

# Global newborn health research priorities identified in 2014: A review to evaluate the uptake

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## Summary

**Background** In 2014, World Health Organization published global research priorities for newborn health till 2025. We conducted this review to summarize completed or ongoing research on the twenty priorities.

**Methods** We conducted searches for twenty questions on MEDLINE via PubMed, Cochrane CENTRAL, Web of Science, clinical trial registries, and funder websites between July 2014 and May 2022. Studies addressing research questions using adequate design were included. Adequacy of uptake of a priority was assessed based on predefined criteria.

**Findings** The uptake of research priorities was high for 8 (40%), moderate for 11 (55%), and one priority, effectiveness of training community health workers (CHWs) to treat neonatal sepsis at home remains unaddressed. Priorities with moderate uptake include effectiveness of simplified neonatal resuscitation programme, simple clinical algorithms for CHWs to neonatal infection, CHWs training in basic neonatal resuscitation, community-initiated kangaroo mother care, perinatal audits, and novel tocolytic agents, scaling-up chlorhexidine cord application, stable surfactant with simpler administration, accurate, affordable methods to diagnose fetal distress, strategies for prevention and treatment of intrauterine growth retardation, and causal pathways for antenatal stillbirths.

**Interpretation** Adequate research was undertaken on pressing global concerns in newborn health. Funders and researchers should reflect on and address less researched areas.

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## Introduction

The world saw an estimated 2.44 million newborn babies die and an additional 1.97 million stillborn in 2019.<sup>1</sup> The proportion of neonatal deaths as a share of under-5 deaths has increased from 41% in 2000 to 47% in 2019. An even greater number of newborns have long-term impairment associated with preterm birth, intrauterine growth restriction (IUGR), congenital anomalies, and other intrapartum insults.

In 2013, a need was identified to define research priorities to address the post-MDG agenda that focused not only on survival but also on the growth and development of children. Therefore, World Health Organization (WHO) coordinated a global exercise to set research priorities for newborn health till 2025.<sup>2</sup> Using the Child

Health and Nutrition Research Initiative (CHNRI) method, a set of 20 top-ranked research priorities were identified in the domains of delivery (how to take effective interventions to every mother and newborn), development (how to improve existing interventions), and discovery (develop new and effective interventions). In this exercise, the following predefined criteria were used for the prioritization of research questions: answerability, efficacy, deliverability, impact, and equity, and the priorities were published as part of the 2014 Lancet Newborn Survival Series (Supplementary Appendix Table 1).<sup>2</sup>

The process of settings research priorities is designed to guide cumulative research effort in a direction that is most productive from a public health viewpoint. It is important to understand if the priority research is being undertaken to fill the most critical knowledge gaps to improve neonatal survival and health. We conducted this review to summarize the research that was completed or is ongoing in the area of the twenty newborn research priorities identified by WHO in 2014.

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## Methods

All original research studies, either published or ongoing that attempt to directly address the top twenty research questions identified in the research prioritization exercise coordinated by the WHO in 2014 were eligible for inclusion in the present review. Studies on broader areas of work, e.g., health systems or upstream determinants that may indirectly influence the research area identified as a priority were not considered.

## Search methods

A systematic literature search was undertaken for all relevant completed and published as well as ongoing studies. We searched MEDLINE via PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) using individual, database-specific search strategies for each of the twenty identified research questions from 1 July 2014 to 31 May 2022 for human studies, with no language restrictions. We also searched trial registers including the WHO trials registry WHO International Clinical Trials Registry Platform (ICTRP; <http://apps.who.int/trialsearch/>), International Standard Randomised Controlled Trial Number (ISRCTN) Registry (<http://www.isrctn.com/>) and Clinical Trials database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

To identify research studies not yet registered, we searched the websites of major research funders in the area of maternal and newborn health to identify relevant research funded or commissioned till May 2022. These funders included the National Institutes of Health (NIH; <https://federalreporter.nih.gov/Projects/SmartSearch/>), Wellcome Trust (<https://wellcome.ac.uk/funding/funded-people-and-projects/grant-funding-data>), Canadian Institute of Health Research (CIHR; <http://webapps.cihr-irsc.gc.ca/decisions/p/main.html?lang=en#sort=namesort%20asc&start=0&rows=20>), Medical Research Council (MRC; <https://mrc.ukri.org/research/funded-research/>), Bill and Melinda Gates Foundation (BMGF; <https://www.gatesfoundation.org/>

[How-We-Work/Quick-Links/Grants-Database](#)) and European Commission (CORDIS; <https://cordis.europa.eu/projects/en>).

