial interventions)	+++	+++	✓	✓
Management of unintended Pregnancy: Medications for induced abortion (Mifepristone, Misoprostol)	+++	+++	✓	✓
Thyroxine for euthyroid women with positive antithyroid antibodies & recurrent miscarriages*	++	++	-	✓
Kegel exercises to reduce stress incontinence*	+	+	✓	✓
Fasting Blood Sugar checking for high risk population for Gestational diabetes mellitus*	+++	+++	✓	✓
Availability of ultrasound	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Foetal echography screening: abnormalities, malformations, growth retardation, Macrosomia*	++	++	-	✓
Prevention and management of HIV and prevention of mother to child transmission in pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Rapid HIV testing	+++	+++	✓	✓
Antiretroviral therapy	+++	+++	✓	✓
Adherence to Antiretroviral medication; mobile phone messages	+++	+++	✓	✓
Management of pre-labour rupture of membranes and preterm labour	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Calcium Channel Blockers for women in preterm labour	++	+++	✓	✓
Antenatal corticosteroids for accelerating foetal lung maturation for women at risk of preterm birth	+++	+++	✓	✓
Antenatal transfer to higher level of neonatal care*	+++	+++	✓	✓
Magnesium sulfate in preterm delivery before 34 weeks for neuro-protection*	+++	+++	-	✓
Antibiotics in management of preterm pre-labour rupture of membranes*	+++	+++	✓	✓
Prevention and management of hypertension in pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Early detection of preeclampsia by signs and symptoms*	+++	+++	✓	✓
(Better) implementation/adherence to protocols for pregnancy-induced hypertension (PIH)*	+++	+++	✓	✓
Antihypertensive drugs to treat pregnancy-induced hypertension (PIH)*	+++	+++	✓	✓
Maternal calcium supplementation (in areas with poor calcium diet)	+++	+++	✓	✓
Antiplatelet drugs for preeclampsia (low dose aspirin)	+++	+++	✓	✓
Use of magnesium sulfate	+++	+++	✓	✓

Early administration of magnesium sulfate (before referral)	+++	+++	✓	✓

III. CHILDBIRTH	Mortality/ Morbidity	Essential	Primary	Referral
External cephalic version (ECV) for breech presentation at term	+++	+++	-	✓
Clean birth and postnatal practices at facility	+++	+++	✓	✓
Birth attendant hand washing before birth	+++	+++	✓	✓
Foetal heart (intermittent) auscultation*	+++	+++	✓	✓
Early referral if prolonged labour*	+++	+++	✓	-
Instrumental vaginal delivery (e.g. Kiwi vacuum extractor)*	+++	+++	✓	✓
Delivery of baby to mother's abdomen*	+++	+++	✓	✓
Antibiotic prophylaxis against streptococcus B*	+++	+++	✓	✓
Induction of prolonged pregnancy	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Induction of labour for prolonged pregnancy with uterotonics (oxytocin, misoprostol)	+++	+++	-	✓
Induction with Foley catheter*	+++	+++	-	✓
Management of postpartum haemorrhage	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Active management of third stage of labour (AMTSL)	+++	+++	✓	✓
Use of uterotonics for PPH prevention: oxytocin preferred (if available), oral misoprostol 2nd choice (when injectable uterotonics not available)	+++	+++	✓	✓
Uterine balloon tamponade (UBT) (condom catheter)	+++	+++	✓	✓
Measurement of blood loss (Blood collection bag, blood collection sheets)*	+++	+++	✓	✓
Recombinant Factor VII in massive PPH*	++	++	✓	✓
Tranexamic acid in post-partum haemorrhage (PPH)*	+++	+++	✓	✓
Uterine massage and emptying the bladder*	+++	+++	✓	✓

