Impact of neonatal resuscitation trainings on neonatal and perinatal mortality: a systematic review and meta-analysis

Archana Patel,1 Mahalaqua Nazli Khatib,2 Kunal Kurhe,1 Savita Bhargava,1 Akash Bang3

ABSTRACT

Background Training of birth attendants in neonatal resuscitation is likely to reduce birth asphyxia and neonatal mortality. We performed a systematic review and meta-analysis to assess the impact of neonatal resuscitation training (NRT) programme in reducing stillbirths, neonatal mortality, and perinatal mortality

Methods We considered studies where any NRT was provided to healthcare personnel involved in delivery process and handling of newborns. We searched MEDLINE, CENTRAL, ERIC and other electronic databases. We also searched ongoing trials and bibliographies of the retrieved articles, and contacted experts for unpublished work. We undertook screening of studies and assessment of risk of bias in duplicates. We performed review according to Cochrane Handbook. We assessed the quality of evidence using the GRADE approach.

Results We included 20 trials with 1,653,805 births in this meta-analysis. The meta-analysis of NRT versus control showed that NRT decreases the risk of all stillbirths by 21% (RR 0.79, 95% CI 0.74 to 0.83), 7-day neonatal mortality by 47% (RR 0.53, 95% CI 0.48 to 0.59), and perinatal mortality by 37% (RR 0.63, 95% CI 0.53 to 0.76). The meta-analysis of pre-NRT versus post-NRT showed that post-NRT decreased the risk of all stillbirths by 12% (RR 0.88, 95% CI 0.83 to 0.94), fresh stillbirths by 26% (RR 0.74, 95% CI 0.61 to 0.90), 1-day neonatal mortality by 42% (RR 0.58, 95% CI 0.42 to 0.76), 7-day neonatal mortality by 18% (RR 0.82, 95% CI 0.73 to 0.93), 28-day neonatal mortality by 14% (RR 0.86, 95% CI 0.65 to 1.13) and perinatal mortality by 18% (RR 0.82, 95% CI 0.74 to 0.91).

Conclusions Findings of this review show that implementation of NRT improves neonatal and perinatal mortality. Further good quality randomised controlled trials addressing the role of NRT for improving neonatal and perinatal outcomes may be warranted.

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INTRODUCTION

Approximately a quarter of 17 million neonatal deaths worldwide are as a result of birth asphyxia.1 A large majority of these deaths occur in low-resource settings and are preventable. Approximately 5%–10% of newborns require some support to adapt to the extrauterine environment and to establish regular respiration.1,2 Simple resuscitative measures are often enough to resuscitate newborns that may even appear to be lifeless at birth. Studies have shown that essential newborn care has been effective in reducing stillbirths (SB).3

In developing countries, measures to improve resuscitative efforts through training of basic steps of neonatal resuscitation are expected to reduce birth asphyxia and neonatal mortality. Numerous studies
have suggested that imparting neonatal resuscitation training (NRT) to healthcare providers involved in delivery process and handling of newborns has the potential to save newborn lives in low-income and middle-income settings.\textsuperscript{4-10} Improvements in knowledge and skills of trainees following training programme in resource-limited settings have been reviewed. However, the impact on perinatal mortality outcomes has not been updated in last 5 years.\textsuperscript{9} The effect estimates of mortality reduction as a result of training of healthcare providers involved in delivery process and handling of newborns needs to be updated to inform hospital administrators and policy-makers the importance of investing in NRT to sustain and improve neonatal survival. A previous systematic review and meta-analysis\textsuperscript{11} assessed knowledge, skills, neonatal morbidity, neonatal mortality in first 7 days after birth and from day 8 to 28. However, it did not include outcomes of stillbirth, 1-day neonatal mortality or perinatal mortality which has been included in our review.

The objective of this review is to assess the impact of NRT programme in reducing stillbirths, 1-day neonatal mortality, 7-day neonatal mortality, 28-day neonatal mortality and perinatal mortality.

\section*{MATERIALS AND METHODS}
\subsection*{Inclusion criteria}
Types of studies
We included relevant randomised, quasi-randomised controlled trials, interrupted time series studies and before–after studies regardless of language or publication status.

Types of participants (population) trained
We considered studies where NRT was provided to healthcare providers (including neonatologists, physicians, nurses, interns, midwives, traditional/community birth attendants, auxiliary nurse midwives, village health workers, paramedics) involved in delivery process and handling of newborns in a community (home-based, rural and village clusters) or a hospital (including district hospitals, health centres, dispensaries, teaching/university hospitals, regional hospital, delivery/hospital centres, local hospitals and tertiary care hospital) setting.

Types of interventions and comparison
Studies in which any NRT was compared with a control group (that received no NRT) or compared with data before the study (pre-NRT vs post-NRT) were included. For this purpose, we considered any NRT programme of healthcare professionals, including the American Academy of Pediatrics’ (AAP) Neonatal Resuscitation Program (NRP), Helping Babies Breathe (HBB) or any other training programme that had NRP or HBB as a clearly mentioned component of training methodology.

\subsection*{Types of outcomes measures}
We included following outcomes in the review:
1. Stillbirths: defined as number of deaths prior to complete expulsion or extraction of products of conception from its mother.
2. Fresh stillbirth: clinically defined as those deaths with no signs of life at any time after birth and without any signs of maceration.
3. 1-day neonatal mortality: defined as number of deaths in first 24 hours of life
4. 7-day neonatal mortality: defined as number of deaths in first 7 days of life
5. Perinatal mortality: defined as number of stillbirths and deaths in the first week of life.
6. 28-day neonatal mortality: defined as number of deaths in the first 28 days of life.