Additionally, we examined the reference lists of included studies and cross-references to all relevant studies. Experts in the relevant domains were consulted where necessary to identify any additional major studies.

## Eligibility criteria

We included studies that addressed the research priority questions using an experimental study design for effectiveness questions and/or implementation research/mixed-methods for questions on scale-up. Observational studies were included only for the last research priority question. Specific inclusion and exclusion criteria for each research priority question are provided in the Supplementary appendix.

## Criteria for determining the uptake of a research priority

The identified research studies on a research priority question were expected to be diverse in terms of the number of studies undertaken, study designs, sample size, and the extent to which they address the research priority question. Therefore, we used pre-specified criteria, inspired by the GRADE approach, to assess these studies and classify the uptake of the research priority question as high, moderate, or low. These criteria are outlined in [Table 1](#).

The criterion score for geographic representativeness was assigned considering all studies included under a research priority question. For the other criteria, each study included under a research priority question was scored for each of the three criteria- study design and risk of bias, directness, and sample size. The criterion score for the research priority question was then assigned considering how many studies met score 2

Criteria	Score 0	Score 1	Score 2
Geographic Representativeness	Single study at a single site in a single country	Studies from 1-2 countries OR a multi-site study in a single country OR multiple studies in a single country	Multiple ( $\geq 3$ ) studies in multiple countries OR Single multi-country study
Study design and risk of bias	Inappropriate study design or very serious risk of bias	Appropriate study design but serious risk of bias	Appropriate study design and no serious risk of bias
Directness	Studies address the priority question indirectly	Studies only partly address the priority question	Studies directly address the priority question
Appropriateness of sample size	No consideration or calculation of sample size.	Sample size calculated, but unclear or inappropriate.	Sample size appropriately calculated, has a baseline and expected change (50% or lower), significance level (0.05 or lower), and power (at least 80%).

**Table 1: Criteria used to assess ongoing and published research to determine the uptake of research priority.**

(<1/3<sup>rd</sup> =score 0; ≥1/3<sup>rd</sup> to <2/3<sup>rd</sup> =score 1; and ≥2/3<sup>rd</sup> =score 2). The overall score for a research priority question was calculated by adding the scores for the four criteria. The extent to which each research priority area was taken up by subsequent research was based on the overall score as 1) High (score 8); 2) Moderate (score 5 to 7); and 3) Low (score ≤4).

The appropriateness of the study design was based on the reported study design, against the benchmark of what research design would have been considered appropriate to answer the research priority questions in 2014 (Supplementary Appendix Table 1). The risk of bias was ascertained and scored for each study that used the recommended study design, i.e., RCT or cluster RCT for effectiveness questions and observational studies for the last question in the discovery domain. For randomized and cluster-randomized trials, we used RoB2<sup>3</sup> and its adaptation for cluster RCTs,<sup>4</sup> and for observational studies we used ROBINS-I.<sup>5</sup> If <1/3<sup>rd</sup> of included studies used the specified design, the criterion score was 'zero', if ≥2/3<sup>rd</sup> of included studies used the specified design but were at serious risk of bias, or if ≥1/3<sup>rd</sup> to <2/3<sup>rd</sup> of included studies used the specified design, criterion score was 1; if ≥2/3<sup>rd</sup> of included studies used the specified design and were at no serious risk of bias, criterion score was 2. While implementation research or mixed-methods studies were eligible for inclusion for scale-up questions, we did not assess them for risk of bias as there is no validated risk of bias tool for assessing the overall risk of bias for such studies.

The assessment for directness was based on an assessment of how closely the population, intervention, comparison, and outcomes were to research answered the research priority question.

We assessed the sample size using the study 'methods' for the intervention studies as we included both published and unpublished research (Table 1). The criteria for effectiveness/intervention studies are outlined in Table 1. We scored the mixed methods/implementation research studies based on whether implementation was at national/subnational till district/woreda/equivalent level (score 2), sub-district level (score 1), or facility/community level (score 0).

### Synthesis of findings

Two review authors (SG, SR) independently reviewed the retrieved references to identify studies addressing each of the twenty research priority questions. The identified studies under each research priority question were listed, and data were extracted on the pre-defined criteria, i.e. number of countries in which research was conducted, study design and risk of bias, and sample size calculation for each study. Both the review authors independently assessed all the studies included for a research question to assign a score for study design and risk of bias, directness, and sample size. All the studies included for a research priority question were

considered together to assign the criterion-specific scores for geographic representativeness. The criterion-specific scores were summed to calculate the overall score for each research priority question.

Guidance was sought from the two study authors (SY, RB) who were involved in the WHO newborn research priority setting exercise in 2014 when clarifications were required. Both these authors also reviewed the included evidence base and the scores assigned for each priority question. Any discrepancies were resolved by mutual discussion between all the four authors.