IV. NEONATAL CARE	Mortality/ Morbidity	Essential	Primary	Referral
Umbilical cord antiseptics in community and primary care settings	+++	+++	✓	✓
Early skin to skin contact	+++	+++	✓	✓
Avoidance of hypothermia (delaying bathing until the second day of life, temperature monitoring)	+++	+++	✓	✓
Early initiation of breastfeeding within 1 hour of life	+++	+++	✓	✓
Exclusive breastfeeding in the first months of life	+++	+++	✓	✓
Prophylactic vitamin K for vitamin K deficiency bleeding in neonates	+++	+++	✓	✓
Antibiotic prophylaxis for neonates at risk of bacterial infection*	+++	+++	✓	✓
BCG vaccination before discharge (In areas where tuberculosis is common)*	+++	+++	✓	✓
Congenital cardiac disease screening*	++	++	-	✓
Advise and teach mother to wash hands after change of nappy (infection prevention)*	+++	+++	✓	✓
Interventions for small and ill babies	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Parents Kangaroo care for preterm and for < 2000g babies	+++	+++	✓	✓
Umbilical cord milking for pre-term babies*	++	++	✓	✓
Nasal continuous positive airway pressure for neonates with respiratory distress syndrome*	+++	+++	-	✓
Antibiotics for sepsis*	+++	+++	✓	✓
Prevention of hypoglycaemia for small for gestational age and preterm babies (monitor glycaemia and early feeding/glucose)*	+++	+++	✓	✓
Neonatal resuscitation and immediate assessment at facility	+++	+++	✓	✓
Danger signs predicting severe neonatal illness to be assessed during postnatal contacts	+++	+++	✓	✓

(predictive for need for hospitalization)				
V. POSTPARTUM*	**Mortality/ Morbidity**	**Essential**	**Primary**	**Referral**
Precautions to avoid endometritis*	+++	+++	✓	✓
Contraception to avoid unwanted pregnancy*	+++	+++	✓	✓

TABLE 2: Delphi-consensus summary table

Discussion

Evidence documents the benefits of eHealth tools in terms of increasing satisfaction of HCPs, de-isolation, acquisition of new knowledge, and their potential impact (largely based on observational studies).[3-13] However, there is little evidence demonstrating that these tools lead to changes in health behaviours, which have a meaningful impact on the patient outcomes. An evaluation of a mobile tool for health workers in India used an approach that is similar to the proposed proxy-indicators, measuring the impact of the mobile tools on key health behaviours.[109] On the one hand this evaluation demonstrated the feasibility of the proposed approach, showing large and statistically significant impacts on many outcomes in the antenatal care domain, on the other hand it accentuated the need to evaluate the impact of eHealth tools on patient outcomes beyond knowledge aquisition.[109] The evaluation showed that even though there were significant impacts on mother's knowledge on exclusive breastfeeding, this did not translate into significant impacts on reported exclusive breastfeeding for 6 months.[109]

The main difficulty of evaluating the impact on patient outcomes can be attributed to the limited identification of measurable and reliable indicators. This systematic review identified a set of proxy-indicators (Table 1) to evaluate the impact of maternal and neonatal eHealth tools in low resource settings on health outcomes. Experts completed the results with additional proxy-indicators like e.g. 'Whooping cough immunization at T2 or T3', and reorganized them in a Delphi consensus (Table 2). Table 3 provides a summarized view on the identified intervention domains of the proxy-indicators, while the granularity of the list of proxy-indicators (Table 2) is necessary to identify the most appropriate proxy-indicators for specific eHealth projects or programs.

Category	Description
Education	Education and training of HCPS for interventions that are targeting behaviour changes, knowledge acquisition, or awareness of patients or HCPs. Examples of proxy-indicators for education are: birth spacing, advice for cessation of alcohol, birth attendant hand washing before birth, or avoidance of hypothermia (delaying bathing until the second day of life, temperature monitoring).
Screening for infectious diseases and risk factors	Interventions for a better availability and implementation of screening for infectious diseases and risk factors. Examples of proxy-indicators are: Nutritional status of mother: BMI, Syphilis screening with treatment, Fasting Blood Sugar checking for high risk population for Gestational diabetes mellitus,
Availability of ultrasound	The availability of ultrasound allows the detection of abnormalities, malformations, growth retardation, and Macrosomia, but is also assumed to improve the number of prenatal care visits of the pregnant women.[110]

