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Effectiveness of the facility based maternal near-miss case reviews in improving maternal and newborn quality of care in low and middle income countries: systematic review

Running title: Effectiveness of NMCR on maternal and newborn quality of care in LMIC

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ABSTRACT

Objectives

The maternal near-miss case review (NMCR) has been promoted by WHO as an approach to improve quality of care (QoC) at facility level. We reviewed the evidence on the effectiveness of the NMCR on QoC and maternal and perinatal health outcomes in low and middle-income countries (LMIC).

Methods

This was a systematic review. Studies were searched for in six electronic databases (MEDLINE, Index Medicus, Web of Science, the Cochrane library, Embase, LILACS), with no language restrictions. Two authors independently screened papers and selected them for inclusion and independently extracted data. Maternal mortality was the primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care: efficacy, safety, efficiency, equity, accessibility and timely care, acceptability and patient-centered care.

Results

Out of 24,822 papers retrieved, 17 studies from 11 countries were included. Maternal mortality measured before and after the implementation of the NMCR cycle significantly decreased (odd ratio (OR) 0.77, 95%CI 0.61 to 0.98, eight studies, 5,5573,043 women; I^2= 39%). A statistically significant reduction in the incidence of uterine rupture, post-partum haemorrhage, and maternal sepsis was observed in three out of six studies. Ten studies reporting on the process of maternal care when measured against pre-defined standards all showed some significant improvement. All studies reported that the NMCR resulted in some amelioration of the facility structure (physical structure, staffing, equipment, training, organization of care). Newborn outcomes were overall poorly reported: four studies showed no significant difference in perinatal mortality. Patient satisfaction and equity were also poorly reported.

Conclusions

Policy makers should consider implementing the maternal NMCR cycle approach among strategies aiming at improving QoC and reducing maternal mortality and morbidity in LMIC. Future studies should document better the effectiveness of the NMCR cycle particularly on outcomes reflecting patient centrality and on cost-effectiveness.

Article summary: strengths and limitations of this study

- The maternal near-miss case review (NMCR) approach has been used in different settings; however, so far no systematic review has ever reported on its effectiveness. The present review fill an existing gap in evidence synthesis by reporting latest evidence on the effectiveness of NMCR cycle as a type of criterion base audit in low and middle-income countries (LMIC).
- Findings of this review are limited by the paucity of existing scientific literature: despite the NMCR approach has been utilised in many countries, such as China, India, South Africa and the WHO European Region, scientific literature reporting on the NMCR effectiveness is relatively scarce.
- Despite the above described limitations, this review collected an appreciable number of studies reporting on the impact of the NMCR cycle from different regions worldwide, including Africa, Europe and Central Asia, South East Asia, Latin America and Caribbean- and adds as a new knowledge that this approach may be effective in reducing maternal mortality, and in improving quality of maternal and newborn health care at facility level.

Keywords

Near miss case review; quality of care; maternal health; perinatal health; low and middle income countries

Disclosure of interests

None competing interest

List of abbreviations

CBAs= controlled before-and after studies

CCTs= controlled clinical trials

ITSs= and intermittent time series

LMIC = low and middle-income countries

NMCR= Near miss cases review

OR= odds ratio

QoC= Quality of care

RCTs= randomised controlled trials (RCTs)

UCBAs=uncontrolled before and after studies

WHO = World Health Organization

BACKGROUND

Ensuring adequate quality of health care is a primary objective of the World Health Organization (WHO) Global Strategy for Women's, Children's and Adolescent's Health 2016-2030 (1,2). Quality in health care is recognized by WHO as essential for the health and well-being of the population, and as a basic aspect of human rights (2,3).

Among different approaches aiming at improving quality of care in maternity services, the maternal near-miss cases review (NMCR) approach was promoted by WHO and partners since 2004 within the strategy Beyond the Numbers (4). The facility-based individual NMCR cycle is defined as a type of criterion-based audits seeking to improve maternal and perinatal health care and outcomes by the review, performed at hospital level, of the care provided to maternal near-miss cases (5). A maternal near miss case is defined as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within six weeks after pregnancy (5).

In the last 20 years, NMCR have been promoted as an alternative way to audit case management, more acceptable for health workers than mortality audits, which have been in use for many years (4,5). In fact, in low mortality settings or at the health service level, the number of maternal deaths is usually insufficient or not representative enough to allow reliable policy guidance (4). Moreover, discussing cases of deaths may have legal implication and may be perceived as challenging by hospital staff (4). Near-miss cases occur more frequently than maternal deaths, their review can directly inform on both strengths and weakness in the process of care, and is usually perceived by staff as more easy to perform than mortality audits (5,6).