The review protocol was not registered as it is not a standard systematic review. Ethics approval does not apply to the current work. All authors had access to the dataset and decided to submit it for publication (SG, SR, SY, RB).

### Role of the funding source

There was no funding source for this study. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

### Results

The uptake of WHO 2014 newborn health research priorities was high for eight out of 20 (40%), moderate for 11 out of 20 (55%), and one priority (5%) was not addressed. The uptake of ten research priorities in the delivery domain was high for six (60%) and moderate for four (40%). In the development domain, the uptake was high for two of five (40%), moderate for two (40%), and one priority was not addressed. The uptake was moderate for all five priorities in the discovery domain (Table 1).

The criterion of geographic representativeness was high for 16 of 20 (80%) questions, that of study design and risk of bias was high for 15 of 20 (75%) questions, that of directness was high for 14 of 20 (70%) questions, and that of appropriateness of sample size was high for 14 of 20 (70%) questions (Table 2).

The summary of criterion-specific and overall scores for each priority research question is provided in Table 2.

A summary of research studies included for the 20 identified research priorities published or registered after the publication of the priorities in 2014 is provided in Table 3.

No studies were identified for the research priority question on the effectiveness of training community health workers (CHWs) to recognize and treat neonatal sepsis at home with oral antibiotics when referral is not possible.

Some other research priority questions scored lower on specific criteria. All research priority areas attracted research from several countries globally, but

Research priorities (in order of priority)	Geographic represent-ativeness	Study design and risk of bias	Directness	Appropriateness of sample size	Uptake of research priority
<b>Delivery domain</b>					
Can a simplified neonatal resuscitation programme delivered by trained health workers reduce neonatal deaths due to perinatal asphyxia?	2	0	2	2	Moderate
How can health workers' skills in preventing and managing asphyxia be scaled up?	2	2	2	2	High
Can simple clinical algorithms used by community health workers identify and refer neonates with signs of infection and consequently reduce newborn mortality?	2	2	1	2	Moderate
How can exclusive breastfeeding in low-resource contexts be promoted to reduce neonatal infections and mortality?	2	2	2	2	High
Can training of community health workers in basic newborn resuscitation reduce morbidity and mortality due to perinatal asphyxia?	1	2	0	2	Moderate
How can the administration of injectable antibiotics at home and first-level facilities to newborns with signs of sepsis be scaled up to reduce neonatal mortality?	2	2	2	2	High
How can facility-based initiation of kangaroo mother care or continuous skin-to-skin contact be scaled up?	2	2	2	2	High
How can chlorhexidine application to the cord be scaled up in facility births and in low neonatal mortality rate settings to reduce neonatal infections and neonatal mortality?	2	2	0	2	Moderate
How can quality of care during labour and birth be improved to reduce intrapartum stillbirths, neonatal mortality, and disability?	2	2	2	2	High
Can community-based extra care for pre-term/low birthweight babies delivered by community health workers reduce neonatal morbidity and mortality in settings with poor access to facility care?	2	2	2	2	High
<b>Development domain</b>					
Can community-based initiation of kangaroo mother care reduce neonatal mortality of clinically stable preterm and low birth-weight babies?	1	2	2	2	Moderate
How can the accuracy of community health workers in detecting key most important high-risk conditions or danger signs in pregnant women be improved?	2	2	2	2	High
Can perinatal audits improve quality of care in health facilities and improve fetal and neonatal outcomes?	1	1	2	2	Moderate

**Table 2** (Continued)

Research priorities (in order of priority)	Geographic represent-ativeness	Study design and risk of bias	Directness	Appropriateness of sample size	Uptake of research priority
Can intrapartum monitoring to enhance timely referral improve fetal and neonatal outcomes?	2	2	2	2	High
Can training community health workers to recognize and treat neonatal sepsis at home with oral antibiotics when referral is not possible reduce neonatal mortality?	0	0	0	0	Not addressed
<b>Discovery domain</b>					
Can stable surfactant with simpler novel modes of administration increase the use and availability of surfactant for preterm babies at risk of respiratory distress syndrome?	2	2	0	1	Moderate
Can the method to diagnose fetal distress in labour be made more accurate and affordable?	2	2	1	1	Moderate
Can strategies for prevention and treatment of intrauterine growth restriction be developed?	2	1	2	1	Moderate
Can novel tocolytic agents to delay or stop preterm labour be developed in order to reduce neonatal mortality and morbidity?	2	2	2	1	Moderate
Can major causal pathways and risk factors for antepartum stillbirth be identified?	2	1	2	0	Moderate