\subsection*{Search strategy}
We searched following electronic databases from inception to July 2016: MEDLINE (PubMed), The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library); Education Resources Information Centre (ERIC), Web of Science, Science Citation Index and Scientific Electronic Library Online. The search strategies for PubMed and CENTRAL can be found in supplementary files S1 and S2 respectively. We also searched for ongoing trials at www.clinicaltrials.gov and www.controlled-trials.com. We searched published abstracts of conferences and examined bibliographies of retrieved articles for additional studies. We contacted and requested experts and authors in this field to provide possible unpublished work.

\subsection*{Study selection and data extraction}
Screening of studies
Two reviewers (MNK and AB) independently examined studies identified by literature search; discarded articles that did not fulfil the inclusion criteria and assessed full texts of all relevant articles for inclusion. A third reviewer (AP) resolved disagreement among the primary reviewers.

Data extraction and management
For all studies that fulfilled the inclusion criteria, two reviewers (KK, SB) extracted data (table 1 and 2). Third review author (AP) cross-checked the data and resolved discrepancies. For studies where required data was lacking or could not be calculated, we requested the corresponding author for details.

Assessment of risk of bias in included studies
Two authors (SB, KK) independently assessed risk of bias for each study using criteria suggested by Cochrane Effective Practice and Organization of Care (EPOC)\textsuperscript{12} and using criteria outlined in Chapter 8 of Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{13} Disagreements were resolved by discussion with the third reviewer (MNK).
### Table 1  Characteristic of included studies

| Sr. No. | Author          | Country                                      | Study design                     | Study period                        | Funding                                                                 |
|---------|-----------------|----------------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------------------------------------------|
| 1       | Bang et al      | India                                        | RCT                               | 36 months (1995–1998)              | ► Ford Foundation USA  
|         |                 |                                              |                                   |                                     | ► The John D & Catherin T MacArthur Foundation USA                       |
| 2       | Ariawan et al   | Indonesia                                    | Pre-Post training                 | NR                                  | NR                                                                      |
| 3       | Carlo et al     | Argentina, Democratic Republic of Congo,     | Pre-Post training and RCT         | 42 months (ENC: Mar 2005 and Feb 2007; NRP: Jul 2006–Aug 2008) | ► NICHD, Global Network for Women’s and Children’s Health Research  
|         |                 | Guatemala, India, Pakistan and Zambia        |                                   |                                     | ► Bill & Melinda Gates Foundation                                       |
| 4       | Carlo et al     | Argentina, Democratic Republic of Congo,     | Pre-Post training and RCT         | 42 months (ENC: Mar 2005 and Feb 2007; NRP: Jul 2006–Aug 2008) | ► NICHD, Global Network for Women’s and Children’s Health Research  
|         |                 | Guatemala, India, Pakistan and Zambia        |                                   |                                     | ► Bill & Melinda Gates Foundation                                       |
| 5       | Gill et al      | Zambia                                        | Prospective, cluster randomised   | 30 months (Jun 2006–Nov 2008)       | ► Boston University and The Office of Health and Nutrition of The United State Agency for International Development  
|         |                 |                                              | and controlled effectiveness study|                                     | ► AAP                                                                   |
|         |                 |                                              |                                   |                                     | ► Unicef                                                                 |
| 6       | Zhu et al       | China                                         | Perspective study, pre-post training (traditional resuscitation vs NRPG) | 24 months (1993–1995)              | NR                                                                      |
| 7       | Deorari et al   | India                                         | Pre-post training ( )             | NR                                  | ► Laerdal Foundation Norway                                               |
| 8       | Jeffery et al   | Macedonia                                     | Pre-Post training ( )             | 60 months (1997–2001)              | ► International Project Unit, Ministry of Health, Macedonia  
|         |                 |                                              |                                   |                                     | ► IDA Credit, World Bank                                                 |
| 9       | Vakrlova et al  | Bulgaria                                      | Pre-Post training ( )             | 48 months (2000–2003)              | NR                                                                      |
| 10      | O'Hare et al    | Uganda                                        | Pre-Post training (historic group vs NRP pilot) | 1 month (Dec 2001–Jan 2002)        | ► Child Advocacy International                                           |
| 11      | Opiyo et al     | Kenya                                         | Pre-Post training ( )             | NR                                  | ► Laerdal Foundation for Acute Medicine  
|         |                 |                                              |                                   |                                     | ► Welcome Trust Senior Research Fellowship Award                        |
| 12      | Boo            | Malaysia                                      | Pre-Post training, prospective observational study | 100 months (Sep 1996–Dec 2004)     | ► Perinatal Society of Malaysia                                           |
| 13      | Sorensen et al  | Tanzania                                       | Prospective study, Pre-Post training | 14 weeks (Jul 2008–Nov 2008)       | ► Danish Society of Obstetrics and Gynecology                            |
| 14      | Hole et al      | Malawi, Africa                                | Pre-Post training ( )             | 30 months (Jun 2007–Dec 2009)      | ► Stanford University School of Medicines, Medical Scholars Research Program  
|         |                 |                                              |                                   |                                     | ► Department of Community Relations at Lucil Packard Children’s Hospital |
| 15      | Msemo et al     | Tanzania                                      | Pre-Post training ( )             | 30 months (2009–2013)              | ► AAP                                                                   |
|         |                 |                                              |                                   |                                     | ► Laerdal Foundation for Acute Medicine                                  |
| 16      | Goudar et al    | India                                         | Pre-Post training (pretraining vs post HBB) | 12 months (Oct 2009–Sep 2010)      | ► AAP                                                                   |
|         |                 |                                              |                                   |                                     | ► Global Implementation Task Force HBB Program,  
|         |                 |                                              |                                   |                                     | ► Laerdal Foundation for Acute Medicine, Stavanger Norway              |

Continued
Data analysis

Measures of treatment effect

We conducted meta-analysis and reported pooled statistics as risk ratios (RR) with 95% confidence interval (CIs) for dichotomous data. We followed recommendations of the Cochrane Handbook for Systematic Reviews of Interventions Sections 9.2 and 9.4 for measuring the effects.