The objective of the NMCR cycle is on identifying areas amenable of improving quality of care, and finding and implementing solutions to the problems identified. Actions for improving quality of care are proposed and agreed by hospital staff, and subsequently monitored to check their implementation (5). This bottom-up approach aims at ensuring local ownership and at facilitating team-building dynamics (5). Beside reviewing clinical management the NMCR can cover other domains involved with the delivery of care, including availability of essential equipment, staffing, training, policies and organization of services (5). According to the WHO guidance (5) patients' experience of care should be collected through interviews and taken into account in developing recommendations aiming at improving quality of care.

The NMCR approach has been used in different settings (5); however, so far no systematic review has ever reported on its effectiveness. The objective of this review is to systematically evaluate and synthesise the evidence on the effectiveness of the NMCR cycle on the quality of care and on maternal and perinatal health outcomes in low and middle-income countries (LMICs).

METHODS

Search strategy and eligibility criteria

In conducting this review we followed the guidelines reported in the PRISMA (Preferred Reporting Items for systematic reviews and meta-analyses) (7). A protocol including detailed methods of the review was developed before starting the review.

We searched up to September 2017 the following databases: MEDLINE through Pubmed (from 1956); LILACS (no date restrictions); Global Index Medicus (no date restrictions); Science Citation Index Expanded (SCI-EXPANDED) through Web of Science (no date restrictions); Social Sciences Citation Index (SSCI) through Web of Science (no date restrictions); Cochrane library (no date restrictions); Embase through OVID (from 1996). The search strategy is reported in **Box 1**. Manual searches of reference lists were also performed. We did not apply any language restrictions.

Studies were eligible for inclusion if they reported on the effectiveness (outcome) on maternal and perinatal health care (population) of the individual NMCR cycle at facility level (intervention), in a LMIC (setting), defined as for the World Bank definition at the time of the study (8). Given the paucity of randomised controlled trials (RCTs) on the subject, we opted for including in this review also non randomized controlled clinical trials (CCTs), controlled before-and after studies (CBAs), uncontrolled before and after studies (UCBAs) and intermittent time series (ITSs). Qualitative studies were excluded. Both studies using the WHO definition of a maternal near-miss case published in year 2011 (9) or previous/locally adapted definitions, such as locally developed disease-specific definitions, were included. Only studies reporting on interventions where the full audit cycle was implemented (ie including implementation of changes) were included, while studies reporting only the descriptive findings of the case review (ie identifications of gaps in case management without developing and implementing recommendations) were not eligible. Abstracts and unpublished reports were also not eligible for inclusion.

Maternal mortality was predefined as our primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care (10), namely: efficacy (eg maternal morbidity), safety (eg adverse events), efficiency (cost), equity (eg equitable care), accessibility and timely care (eg access to care), acceptability and patient-centered care (eg patients' satisfaction). Effectiveness on the quality of care is reported according the Donabedian model of quality improvement, which differentiate in between: i) outcomes of care (eg health outcomes, costs, satisfaction), ii) process of care (eg diagnosis and treatment); iii) and

inputs/structure (eg physical structure, staffing, equipment and supplies, training, policies and organization of care) (11).

Data collection and analysis

Studies were selected for inclusion by two independent authors in two teams (VC and AE, ML and SR). Any disagreement was resolved through discussion. The full text of all eligible citations was examined in detail. Two authors (ML, SR) extracted data from included studies, using a pre-piloted data-extraction form. Disagreements were resolved by discussion between the two authors and consensus with a third author.

We extracted information regarding: study setting, design and duration; characteristics of the intervention; type of outcomes evaluated; effectiveness of the NMCR on the outcomes. For the study with ITS design we included in the metanalysis of maternal mortality the first and the last time point reported. Data on effectiveness were extracted as crude numbers or percentages. When meta-analysis was possible and appropriate, for each outcome factor we generated a pooled odds ratio (OR) using the Mantel-Haenszwel weighting method (12). Pooled data were presented in forest plots; data that could not be meta-analyzed were presented in tables and text. We tested the null hypothesis that all studies evaluate the same true effect by the Cochran's Q test, with two-sided $p<0.05$ considered statistically significant.

The degree of heterogeneity between studies was assessed by visual inspection of the forest plots and I-squared (I2) statistic with its 95% confidence intervals. Heterogeneity was considered low for I^2 values between 25% and 50%, moderate for value between 50% and 75%, and high for values over 75% (12).