**Table 2: Summary of the overall score for each research priority question.**

effectiveness of training of CHWs in basic newborn resuscitation and perinatal audits were addressed only by one study from one country, and effectiveness of community-initiated Kangaroo Mother Care (KMC) was evaluated only by two studies in two countries. All research priority areas had studies with appropriate design but four. These were: effectiveness of simplified neonatal resuscitation programme delivered by trained health workers which included all non-randomized studies (before-after intervention studies), effectiveness of perinatal audits which included a single cluster randomized trial at high risk of bias, strategies for prevention and treatment of intrauterine growth restriction that included multiple randomized studies at serious risk of bias, and causal pathways and risk factors for antepartum stillbirth where close to half of the identified studies were descriptive.

All but five research priority areas were addressed directly by most studies. Studies evaluating the effectiveness of simple clinical algorithms used by CHWs to identify neonates with signs of infection mostly evaluated this as part of a broader package of interventions. Same applied to the only study that addressed the effectiveness of CHWs training in basic newborn resuscitation. Only one study evaluated the scale up of chlorhexidine cord application. In discovery domain,

most studies evaluated simpler modes of surfactant administration likely to result in increased use but only one study tested a stable surfactant that may improve its availability. Studies on methods to diagnose intrapartum fetal distress focused primarily on accuracy and few evaluated low-cost options.

The sample size criterion was adequate for all research priority questions in the delivery and discovery domains but all studies in the discovery domain had unclear or inappropriate sample size.

A list of studies included for each research priority question with information on criteria used for scoring is provided in Supplementary Appendix Table 2.

## Discussion

Our review shows that the uptake of WHO 2014 newborn health research priorities was high for eight (40%), moderate for 11 (55%) and one priority was not addressed (5%). The uptake of research was high for six of the ten priorities in the delivery domain (60%), two of the five priorities in the development domain (40%), and none of the five priorities in the discovery domain (0%). It is encouraging to note that substantial research has been undertaken on most of the identified priorities, across most low- and middle-income as well as

Research question	Number of studies and countries	Study design	Interventions assessed in different studies
<b>Delivery domain</b>			
Can a simplified neonatal resuscitation programme delivered by trained health workers reduce neonatal deaths due to perinatal asphyxia?	Five studies conducted in five countries (Mali, India, Sudan, Kenya, and Tanzania) were identified.	No randomized trials were identified. All five studies were before-after intervention studies with enrolling several thousand births.	All studies evaluated the effectiveness of the Helping Babies Breathe (HBB) programme on perinatal outcomes including mortality.
How can health workers' skills in preventing and managing asphyxia be scaled up?	Eleven studies conducted in ten countries (Nigeria, Nepal, Kenya, Ethiopia, Uganda, Rwanda, Ghana, Tanzania, India, and the Dominican Republic) were identified.	Five studies used mixed methods, four studies were randomized or cluster-randomized trials, and two were before-after intervention studies. All were large studies involving multiple health facilities and several hundred providers.	Approaches to improve health worker's skills in preventing and managing asphyxia included virtual reality or video for training, simulation/simulator-based training, the addition of video de-briefings to HBB training, a mobile app with animated videos and clinical management instructions, structured on-the-job training, peer-assisted learning after onsite low-dose high-frequency HBB training, practice improvement package, and integrating HBB with quality improvement and other training(s) for newborn care.
Can simple clinical algorithms used by community health workers identify and refer neonates with signs of infection and consequently reduce newborn mortality?	Nine studies were identified from seven countries (Bangladesh, India, Cambodia, Mali, Kenya, Ghana, Guinea-Bissau)	Six were randomized or cluster-randomized trials, one quasi-experimental, one interrupted time-series, and one secondary analysis of cluster randomized trial. Six were large community-based studies and all enrolled more than a hundred community health workers (CHWs).	Studies evaluated mobile technology to support CHWs in case identification and management or CHW training and capacity building to identify local or systemic infection.
How can exclusive breastfeeding in low-resource contexts be promoted to reduce neonatal infections and mortality?	Forty nine studies from 27 countries evaluating the effectiveness of health system interventions to improve exclusive breastfeeding (EBF) were identified.	Thirty-four studies were randomized or cluster randomized trials, seven were quasi-experimental, seven were before-after intervention studies and one was a pragmatic trial. The sample size ranged from a hundred to several thousand women.	Interventions included home visits by CHW/peer counselors, mother/peer group sessions/men's club, combined peer group/home visits, mobile- or telehealth-based education, counseling, support and motivation, and monitoring of lactation and breastfeeding, in-person breastfeeding education and counseling, community mobilization activities, interpersonal counseling and communication, and mass media approaches, Baby-Friendly Hospital Initiative, quality improvement, and multi-modal or other interventions like monthly financial incentives.
Can training of community health workers in basic newborn resuscitation reduce morbidity and mortality due to perinatal asphyxia?	One study was identified from Pakistan.	The study was a large cluster RCT enrolling 27 clusters with approx. 500,000 population.	Training on the neonatal bag and mask resuscitation and oral antibiotic therapy for suspected neonatal infections was added to the basic preventive and promotive interventions package delivered by community-based lady health workers.
How can the administration of injectable antibiotics at home and first-level facilities to newborns with signs of sepsis be scaled up to reduce neonatal mortality?	Twelve studies were identified from five countries (India, Pakistan, Bangladesh, Nigeria, and Ethiopia)	All were implementation research studies. Nine were large district or province-level studies, one was conducted in ten sub-districts, one in a sub-district block, and one in a community with 50,000 population.	All studies evaluated the scale-up of management of possible serious bacterial infection of young infants (0-59 days) in primary health care facilities and community settings where referral is not feasible.