Assessment of heterogeneity

We assessed heterogeneity amongst studies by inspecting forest plots for the overlap of confidence intervals, analysed statistical heterogeneity through $X^2$ test (P value >0.10) and quantified through $I^2$ statistics (Chapter 9.5 of Cochrane Handbook for Systematic Reviews). We regarded heterogeneity as substantial if in the $X^2$ test for heterogeneity there was either $I^2>50\%$, or P value $<0.10$. We interpreted $I^2$ values between 0% and 40% as possibly unimportant, 30% and 60% as possibly significant, 50% and 90% as possibly substantial and 75% and 100% as possibly considerable.

Assessment of reporting bias

We used funnel plots for assessment of publication bias if ten or more studies were included in a meta-analysis.

Data synthesis and analysis

We analysed the data using Review Manager V.5.3 software. We conducted meta-analyses for individual studies and reported pooled statistics as relative risk (RR) between experimental and control groups with 95% CI. We explored possible clinical and methodological reasons for heterogeneity, and in the presence of significant heterogeneity, we carried out sensitivity analysis and employed inverse-variance method with Random-effects model. We did not pool randomised and non-randomised (pre–post NRT) studies in the same meta-analysis.

Summary of findings table

We created ‘summary of findings’ (SoF) table using five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence. We used methods and recommendations described in Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions using GRADEpro software. GRADE working Group grades of evidence were used in the SoF.

RESULTS

Search results

We identified 148 records through database searching and 11 records through other sources. After initial screening on the basis of title and abstract, we assessed 47 full-text articles for eligibility and finally included 20 articles in the meta-analysis. The screening details are presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (figure 1).
### Table 2  Characteristic of included studies (training and outcomes)