Management of unintended Pregnancy	The better availability and implementation of the management of unintended pregnancy. Examples of a proxy-indicator is medications for induced abortion (Mifepristone, Misoprostol)
Timely referral	Timely identification and referral of pregnancy related complications and emergencies are key factors to reduce maternal and new-born mortality.[111] Examples of proxy-indicators are: Antenatal transfer to higher level of neonatal care, early identification of danger signs predicting severe new-born illness to be assessed during postnatal contacts (predictive for need for hospitalization)
Prevention and Management of HIV	Interventions for a better availability and implementation of interventions to prevent and manage HIV. Examples of proxy-indicators are: Rapid HIV testing, Adherence to Antiretroviral medication; mobile phone messages.
Management of pre-labour rupture of membranes and preterm labour	Interventions for a better availability and implementation of interventions to manage pre-labour rupture of membranes and preterm labour. Examples of proxy-indicators are: calcium channel blockers for women in preterm labour, antenatal corticosteroids for accelerating foetal lung maturation for women at risk of preterm birth or antibiotics in management of preterm pre-labour rupture of membranes.
Prevention and Management of Hypertension in Pregnancy	Interventions for a better availability and implementation of interventions to prevent and manage hypertension in pregnancy. Examples of proxy-indicators are: (better) implementation/adherence to protocols for pregnancy-induced hypertension (PIH), antiplatelet drugs for preeclampsia (low dose aspirin), and the use of magnesium sulfate.
Induction of prolonged pregnancy	Interventions for an induction of prolonged pregnancy. Examples of proxy-indicators are: induction of labour for prolonged pregnancy with uterotonics (oxytocin, misoprostol), or induction with Foley catheter.
Management of postpartum haemorrhage	Interventions for a better prevention and management of postpartum haemorrhage. Examples of proxy-indicators are: Use of uterotonics for PPH prevention: oxytocin preferred (if available), oral misoprostol 2nd choice (when injectable uterotonics not available), the measurement of blood loss (blood collection bag, blood collection sheets), or tranexamic acid in post-partum haemorrhage (PPH).
Interventions for small and ill babies	Interventions for a better availability and implementation of interventions for small and ill babies. Examples of proxy-indicators are: parents kangaroo care for preterm and for < 2000g babies, or neonatal resuscitation and immediate assessment at facility.

TABLE 3: Categories of proxy-indicators

Some of the via the Delphi consensus identified supplementary proxy-indicators were not determined in the systematic review, as there were no direct relation to outcomes. They were however added by the experts as they provide essential information for a better case management that may lead to improved outcomes, e.g. measurement of blood loss (Blood collection bag, blood collection sheets),[112] or nutritional status of mother (BMI).[113] For example, systematically collecting information on blood loss does not prevent PPH, but early detection of excess bleeding may allow for fast and efficient treatment. [112]

The experts also added more general proxy-indicators like 'Antihypertensive drugs to treat pregnancy-induced hypertension (PIH)' in addition to the more specific ones, like e.g. antiplatelet drugs for preeclampsia (low dose aspirin), which were identified in the systematic review. Furthermore, some additional proxy-indicators measure whether cases are managed better, which is assumed to improve outcomes, e.g. early referral if prolonged labour, or antenatal transfer to higher level of neonatal care. [111] In practice they will need to be mapped to the local context, as the appropriate time for referral in case of e.g. prolonged labour varies depending on the location and context (availability of medication and of the facility.

Moreover the experts identified 'Tranexamic acid in post-partum haemorrhage' in the Delphi consensus as an additional proxy-indicator. The systematic review did not identify this due to in-conclusive literature, or poor quality evidence at the time of the systematic review. But recently a new randomised, double blind, placebo-controlled trial was published, concluding that tranexamic acid reduces PPH death of

clinically diagnosed women, and that early treatment seems to optimize benefits.[114]

Limitations

The proxy-indicators are probably more suitable to evaluate maternal and neonatal eHealth programs or components of a program. For specific maternal/neonatal eHealth programs or projects (e.g. targeted at HIV infected mothers) additional indicators might be identifiable (e.g. vertical transmission of HIV/AIDS). Some proxy-indicators may also have been overlooked as unforeseen, and disruptive uses of eHealth may emerge and offer unexpected ways to improve practices.