Table 3 (Continued)

Research question	Number of studies and countries	Study design	Interventions assessed in different studies
How can facility-based initiation of kangaroo mother care (KMC) or continuous skin-to-skin contact be scaled up?	Four studies were identified- one was conducted in India and Ethiopia, and the rest three were from the Philippines, India, and Ethiopia.	Three were implementation research/mixed-methods studies, and one was a before-after intervention study. All were large studies conducted at scale- one included a district each from two countries (~8 million population), one was a national level scale-up, two others included 10 and 22 hospitals/ health centers respectively.	Three studies used actions across multiple health system building blocks while one study implemented community-based promotion of skin-to-skin contact by trained health workers as part of a multi-level facility and community intervention.
How can chlorhexidine application to the cord be scaled up in facility births and in low neonatal mortality rate settings to reduce neonatal infections and neonatal mortality? <sup>21</sup>	Six studies were identified from five countries (Bangladesh, Uganda, Tanzania, Zambia, and India).	Five studies were randomized trials and one used mixed-methods to evaluate national-level scale-up. Three of the four RCTs were large enrolling several thousand newborns.	The national scale-up included the incorporation of intervention into national policy with product and application, guidelines, capacity building of health providers, social- and behavior change communication activities, supply chain management, strengthening of monitoring and health and logistics management information systems. Randomized trials evaluated the efficacy of 4% chlorhexidine cord care on neonatal infections, mortality, or cord colonization
How can quality of care during labour and birth be improved to reduce intrapartum stillbirths, neonatal mortality, and disability?	Twenty-seven studies conducted in 21 countries were included, of which four were multi-country studies.	Eighteen studies were randomized or cluster randomized trials, two were quasi-experimental and seven were before-after intervention studies. Most were multi-facility studies.	Key interventions included the use of WHO safe childbirth checklist, multi-component quality improvement (QI) packages involving training and capacity building of providers, use of checklists, periodic assessments, data collection and use to identify quality gaps, and activities to improve adherence to evidence-based practices through QI teams and structured QI approaches, Safer Birth Bundle, <sup>b</sup> Safe Delivery app, <sup>c</sup> ALERT intervention, <sup>d</sup> a multi-professional intrapartum emergencies training course for local maternity staff, simulation-based emergency obstetric and neonatal and team training programme, context-tailored clinical guidelines and training, self-managed continuous monitoring for maintaining high-quality care, onsite nurse mentoring, and a solar electric system providing lighting and power for charging phones and small medical devices in rural health facilities.
Can community-based extra care for preterm or low birth weight babies delivered by community health workers reduce neonatal morbidity and mortality in settings with poor access to facility care?	Five studies were identified from three countries (India, Tanzania, and Uganda).	All studies were large community-based randomized or cluster randomized trials.	All studies evaluated home-based neonatal care and counselling by CHWs with extra visits for small or low birth weight babies, except one where the primary focus of the intervention was to support community KMC for low birth weight babies.
<b>Development domain</b> Can community-based initiation of kangaroo mother care reduce neonatal mortality of clinically stable preterm and low birthweight babies?	Two studies were identified from two countries (India and Pakistan)	One study was a cluster-randomized trial and the other was a randomized trial both enrolling more than a thousand newborns.	Both studies evaluated the effectiveness of community-initiated KMC by trained CHW on the survival of low birth weight infants.