| Sr. No. | Author | Duration | Training setting | Type | Trainers | Trainees | Assessment | No. of births | Outcomes |
|---------|--------|----------|------------------|------|----------|----------|------------|--------------|----------|
|         |        |          |                  |      |          |          |            | A: control/pre | B: intervention/post | A: inclusion | B: exclusion |
| 1       | Bang et al | NR | Community (86 villages) | A package of home-based neonatal care, health education including ENC, Suction, stimulation, Artificial respiration by mouth to mask and tube and mask | Community birth attendants | Village health workers | NR | A: 1159 B: 1005 | 1. SB | 2. NMR: day 7 | 3. Perinatal mortality |
| 2       | Ariawan et al | NR | Community | NRT including Use of tube mask, Refresher training at 3, 6 and 9months, use of video, Post resuscitation care | Midwives | NR | A: 9816 B: 16053 | 1. SB | 2. NMR: day 28 |
| 3       | Carlo et al | 3 days | Rural communities (7 sites in 6 countries for ENC; 88 for NRP) | ENC sensitisation followed by in-depth NRT including Initial resuscitation steps BMV AAP-trained trainer Research staff, either a physician or nurse Community birth attendants | NR | A: 359 B: 273 | A: 35017 B: 29715 | 1. SB | 2. FSB | 3. NMR: day 7 | 4. PMR |
| 4       | Carlo et al | 3 days | Rural communities (7 sites in six countries for ENC; 88 for NRP) | ENC sensitisation followed by in-depth NRT including Initial resuscitation steps BMV AAP-trained trainer Research staff, either a physician or nurse Community birth attendants | NR | A: 35017 B: 29715 | A: 35017 B: 29715 | 1. SB | 2. FSB | 3. NMR: day 7 | 4. PMR |
| 5       | Gill et al | 2 weeks | Community (rural district setting) | NRT modified from AAP/AHA including Initial steps PPV Use of manikins to demonstrate and practice skills | 60 Community birth attendants/ TBAs | One to one skills assessment | A: 1536 B: 1961 | A: NR | 1. NMR: day 1 | 2. NMR: day 7 | A: NR | B: NR |
| 6       | Zhu et al | NR | Hospital (1 hospital) | NR | Hospital birth attendants | NR | A: 1722 B: 4751 | A: NR | 1. NMR: day 1 | 2. NMR: day 7 | A: NR | B: NR |
| 7       | Deorari et al | NR | Hospital (14 teaching hospitals) | AAP/AHA-modified NRT with ToT approach | 2 Faculty member trainer per facility Hospital-based birth attendants | No skills assessment | A: 7070 B: 25713 | A: NR | 1. NMR: day 28 | A: NR | B: NR |
| 8       | Jeffery et al | 9 weeks | Hospital (3 tertiary care, 13 district hospitals) | A package of perinatal practices with NRT | Australian-trained Macedonian teachers (doctors and nurses) | Doctors and nurses | MOQ, SAQ and OSCE (practical test) | A: 69840 B: 45458 | 1. SB | 2. NMR: day 7 | 3. PMR | A: NR | B: NR |
| 9       | Vakrilova et al | NR | Hospital (delivery rooms of city hospitals) | French–Bulgarian Program on NRT | Neonatologist Obstetrician Midwives | NR | A: 67948 B: 674-67 | A: NR | 1. NMR: day 7 | A: NR | B: NR |
| 10      | O’Hare et al | 10 days training (5 days classroom+5 days delivery suite) | Hospital (1 teaching hospital) | NRT including Airway management BMV Cardiac massage Use of manikins to demonstrate and practice skills | 5 members of nursing staff | NR | A: 1296 B: 1046 | 1. SB | 2. NMR: day 28 | A: NR | B: NR |
| 11      | Opio et al | 1 day | Hospital (1 maternity hospital) | NRT including Initial steps BMV (use of bag valve mask device) CC Use of manikins to demonstrate and practice skills | Instructor completed Kenya Resuscitation Council Advanced Life Support Generic Instructor Course | Nurse/midwives | MOQ and formal test scenario evaluating skills | A: 4084 B: 4302 | 1. SB | 2. NMR: day 28 | A: NR | B: NR |
| Sr. No. | Author | Duration | Training setting | Type | Trainers | Trainees | Assessment | No. of births | Criteria for delivery outcomes |
|--------|--------|----------|------------------|------|----------|----------|------------|--------------|-----------------------------|
| 12     | Boo    | NR       | Hospital         | AAP-NRT tailored to local needs including: | 37 Core instructors | 14,575 | Written and practical test | A: 5,417 | 1. SB |
|        |        |          |                  | Initial steps | Doctors and nurses | | | B: 465 | 2. NMR: day 28 |
|        |        |          |                  | BMV | | | | | 3. PNMR |
|        |        |          |                  | CC | | | | | A: NR |
|        |        |          |                  | ET | | | | | B: NR |
|        |        |          |                  | ToT approach, a national-level training programme | | | | | |
| 13     | Sorensen et al | 2 days | Hospital (1 referral hospital) | ALSO a widespread EmONC including: | NR | | | A: 577 | 1. SB |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | B: 565 | 2. FSB |
|        |        |          |                  | Paediatrics residents from Stanford University | | | | | |
| 14     | Hole   | 1 day    | Hospital (1 university hospital and 1 referral hospital) | AAP modified NRT to include: | NR | | | A: 3,44 | 1. NMR: day 28 |
|        |        |          |                  | Initial steps | Physician | | | B: 3,51 | 2. FSB |
|        |        |          |                  | BMV | Clinical officers | | | | |
|        |        |          |                  | CC and special consideration | Midwives | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | ToT approach | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
| 15     | Msemo  | 1 day    | Hospital (3 referral hospitals, 4 regional hospitals and 1 district hospital) | HB2 training including: | 40 Trainers | Hospital birth attendants | Practical test | A: 8,124 | 1. SB |
|        |        |          |                  | Initial steps | | | | B: 7,850 | 2. FSB |
|        |        |          |                  | BMV | | | | | |
|        |        |          |                  | ToT approach | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
| 16     | Goudar  | 1 day    | Hospital (primary health centres and rural and urban hospitals) | HB2–AAP-based NRT including: | 18 Master trainers trained by AAP | 599 Birth attendants | Written and verbal MQO, BMV by demonstration—OSCE | A: 4,187 | 1. SB |
|        |        |          |                  | Initial steps | Physicians and nurses | | | B: 5,41 | 2. FSB |
|        |        |          |                  | BMV | | | | | |
|        |        |          |                  | ToT model | | | | | |
|        |        |          |                  | Paired teaching | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
| 17     | Vossius | 1 day    | Hospital (1 tertiary hospital) | HB2–AAP-based NRT including: | 40 Master trainers | Hospital-based birth attendants | Knowledge and technical skills | A: 4,876 | 1. FSB |
|        |        |          |                  | Initial steps | | | | B: 4,734 | 2. NMR: day 7 |
|        |        |          |                  | BMV and resuscitation | | | | | |
|        |        |          |                  | Simulation-based training using manikins | | | | | |
|        |        |          |                  | ToT approach | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
|        |        |          |                  | Use of manikins to demonstrate and practice skills | | | | | |
| 18     | Ashish | 2 days   | Hospital (1 tertiary hospital) | HB2–AAP-based NRT with QIC; train the trainer model, paired teaching | NR | | | A: 9,588 | 1. SB |
|        |        |          |                  | | | | | B: 1,5520 | 2. FSB |
|        |        |          |                  | | | | | | 3. NMR: day 1 |
|        |        |          |                  | | | | | | 4. PNMR |
|        |        |          |                  | | | | | | A: NR |
|        |        |          |                  | | | | | | B: NR |

Table 2 Continued
| Sr. No. | Author            | Duration | Training setting          | Type                                      | Trainers                                      | Trainees                              | Assessment                  | No. of births | Criteria for delivery outcomes |
|--------|-------------------|----------|---------------------------|-------------------------------------------|-----------------------------------------------|----------------------------------------|-----------------------------|---------------|-------------------------------|
| 19     | Bellad et al      | 3 days   | Hospital (39 primary, 21 secondary and 11 tertiary facilities) | HBB-AAP-based NRT including               | ► Neonatologists                              | Hospital-based birth attendants       | MOQ, OSCE for skills assessment | A: 15322       | 1. FSB                        |
|        |                   |          |                           | ► Initial steps                            | ► Neonatologists                              | Hospital-based birth attendants       |                             | B: 15985       | 2. NMR: day 1                 |
|        |                   |          |                           | ► Simulation, suctioning                   | ► Paediatricians                               |                                        |                             |               | 3. NMR: day 7                 |
|        |                   |          |                           | ► BMV                                     | ► Obstetricians                                |                                        |                             |               | 4. NMR: day 28                |
|        |                   |          |                           | ► Refresher training                       | ► Nurses                                      |                                        |                             |               | 5. PNMR                       |
|        |                   |          |                           | ► QI activities                            |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► ToT model                               |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► Paired teaching                          |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► Use of manikins to demonstrate and practice skills |                                               |                                        |                             |               |                               |
| 20     | Patel et al**     | 3 days   | Hospital (2 primary, 4 secondary and 7 tertiary facilities) | HBB-AAP-based NRT including               | ► Neonatologists                              | Hospital-based birth attendants       | MOQ, OSCE for skills assessment | A: 38078       | 1. SB                         |
|        |                   |          |                           | ► Initial steps                            | ► Neonatologists                              | Hospital-based birth attendants       |                             | B: 40870       | 2. FSB                        |
|        |                   |          |                           | ► Simulation, suctioning                   | ► Paediatricians                               |                                        |                             |               | 3. NMR: day 1                 |
|        |                   |          |                           | ► BMV                                     | ► Obstetricians                                |                                        |                             |               | 4. NMR: day 2                 |
|        |                   |          |                           | ► Refresher training                       | ► Nurses                                      |                                        |                             |               | 5. PNMR                       |
|        |                   |          |                           | ► QI activities                            |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► ToT model                               |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► Paired teaching                          |                                               |                                        |                             |               |                               |
|        |                   |          |                           | ► Use of manikins to demonstrate and practice skills |                                               |                                        |                             |               |                               |