The Cochrane 'Risk of bias' tool modified with the Cochrane Effective Practice and Organization of Care Group (EPOC) criteria for ITSs (12) was used to assess the risk of bias in included studies. We aimed at performing the following sensitivity analyses: i) removing the studies with high risk of bias; ii) removing studies including less than 300 cases and less than 30 events (ie cases of maternal death or perinatal death). We performed a subgroup analysis exploring the effect of NMCR in low income countries (defined as for the World Bank definition at the time of the study (8)) compared to middle income countries.

RESULTS

Characteristics of the studies

The search yielded overall 24,822 records (**Figure 1**). Overall 17 papers (13-29) from Africa (Ghana, Ethiopia Malawi, Nigeria, Tanzania, Uganda), Europe and Central Asia (Kazakhstan, Moldova), South East Asia (Malaysia, Vietnam) and Latin America and Caribbean (Jamaica) met the inclusion criteria.

Characteristics of the study settings and design are summarized in **Table 1**. All except one study (23) were published during the last 15 years. Two papers referred to the same experience (20, 21); findings from these studies are jointly reported in the tables, and we used the most recent reference (20) to identify them. All studies were uncontrolled before and after-studies (UCBAs), describing the effectiveness of the NMCR cycle with a before and after analysis, except for two studies with ITS design (13, 22). Studies duration ranged from a minimum of 6 months (27) to a maximum of 26 months (29). Thirteen studies were held in low-income countries (13-15,17,19,22-27,28,29), two in upper middle-income countries (16,20), and one in a lower middle-income country (18). Ten studies were held in an urban setting (13-17,19,20,25,28,29), three in a rural setting (22,24,27), and three in a mixed setting (18,23,26). One study was multi-centered (Ghana and Jamaica) (29). Among the 16 experiences reported, nine were of large size: three studies in Malawi enrolled respectively 73, 29 and 13 facilities of different level and type (22,26,27), while another study in Malawi was conducted in one referral hospital plus several (number not further specified) health centres (24); a study in Ethiopia involved 10 public hospitals (17); studies in Kazakhstan, Vietnam, Ghana, Jamaica and Moldova involved six, five, four and three hospitals respectively (20,23,29,18). The remaining seven studies took place in one teaching/tertiary level care hospital each.

Characteristics of the intervention are summarized in **Table 2**. In eight studies cases were audited prospectively (15,17,18,20,22,24-26); in another five studies audits were conducted retrospectively in a first phase then prospectively in the second phase (16,19,23,28,29); in three studies cases were audited only retrospectively (12,13,27). While in all cases the internal staff within the facility was involved in developing the recommendations, studies differed by who performed the case reviews: in most experiences audits were conducted by internal staff within the facility/ies, with the exception of four cases where a study investigator/physician audited the cases against pre-defined criteria and later presented it to hospital staff (13,19,25,29) and two cases where this information was not specified (15,16). Type of obstetric complications selected for audit included: severe pre-eclampsia/eclampsia (13,16,19,22,23,25-29), post-partum haemorrhage (13,20,22,23,25-27,29), obstructed labour (14,15,23,26,27,29), uterine rupture (24,25,29), infections (23,25,27), complications of abortion (27). Five studies focused on one complication only (14-16,24,28) while

in all other studies more than one condition was audited. In three studies cases of maternal mortality were audited together with cases of near-miss (17,22,26). The criteria for case selection was "all cases occurring in the study period", except in one experience in Malawi where cases of particular educational interest were selected (24), and a study in Moldova were, despite no pre-defined criteria, it was observed that cases "more likely to lead to praises for the maternity team" were selected (18). Number of total cases audited in each study ranged widely, from 30 cases (18) to 2568 cases (17).

Only in four experiences women were interviewed (14,15,18,20), but in one of them this was explicitly merely for recording bureaucratic details (15), rather than for the purpose of collecting women views and perspectives on quality of care received. Most studies associated to the audits additional interventions, such as development/dissemination of guidelines, training, definitions of standards, advocacy among key stakeholders. In one study, information for patients related to the NMCR was also developed (16).

As reported in **Table 3**, types of outcomes evaluated in the studies reported mostly on two dimensions of quality of care (10): effectiveness and accessibility and timely care. Outcomes related to the other dimension of quality of care, such as patient centrality and acceptability (eg patient satisfaction), efficiency and equity, safety (eg rate of adverse events, incident reporting) were not explored, with the exception of one study in Kazakhstan reporting on improved patients satisfaction (20) and one in Moldova reporting improved attitude towards patients (18).