Table 3 (Continued)

Research question	Number of studies and countries	Study design	Interventions assessed in different studies
How can the accuracy of community health workers in detecting key most important high-risk conditions or danger signs in pregnant women be improved?	Nine studies were identified from thirteen countries of which one was a multi-country study.	Eight were randomized or cluster randomized trials and one was a quasi-experimental study. All cluster RCTs were large with a sample size in thousands.	Three studies evaluated community-based interventions for pre-eclampsia including community engagement, mobile health-guided clinical assessment, and referral based on algorithm-defined risk by CHWs. One study evaluated a vital signs device to measure blood pressure (BP) and pulse with a traffic-light early warning system in women with obstetric haemorrhage, sepsis, or pregnancy hypertension. Others assessed smartphone-based monitoring of BP, oxygen saturation, and doppler with decision-support systems, education, and continuous quality improvement approach to improve CHW accuracy in detecting high-risk pregnancies.
Can perinatal audits improve quality of care in health facilities and improve fetal and neonatal outcomes?	One study was identified from France.	The cluster-randomized trial from France reviewed more than two thousand morbidity or mortality cases from 95 maternity units.	Interventions included information on national guidelines on morbidity/mortality case management combined with a series of morbidity/mortality conferences to review perinatal morbidity/mortality cases.
Can intrapartum monitoring to enhance timely referral improve fetal and neonatal outcomes?	Thirteen studies from nine countries were identified (Australia, Bangladesh, Egypt, Tanzania, Uganda, Kenya, Norway, UK, and Ireland).	Eleven were randomized or cluster randomized trials, one was quasi-randomized and one was a cross-over study. Eleven studies were large enrolling more than a thousand women.	Studies evaluated fetal heart rate monitors, cardiotocography, various types of fetal dopplers (continuous, hand-held, and wind-up fetal dopplers), electronic partographs, and different types of partographs or guidelines of use and an e-learning education package about the importance of a recent change in the frequency of fetal movements and how to manage reduced fetal movement for clinical staff with a leaflet for pregnant women
Can training community health workers to recognise and treat neonatal sepsis at home with oral antibiotics when referral is not possible reduce neonatal mortality?	No eligible studies were identified	Not applicable	Studies evaluating oral Amoxycillin given by CHWs for fast breathing in young infants aged 7-59 days of age were excluded as this is no longer considered neonatal sepsis or possible serious bacterial infection in a young infant (0-2 months of age). <sup>6</sup>
<b>Discovery domain</b>			
Can stable surfactant with simpler novel modes of administration increase the use and availability of surfactant for preterm babies at risk of respiratory distress syndrome?	Thirty one studies conducted in 20 countries were identified of which two were multi-country studies.	Twenty nine studies were randomized trials including one phase I trial, one was before-after intervention, and one was a non-randomized intervention study. Most studies had a small sample size.	Studies examined the less- or minimally-invasive methods of surfactant administration given through aerosolization or vibrating mesh atomization (nebulization), intra-pharyngeal instillation, laryngeal mask, or a thin catheter. Only one small study evaluated a synthetic surfactant (CHF5633) for respiratory distress syndrome.
Can the method to diagnose fetal distress in labour be made more accurate and affordable?	Nineteen studies conducted in 13 countries were identified.	Seventeen were randomized trials and two were two diagnostic accuracy studies.	Studies evaluated computerized or automated analysis of cardiotocography (CTG) or fetal heart rate patterns or quantitative CTG, CTG plus fetal electrocardiography or external fetal electrocardiography alone, hand-held or wind-up or continuous fetal doppler, Cerebro-umbilical ratio and serum Placental Growth Factor, electrohysterography, different types of external

Table 3 (Continued)