*Data for this study has been taken from Lee et al.*

**Data for very low birth weight (<1500 g).**

***Unpublished data obtained via personal communication with the author.

AAP, American Academy of Pediatrics; AHA, American Heart Association; ALSO, Advanced Life Support in Obstetrics; BMV, bag and mask ventilation; BW, birth weight; CC, chest compression; EmONC, Emergency Obstetrics & Neonatal Care; ENC, essential newborn care; ET, endotracheal tube; FBOS, frequent brief onsite simulation; FSB, fresh stillbirth; GA, gestational age; HBB, helping babies breathe; MCQ, multiple choice questions; NICHD, National Institute of Child and Human Development; NMR, neonatal mortality rate; NORAD, Norwegian Agency for Development Cooperation; NR, not reported; NRPO, Neonatal Resuscitation Program Guidelines; NRT, neonatal resuscitation training; OSCE, objective structured clinical examination; PNMR, perinatal mortality rate; PPV, positive pressure ventilation; QI, quality improvement; QA, quality improvement cycle; RCT, randomised control trial; SAQ, short answer questions; SB, stillbirth; TBA, traditional birth attendant; ToT, training of trainer; wks, weeks.
Amongst included studies, two randomised trials addressed the efficacy of NRT in improving neonatal and perinatal outcomes, whereas 18 were pre–post studies. A full description of each study is included in table 1 and 2. All studies were from low-income and middle-income countries. Four studies were done in community setting, whereas 16 studies were carried in hospital setting. Carlo et al. 17, 18 assessed baseline neonatal and perinatal outcomes, whereas 16 were pre–post studies. A full description of each study is included in table 1 and 2. All studies were from low-income and middle-income countries. Four studies were done in community setting, whereas 16 studies were carried in hospital setting. Carlo et al. 17, 18 assessed baseline neonatal and perinatal outcomes, whereas 16 were pre–post studies. A full description of each study is included in table 1 and 2. All studies were from low-income and middle-income countries. Four studies were done in community setting, whereas 16 studies were carried in hospital setting.

Table 3 Risk of bias assessment across studies

| Adequate sequence generation? | High risk | Low risk |
|-------------------------------|-----------|----------|
| Allocation concealment?       | High risk | Low risk |
| Incomplete outcome data addressed? | High risk | Low risk |
| Free of selective reporting?  | Low risk  | Low risk |
| Free of other bias?           | Unclear risk | Low risk |
| Baseline outcomes similar?    | Low risk  | Low risk |
| Free of contamination?        | Low risk  | Low risk |
| Baseline characteristics similar? | Unclear risk | Low risk |
and compared them to outcomes of those clusters that received ENC + post ENC in-depth NRT. We therefore did not include this study in the NRT versus control analysis because the control group had also received NRT as a part of ENC training.

The study from Kenya had a complex design of randomisation of health workers to two groups—early training (phase I) or late training (phase II) and did not include a control group without training. Therefore, we analysed this study as before–after study where the rate of stillbirths prior to any training were compared with the rate of stillbirths after all phases of training.

Participants of the NRT programme differed across studies and included village health workers, community birth attendants, community birth attendants/traditional birth attendants, hospital-based birth attendants, or hospital-based birth attendants including high-level and mid-level staff/specialists.

Different types of training employed by studies included AAP, HBB or NRP curricula, AAP/American Heart Association (AHA), basic neonatal resuscitation and ENC, home-based neonatal care, basic training with mouth to mask or tube and mask resuscitation, Advanced Life Support in Obstetrics (ALSO), Bulgarian program on NRT. The duration of NRT also differed across studies.

We also included two unpublished trials after permission from authors (tables 1 and 2).

### Excluded studies

Studies that included interventions that did not qualify as NRT were excluded from the review. These included trainings in safe birthing techniques, Emergency Obstetric and Neonatal Care (EmONC), ENC, promotion of antenatal care and maternal health education, and newborn care intervention package.

Other interventions that did not qualify as NRT or included interventions like neonatal intensive care unit/special neonatal care unit training were also excluded.

Studies in which desired outcomes (fetal and neonatal outcome) were not assessed or only trainees/training outcomes were assessed were also excluded from the analysis.

Some studies that were subgroups of larger studies like Ersdal et al., Matendo et al., Matendo et al., and Vossius et al. were not included. However, Vossius et al. was included.
Figure 5  Forest plot comparing perinatal mortality between the NRT and the control groups. NRT, neonatal resuscitation training.

in the analysis for outcomes where data from Msemo et al were not available.

Risk of bias in included studies has been depicted in table 3.

Effects of interventions

Neonatal and perinatal outcomes were reported in majority of included studies. The overall analysis showed a trend towards reduction in neonatal deaths, early neonatal deaths, perinatal deaths and stillbirths with NRT; most of which are statistically significant.