Application

When applied in future studies, proxy-indicators related to the eHealth intervention are identified from Table 2. Some of them need to be mapped to the local context, practices, and available resources. For example 'the use of uterotonics for PPH prevention': oxytocin is the preferred choice when available, while oral misoprostol should be the second choice, when injectable uterotonics are not available for treatment.[71 106] The proxy-indicators can detect and attest changes in behaviour and may explain changes in mortality, even if causality cannot be formally demonstrated.

The local mapping enables the utilisation of the proxy-indicators in various contexts, while the 'high level' of the indicators allows systemically collecting data from different projects and programs (collective data/evidence). Because of the mapping it is the same proxy-indicator for different context, measuring what is locally and temporally relevant, and therefore sustainable.

Table 2 could also serve as a checklist when implementing a project or as a basis for the baseline questionnaire, and for creating the didactic contents.

Conclusion

The identified proxy-indicators provide a workable approach to measuring the impact of eHealth interventions on maternal and neonatal health. However, their validation and calibration in various settings with different methodologies is still required.

The availability of indicators (direct and proxy) facilitates consistent outcome measurements and comparability of studies,[29] and this methodology could be applied to other domains, e.g. chronic diseases.

This implementation research aims at creating evidence to support decision-makers to answer questions like "why should we invest in eHealth rather than medical staff, immunization or medications?" and to identify and implement solutions with the greatest potential impact on health. The availability of indicators and the possibility to measure and demonstrate scientific evidence for medical benefits that is based on reliable indicators, will accelerate decision-makers' ability to institutionalize eHealth activities and to commit strategically at the regional and national level.

Contributors

CP designed the work with input from AG. CP designed the protocol with input of AG and LH. CP did the initial screening of studies. CP and LH rated the studies, AG solved discrepancies in the ratings. CP extracted the data, which was thoroughly checked and verified by LH. CP drafted the article. AG and LH

made a critical revision of the article. CP, AG and LH gave their final approval of the version to be published.

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Figure Legend

Figure 1: Flow chart of study selection for inclusion in the systematic review.

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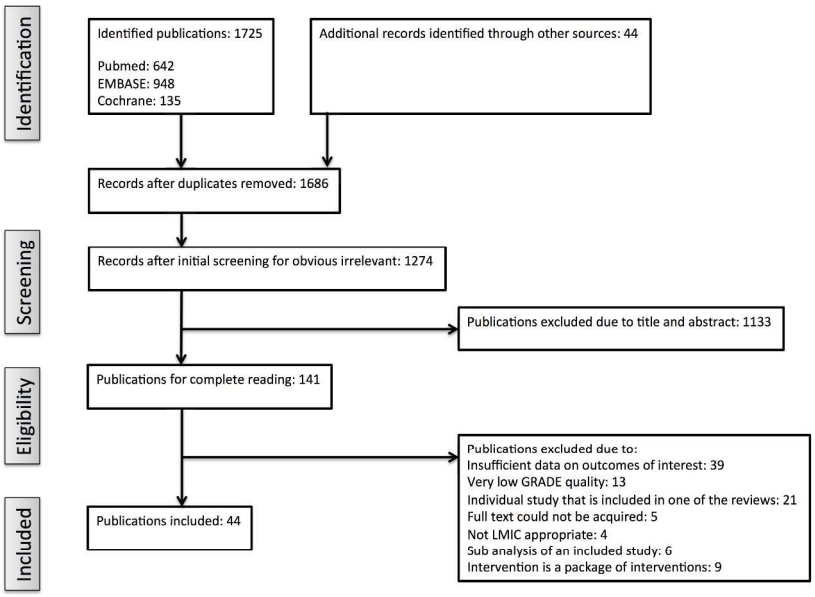

Figure 1 - Study flow diagram

297x209mm (300 x 300 DPI)

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See supplementary file search strategy PM
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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