Research question	Number of studies and countries	Study design	Interventions assessed in different studies
Can strategies for prevention and treatment of intrauterine growth restriction be developed?	Thirty-three studies were identified from 15 countries.	Thirty-two studies were randomized and one was a non-randomized trial.	monitors to record uterine and fetal parameters, manual fetal stimulation and second-line tests like fetal scalp stimulation and fetal blood sampling. None of the studies addressed both the accuracy and affordability. Modalities studied include PDE -5 inhibitors like Sildenafil or Tadalafil, nitric oxide donor Penta- erythritol-tetranitrate, anticoagulants like low molecular weight heparin, tinzaparin, and enoxaparin alone or in with aspirin, low dose aspirin alone or with Omega-3 or vitamin E, L Arginine, dydrogesterone or vaginal progesterone with Omega 3, selenium and zinc supplementation, fortified balanced energy-protein supplementation, Mediterranean diet or mindfulness-based stress reduction, plasma expanders, and positive pressure airway in women with obstructive sleep apnea.
Can novel tocolytic agents to delay or stop preterm labour be developed in order to reduce neonatal mortality and morbidity?	Twenty-eight studies conducted in 25 countries were identified of which four were multi-country studies	All were randomized trials including one phase-2 trial.	Tocolytics included potassium channel activator nicorandil, vaginal, oral, and rectal progesterone or synthetic progesterone (Dydrogesterone), 17 Alpha-hydroxyprogesterone Caproate (17OHPC), PGF2 alpha receptor antagonist OBE022 alone or in combination with other agents, oxytocin receptor antagonists –Atosiban, Montekulast, calcium-channel blocker nifedipine alone or with indomethacin or nitroglycerine patch and magnesium sulphate.
Can major causal pathways and risk factors for antepartum stillbirth be identified?	Fourteen studies from seven countries and two multi-country studies were identified.	Five were cohort studies, two were case-control one case-cross-over, and the rest six were descriptive studies.	Studies examined the roles of genotype, genetic variants or chromosomal abnormalities, cardiac arrhythmias, cardiac ion channelopathies or pathogenic single nucleotide variants in genes associated with cardiac channelopathies and cardiomyopathies, fetal electrophysiological abnormalities, vascular lesions of malperfusion in the placentas, elevated Factor VIII activity, differential expression of circulating mRNAs, cell-free DNA, chronic deciduitis, maternal hemoglobin, DDT exposure, and air pollution, and mechanisms of death in structurally normal stillbirths.

**Table 3: Summary of research studies included in the area of twenty priority research questions published/registered after 2014.**

<sup>a</sup> It was not considered mandatory that studies had applied the intervention “at scale” as WHO recommends clean, dry cord care for all births (WHO postnatal care guidelines, 2022; under preparation for publication).

<sup>b</sup> Safer Birth Bundle is a set of tools for training and therapy to improve the monitoring of labor (using Moyo FHR monitors<sup>®</sup>) and neonatal resuscitation (using upright bag-masks<sup>®</sup>, NeoBeat<sup>®</sup> newborn heart rate meters and NeoNatalie live training manikins<sup>®</sup>).

<sup>c</sup> Safe Delivery app is a smartphone application that provides skilled birth attendants with direct and instant access to evidence-based and up-to-date clinical guidelines on Basic Emergency Obstetric and Neonatal Care.

<sup>d</sup> The ALERT intervention includes four components-end-user participation for co-designing intervention, competency-based training, quality improvement supported by data from a clinical perinatal e-registry, and empowerment and leadership mentoring of maternity unit leaders complemented by district-based bi-annual coordination and accountability meetings.

high-income countries. While it is not possible to evaluate causation, we believe that the WHO research prioritization exercise may have played an important role in the process.

The delivery domain explores how to take effective interventions to every mother and every newborn baby. High uptake of research in 60% and moderate uptake in the rest 40% of questions in this domain reflects the relevance of the identified priorities in diverse global contexts. The development domain aims to improve existing interventions. High uptake of research for 40% and moderate uptake for the other 40% of questions underlines the importance of exploring the need to suitably adapt, modify or extend the scope of the existing interventions to increase their applicability and uptake. Research priorities in the discovery domain emphasize the need to invest in science and technology to expand the arsenal of effective interventions, none of which saw high uptake of research. This could be due to the difficulty in undertaking such studies due to lack of specific expertise, resources including laboratory or technological support, and limited research capacity in many settings. Translational research on problems including IUGR specific to the low-resource settings is essential to finding relevant solutions, and the capacity for basic science research should be strengthened in such settings.

One research priority that was not followed by further research was the recognition and treatment of newborn sepsis by CHWs at home with oral antibiotics when referral is not possible. Neonatal infections contribute to almost one-third of global neonatal mortality.<sup>7</sup> Given the persisting low rates of care-seeking for neonatal illnesses in most low- and middle-income countries,<sup>8</sup> exploring the effectiveness of community-based treatment is important. However, soon after the publication of the priorities in 2014, it was evident through global discussions that the research and programme communities in countries are not ready to engage CHWs in administering antibiotics to treat newborn sepsis at home. Thereafter, WHO supported several studies to address the research question on the effectiveness of outpatient treatment of young infants with possible serious bacterial infections using simplified regimens of injectable and oral antibiotics provided by an appropriately trained provider when referral is not feasible.<sup>9–11</sup> This emphasizes the need to contextualize the research priority according to the settings in which it would be applied.