NRT versus control

The meta-analysis for NRT versus control shows that NRT decreases the risk of all stillbirths by 21% (RR 0.79, 95% CI 0.44 to 1.41; participants=5661; studies=2; I²=67%) (figure 2), 7-day neonatal deaths by 47% (RR 0.53, 95% CI 0.38 to 0.73; participants=5518; studies=2; I²=0%) (figure 3), 28-day neonatal deaths by 50% (RR 0.50, 95% CI 0.37 to 0.68; participants=5442; studies=2; I²=0%) (figure 4), and perinatal deaths by 37% (RR 0.63, 95% CI 0.42 to 0.94; participants=5584; studies=2; I²=68%) (figure 5). The effect was significant for any 7-day neonatal mortality, 28-day neonatal mortality and perinatal mortality. Significant heterogeneity was observed in analysis of total stillbirths and perinatal mortality.

The grade of quality of evidence for the meta-analysis of the trials was moderate to high (table 4).

Post-NRT versus pre-NRT

The meta-analysis of post-NRT versus pre-NRT shows that post-NRT decreases the risk of all stillbirths by 12% (RR 0.88, 95% CI 0.83 to 0.94; participants=1425,540; studies=12; I²=47%, figure 6), fresh stillbirths by 26% (RR 0.74, 95% CI 0.61 to 0.90; participants=296,819; studies=8; I²=84%, figure 7), 1-day neonatal mortality by 42% (RR 0.58, 95% CI 0.42 to 0.82; participants=280,080; studies=6; I²=89%, figure 8), 7-day neonatal mortality by 18% (RR 0.82, 95% CI 0.73 to 0.93; participants=360,383; studies=7; I²=71%, figure 9), 28-day neonatal mortality by 14% (RR 0.86, 95% CI 0.65 to 1.13; I²=0%) (figure 10).
participants=1 116 463; studies=7; I²=95%, figure 10) and perinatal mortality by 18% (RR 0.82, 95% CI 0.74 to 0.91; participants=1 243 802; studies=6; I²=90%, figure 11). The changes were significant in all the outcomes; except 28-day neonatal mortality. Heterogeneity was significant in all outcomes except all stillbirths. We created a funnel plot for all stillbirths, which showed asymmetry, thereby indicating a publication bias (figure 12).

The quality of evidence for NRT versus control was very low for SB and 1-day neonatal mortality, high for 7-day and 28-day neonatal mortality and moderate for perinatal mortality (table 4). The quality of evidence for post-NRT versus pre-NRT was very low for all our outcomes (table 5).

**DISCUSSION**

This meta-analysis assessed the impact of any NRT programme either by itself or as a part of newborn care package on rates of stillbirths, perinatal mortality, all-cause neonatal mortality on day-1, up till day-7 and till 28th day after birth. We did not evaluate intrapartum-related neonatal deaths or asphyxia/cause-specific neonatal mortality. Mortality in neonates <7 days of life is a proxy measure for intrapartum-related deaths.43 78 Meta-analysis of before–after studies showed a significant reduction in all stillbirths by 12% (12 studies) and of FSB by 26% (8 studies). The reduction in fresh stillbirths can be attributed to NRT that helps in resuscitating neonates that appear lifeless at birth.17 18 Of 12 studies, seven studies reported a significant and one study reported a non-significant reduction in fresh stillbirths. However, a non-significant increase in risk of stillbirths was reported in three African studies which blunted the impact of NRT on reduction of stillbirths.

There was reduction in 1-day mortality of 42% (6 studies) and that of 7-day mortality was 18%. All studies included in the analysis (figures 8 and 9) showed a

| Study or Subgroup | NRT–Post Events | Total | NRT–Pre Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Year |
|-------------------|-----------------|-------|-----------------|-------|--------|----------------------------|------|
| Gopi et al. 2008, Kenya | 80 | 4502 | 80 | 4502 | 54 | 4084 | 10.6% | 1.41 [1.00, 1.94] | 2008 |
| Carlo et al. 2010, 6 countries (1) | 336 | 29715 | 445 | 35017 | 14.7% | 0.89 [0.77, 1.02] | 2010 |
| Carlo et al. 2010a, 6 countries (2) | 65 | 273 | 117 | 359 | 12.4% | 0.73 [0.56, 0.95] | 2010 |
| Msemo et al. 2013, Tanzania | 1151 | 76300 | 155 | 8124 | 14.5% | 0.76 [0.64, 0.89] | 2013 |
| Goudar et al. 2013, India | 49 | 5411 | 70 | 4137 | 10.2% | 0.54 [0.38, 0.78] | 2013 |
| Patel et al. 2016, India (Nagpur) (3) | 460 | 40870 | 478 | 38078 | 14.9% | 0.90 [0.79, 1.02] | 2015 |
| Bellad et al. 2016, Kenya & India (4) | 95 | 11612 | 144 | 11179 | 12.4% | 0.64 [0.49, 0.82] | 2016 |
| Ashish et al. 2016, Nepal (5) | 50 | 15520 | 86 | 9588 | 10.5% | 0.56 [0.25, 0.91] | 2016 |
| Total (95% CI) | 186203 | 110016 | 100.0% | 0.74 [0.61, 0.90] | |

| Total events | 2266 | 1549 |

Heterogeneity: Tau² = 0.06; Chi² = 44.52; df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 3.08 (P = 0.002)

**Footnotes**

(1) Carlo et al. 2010 18
(2) Carlo et al. 2010 17. Data for very low birth weight infants
(3) Unpublished data obtained via personal communication
(4) Data for two sites: Kenya and India (Belgium)
(5) Unpublished data obtained via personal communication
The meta-analysis showed a non-significant reduction of 14% in 28-day mortality. Of the seven included studies only two studies reported a significant reduction in mortality. Resuscitation at delivery helps to reduce neonatal mortality in the first hour of birth when the neonate is at the highest risk of intrapartum-related deaths and the impact diminishes subsequently. For reduction of 28-day neonatal mortality, post-resuscitation specialised care for survivors is required and only NRT is unlikely to have the desired impact on 28-day neonatal mortality.