For other priorities with moderate uptake, we need to understand the reasons to suitably adapt and modify the scope of the priority questions and improve their applicability to the changing context. No randomized trials compared a simplified neonatal resuscitation programme delivered by trained health workers to the standard neonatal resuscitation programme or no training, as the implementation of the standard resuscitation

programme may not be feasible in some settings. Research on training CHWs in basic newborn resuscitation and community-initiated KMC has only been conducted in a few settings. These interventions are a significant departure from the traditional service delivery in terms of place of service delivery (facility vs. community) and provider (medically trained health care professional vs. CHW), and it appears that evidence for the safety and effectiveness of such interventions is required from few settings before others would replicate. The research priority on chlorhexidine cord application concerned scale-up in the facility and low neonatal mortality settings, which is contradictory to the almost simultaneously published WHO recommendations. This exemplifies the need to consider the updated evidence regarding various priorities which are generally an expert-consensus-based process, and apply mid-course corrections. Perinatal audits also had a moderate uptake and may reflect concerns around responsibility assignment for perinatal death. Most studies evaluating the use of simple clinical algorithms by CHWs for the identification of newborn illness did so as part of an intervention package and were not designed to answer the specific research question. This could be driven by operational feasibility within programmatic settings, though only the interventions with demonstrated effectiveness should ideally be included in such packages.

We are mid-way between the completion of the Millennium Development Goals era (2010) and the target year for achieving the Sustainable Development Goals (2030), and this is an opportune time to review the research agenda for newborn health. The available evidence should be used to formulate recommendations on priorities that have been addressed. Priorities with moderate uptake should be reviewed and adapted to the changing context considering available evidence, and large, rigorous multi-country studies should be undertaken to address them. New, emerging priorities relevant to the present and future needs should also be formulated to drive the research agenda in the coming years. Increased funding could avert a higher proportion of neonatal deaths,<sup>12</sup> yet the programme and research funding is lowest for newborn health.<sup>13,14</sup> Information on biomedical grants awarded in 2019 by 11 funders shows that of 80,178 grants, only 501 (0.6%) were for perinatal conditions. Additionally, large inequities exist in present research funding for newborn health as compared with other diseases globally, and between different neonatal disorders themselves.<sup>15</sup> A renewed research agenda might help reorient adequate research and resources towards priorities that can have maximum impact on newborn health to meet the goal of neonatal survival and beyond. Research uptake depends not only on the availability of funds but also on the research priorities of the funders. Therefore, involving funder organizations in the priority setting process

and advocacy for the identified research priorities among diverse stakeholders and funders will be important.

Our literature search suggests that this is one of the first exercises to systematically evaluate the usefulness of a global research prioritization effort. It fills an important gap in knowledge about the value of priority setting exercises in shaping the global research agenda considering the great effort, resources, and collaboration required to undertake such work at a global level. The strengths of the present work include an extensive review of the existing body of evidence using individual search strategies for each question, and evaluation of the body of evidence against pre-defined criteria independently by multiple experts.

Limitations include the use of new scoring criteria developed through expert consensus as there are no established methods tested for an evaluation of this kind. However, we followed a systematic process and documented it thoroughly, making it reasonably reproducible. We acknowledge that all the criteria do not carry equal weightage and the implications of similar scores for different criteria would differ. We took this approach to simplify the scoring. It was beyond the scope of current work to cross-verify the study design. We might also have missed some studies despite a comprehensive search. Additionally, peer-reviewed literature might not have captured studies that were undertaken in the research priority areas but were either not registered or reported. However, we searched clinical trial registries and reference lists of included studies and are unlikely to have missed any major studies. Since WHO coordinated the research prioritization exercise and also conducted the present evaluation, potential bias in assessment and interpretation is possible. We have provided the details of all studies included for each research priority to allow an external reviewer to assess whether it meets the pre-specified criteria or not.

The global research prioritization exercise for newborn health undertaken by the WHO in 2014 was successful in generating interest in the research community and driving research on some of the most pressing global concerns in the area of newborn health. Funders and researchers should contemplate reasons for less research in some areas, modify the existing priorities to accommodate the changing context and new evidence, identify new, emerging priorities, and direct efforts towards filling the key gaps in knowledge in the priority areas to reshape the future of newborn health.

#### Contributors

RB conceptualized the study. SG and SR conducted literature search, identified eligible studies, extracted data, and performed initial scoring. RB and SY supervised and provided technical inputs at all stages of the study,

independently reviewed included studies and scored and verified the underlying data. SG prepared the first draft, SR, SY, and RB reviewed, commented on, and approved the final manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

#### Data sharing statement

All data used for the study has been included in the manuscript and supplementary material. The search strategies are available on request to the corresponding author.

#### Declaration of interests

SG, RB and SY are staff members and SR is a consultant for WHO. The authors alone are responsible for the views expressed in this publication; they do not represent the decisions, policy, or views of WHO or the institutions with which the authors are affiliated.

#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2022.101599](https://doi.org/10.1016/j.eclinm.2022.101599).

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