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### Figure 8
Forest plot comparing 1-day neonatal mortality between the post-NRT and the pre-NRT groups. NRT, neonatal resuscitation training.

| Study or Subgroup | NRT–Post Events | NRT–Pre Events | Weight | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|--------|------------------------------|
| Bellad et al. 2016, Kenya & India (1) | 222 | 15822 | 195 | 15014 | 14.5% | 1.08 [0.89, 1.31] |
| Carlo et al. 2010, 6 countries (2) | 543 | 29247 | 793 | 34460 | 20.2% | 0.81 [0.72, 0.90] |
| Jeffery et al. 2004, Macedonia | 448 | 44929 | 927 | 68587 | 20.0% | 0.74 [0.66, 0.83] |
| Vakrlova et al. 2005, Bulgaria | 314 | 67647 | 367 | 67948 | 17.8% | 0.86 [0.74, 1.00] |
| Zhu et al. 1997, China | 16 | 4751 | 17 | 1722 | 3.0% | 0.34 [0.17, 0.67] |
| Total (95% CI) | 167311 | 193072 | 100.0% | 0.82 [0.73, 0.93] |

**Footnotes:**
(1) Data for two sites: Kenya and India (Belgum)
(2) Carlo et al. 2010
(3) Carlo et al. 2010
(4) Data for very low birth weight infants

### Figure 9
Forest plot comparing 7-day neonatal mortality between the post-NRT and the pre-NRT groups. NRT, neonatal resuscitation training.

| Study or Subgroup | NRT–Post Events | NRT–Pre Events | Weight | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|--------|------------------------------|
| Bellad et al. 2016, Kenya & India (1) | 901 | 25713 | 764 | 7070 | 15.2% | 0.94 [0.82, 1.07] |
| Ariawan et al. 2006, Indonesia | 138 | 16003 | 124 | 9816 | 14.1% | 0.68 [0.53, 0.87] |
| Opiyo et al. 2008, Kenya | 91 | 4156 | 107 | 3968 | 13.6% | 0.81 [0.62, 1.07] |
| Boo et al. 2009, Malaysia | 1760 | 463241 | 3667 | 539295 | 15.7% | 0.56 [0.53, 0.59] |
| Hole et al. 2012, Africa | 77 | 3515 | 72 | 3449 | 13.1% | 1.03 [0.76, 1.44] |
| Goudar et al. 2013, India | 103 | 5288 | 73 | 4063 | 15.4% | 1.08 [0.81, 1.46] |
| Bellad et al. 2016, Kenya & India (1) | 280 | 15822 | 242 | 15014 | 14.9% | 1.10 [0.93, 1.30] |
| Total (95% CI) | 3350 | 582675 | 100.0% | 0.86 [0.65, 1.13] |

**Footnotes:**
(1) Data for two sites: Kenya and India (Belgum)

### Figure 10
Forest plot comparing 28-day neonatal mortality between the post-NRT and the pre-NRT groups. NRT, neonatal resuscitation training.

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reduction with an exception of one study. Failure to observe reduction in mortality in Bellad et al could be due to two reasons. First, NRT was provided in diverse health systems within a short period of time. Second, mortality was not assessed in facilities where training was imparted but was measured in the population.

The meta-analysis showed a non-significant reduction of 14% in 28-day mortality. Of the seven included studies only two studies reported a significant reduction in mortality.
Trials that randomise facilities to NRT versus controls (where NRT is not a standard practice) would be ideal to assess the reduction in neonatal mortality. Trials are also likely to result in higher impact as compared with before–after studies as other changes at health facilities or in communities during the time period of before–after studies can confound the results. Because NRT is a standard practice and randomising individuals or clusters to no resuscitation training is unethical, there were only two trials available for the meta-analysis.20 21 They showed a reduction of 7-day neonatal mortality and 28-day mortality by 47% (figure 3) and 50% (figure 4), respectively. The perinatal mortality reduced by 37% (figure 5) with no significant reduction in SB rates.

Previously, an expert panel published a systematic review for community-based studies and conducted a meta-analysis that evaluated whether NRT reduced all-cause neonatal mortality in the first 7 days of life. They reported a 38% reduction in mortality which is larger than the 18% (7 studies) reduction observed in the current meta-analysis. Our meta-analysis included community-based studies that resulted in a smaller effect size. Community-based studies (trials or before–after) report a smaller reduction effect on any day neonatal mortality.8 17 18 47 The reduction in effect size of neonatal mortality in these studies can arise due to several reasons. All births in the intervention community may not be attended by birth attendants trained in neonatal resuscitation, especially if it is a home delivery.81 82 Second, women may decide to deliver at facilities or homes outside communities where NRT has been imparted. Finally, assessing mortality outcomes in the community can be challenging. Another meta-analysis was published in Cochrane which evaluated outcomes such as knowledge, skills, neonatal morbidity, neonatal mortality in first 7 days after birth and from day 8 to 28. This analysis did not include stillbirths, 1-day neonatal mortality or perinatal mortality that was included in the current meta-analysis.

The current meta-analysis consists largely of before–after studies with lack of concurrent control group that limits isolation of effect of resuscitation training alone from other changes at health facilities or in communities during the time period. Other limitation is lack of consistency of settings, duration of training, varying study designs and lack of consistent outcomes which contributed to substantial heterogeneity. Lack of subgroup analysis of type of health facilities may be perceived as a limitation. An improvement in mortality would be maximised in low-resource settings with poor quality of care. However, it is presumed that there is regular training of health workers in basic resuscitation skills in higher levels of care that would translate to higher quality of care. Our recent study that evaluated the knowledge and skills of trainees in HBB included 384 tertiary-level facilities in India. Only 3% of physicians and 5% of nurses were able to pass the pre-training bag and mask resuscitation skill assessment. Therefore, in the absence of reporting of pre-training skills of health workers in low-resource or high-resource settings or any indicator of quality of care, it would be erroneous to conduct a subgroup analysis based merely on resource settings and mostly will not change the results or the main message of this meta-analysis. We emphasise that despite the heterogeneity in settings, type
### Table 5  Summary of findings for Post-NRT versus Pre-NRT groups

| Outcomes                  | Anticipated absolute effects (95% CI) Risk with pre-NRP | Anticipated absolute effects (95% CI) Risk with post-NRP | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) |
|---------------------------|--------------------------------------------------------|---------------------------------------------------------|-------------------------|-------------------------------|---------------------------------|
| All stillbirths           | 8 per 1000                                              | 7 per 1000 (7 to 8)                                      | RR 0.88 (0.83 to 0.94)  | 1 425 540 (12 observational studies) | ☟◯◯◯ Very low ††                |
| Fresh stillbirths         | 15 per 1000                                             | 11 per 1000 (9 to 13)                                    | RR 0.74 (0.61 to 0.90)  | 296 819 (8 observational studies) | ☟◯◯◯ Very low †§                |
| 1-day neonatal mortality  | 8 per 1000                                              | 5 per 1000 (4 to 7)                                      | RR 0.58 (0.42 to 0.82)  | 280 080 (6 observational studies) | ☟◯◯◯ Very low †§                |
| 7-day neonatal mortality  | 13 per 1000                                             | 11 per 1000 (9 to 12)                                    | RR 0.82 (0.73 to 0.93)  | 360 383 (7 observational studies) | ☟◯◯◯ Very low †                |
| 28-day neonatal mortality | 8 per 1000                                              | 7 per 1000 (5 to 9)                                      | RR 0.86 (0.65 to 1.13)  | 1 116 463 (7 observational studies) | ☟◯◯◯ Very low ††                |
| Perinatal mortality       | 14 per 1000                                             | 12 per 1000 (10 to 13)                                   | RR 0.82 (0.74 to 0.91)  | 1 243 802 (6 observational studies) | ☟◯◯◯ Very low §§ ¶¶            |

*Pre–post studies. Quality of evidence downgraded by one for risk of bias (table 1 and 2).†Studies differ in the settings, type of NRP, duration and type trainees. Quality of evidence downgraded by one for indirectness (table 1 and 2).‡Publication bias detected in the funnel plot. Quality of evidence downgraded by one for publication bias (figure 12).§Although I² is 84%, the effect estimates of all included studies do not differ in the direction of effect. Quality of effect downgraded by one for inconsistency (figure 7).¶Although I² is 89%, the effect estimates of all the included studies (except Bellard et al.) do not differ in the direction of effect. Quality of effect downgraded by one for inconsistency and imprecision (figure 10).**Although I² is 71%, the effect estimates of all the included studies (except Bellard et al.) do not differ in the direction of effect. Quality of effect downgraded by one for inconsistency (figure 8).††I² is 95% and the effect estimates cross the life of no effect. Quality of evidence downgraded by two for inconsistency and imprecision (figure 10).‡‡The effect estimate crosses the line of no effect. Quality of evidence downgraded by one for imprecision (figure 10).§§Although I² is 90%, the effect estimates of all the included studies do not differ in the direction of effect. Quality of effect downgraded by one for inconsistency (figure 11).¶¶Studies differ in setting, type of NRP and trainees. Quality of evidence downgraded by one for indirectness (table 1 and 2).

NRP, Neonatal Resuscitation Program; NRT, neonatal resuscitation trainings; RR, risk ratio; SB, stillbirths.

of training, type of trainees, and the duration of training, this study showed an improvement in mortality at and soon after birth.

To conclude, NRT resulted in reduction in stillbirths and improved survival of newborns. The impact on survival of newborns can be further improved by providing a continuum of care beyond 7 days which is not addressed by NRT alone.

The meta-analysis performed showed beneficial effect of NRT in improving neonatal and perinatal outcomes. The models of training were not consistent across studies, with variations in training, trainee and setting. Generalisation of results of the pooled analysis to many currently available programmes may not be appropriate. There was evidence of heterogeneity across studies in our meta-analyses; however, overall there is consistency in the direction of effect.

This review identified several important limitations of the current evidence from included studies. Due to inadequate information about the methodology followed and variety of resuscitation programmes in included studies, the quality of the evidence was downgraded for risk of bias and indirectness resulting in inability to adequately assess the effects of this intervention.

### Conclusions

**Implications for Practice**

This review shows that the implementation of NRT improves neonatal and perinatal outcomes.

**Implications for Research**

Further good quality, multicentric randomised controlled trials addressing the role of NRT for improving neonatal and perinatal outcomes may be warranted. Impact of NRT...
on improving neonatal and perinatal outcomes as well as the best combination of settings and type of trainee should be established in future trials. More studies need to be done to assess the frequency with which NRT needs to be conducted to sustain the existing effect on perinatal mortality reduction.

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Contributors AP: conception of the work, design of the work, manuscript drafting with final approval of the version to be published. MNK: developed and run the search strategy, screened and selected studies, and did meta-analysis, GRADE assessment and manuscript drafting. KK and SB: involved in preparation of characteristics of study tables, data acquisition and manuscript drafting. AB: screening and selection of studies, data acquisition and manuscript drafting.

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