Effectiveness of the NMCR cycle

Effectiveness on health outcomes

In a meta-analysis of eight studies from seven countries in Africa, Latin America and Asia maternal mortality measured before and after the implementation of the NMCR cycle significantly decreased (OR 0.77, 95%CI 0.61 to 0.98, 5,5573,043 women**, Figure 2**), with low heterogeneity between studies (I^2= 39%). An additional study from Uganda reported to have observed a reduction in maternal mortality, but quantitative data were not made explicit (15).

Three out of six studies reported a statistically significant reduction in the incidence of the following preventable obstetric complications: uterine rupture, major post-partum haemorrhage, and maternal sepsis (15,22,24, **Table 4**).

Newborn outcomes were overall poorly reported. Of five studies documenting perinatal mortality, fours could be included in the meta-analysis, showing no significant differences in perinatal deaths

in the before and after period (OR 0.92, 95%CI 0.65, 1.30, **Figure 3**) with low heterogeneity between studies (I^2= 40%). The fifth study (14), conducted in Uganda, reported a significant reduction in the incidence of a combined outcome including perinatal severe morbidities, deaths and stillbirths (**Table 4**). One study in reported on number of newborns admitted to ICU, without statistical difference in the before and after NCMR period (15). Another single study reported on Apgar score birth weight, without changes in the before and after period (16).
One study reported increased patient satisfaction after the implementation of the NMRC cycle (20).

Effectiveness on process outcomes

The effectiveness of the NMCR on the process of care is synthetized in **Table 5.** Ten studies reported on the process of care when measured quantitatively against pre-defined standards and all showed some significant improvements (13-16,19,23,25,27,28,29). Six studies reported other findings, such as improved case documentation, referral, use of partograph, monitoring and teamwork (14,17,18,20,22,26).

Effectiveness on structure outcomes

Effectiveness on the structure is detailed in **Table 6**. All studies reported some improvements in one or more domains. Overall most frequent changes relate to: purchasing of essential equipment and supplies; training, monitoring and supervision; policies and organization of care (including reorganisation of services, standardisation of case management through guidelines, checklists and monitoring forms, rational use of staff).

Risk of bias and other analyses

All studies were rated as a high risk of bias based on the Cochrane and EPOC criteria (**Table S1**), mostly due to the study design (NCBA or ITS studies).
The sensitivity analysis showed that when studies with a very small sample size were excluded, the effect of the NMCR on maternal mortality become stronger than when all studies were included (OR 0.71, 95%CI 0.55 to 0.90, three studies I^2=86% **Figure S1).** The effect of NMCR on perinatal mortality did not significantly changed in the sensitivity analysis (**Figure S2**).
In the subgroup analysis, the effect of NMCR on maternal mortality was statistically significant in low income countries (R 0.77, 95%CI 0.60 to 0.98, 7 studies), while only one small study could be included in the category middle income countries, without statistical significance (**Figure S3).** The effect of NMCR on perinatal mortality was not affected by subgroup analysis (**Figure S4).**
Funnel plots did not suggest publication bias (**Figure S5 and S6**).

DISCUSSION

This review suggests that the facility based individual maternal NMCR cycle may be an effective strategy for reducing maternal mortality in high burden countries, and for improving overall quality of maternal care in LMIC. Results of a pooled analysis of findings from eight studies in seven countries showed that the NMCR cycle significantly reduced maternal mortality (OR 0.77, 95%CI 0.61 to 0.98, Figure 2), with low heterogeneity of results (I^2=39%). Out of ten studies reporting on the process of care when measured against pre-defined standards all showed some statistically significant improvement. Additionally, in all studies the implementation of the NMCR cycle resulted in some amelioration in the structure of the hospital, such as an increased availability of essential equipment and supplies, training, monitoring and supervision, and the implementation of new policies and better organization of services. Three out of six studies reported a significant reduction in the incidence of preventable obstetric complications such as uterine rupture, major post-partum haemorrhage, and maternal sepsis.

Previous systematic reviews had observed a benefit of criterion-base audits in improving the quality of obstetric care (30-32). However, a review on the effectiveness of criterion-base audits in LMIC published some years ago concluded that despite criterion-base audits being increasingly used, few studies had reported on their effectiveness (33). The present review retrieved all latest evidence on the effectiveness of NMCR cycle as a type of criterion base audit, synthesized studies from LMIC in different geographical regions- including Africa, Europe and Central Asia, South East Asia, Latin America and Caribbean- and adds as a new knowledge that this approach may be effective in reducing maternal mortality and in improving quality of health care provided.

Findings of this review are limited by the paucity of existing scientific literature: through the study screening it become evident that the NMCR approach has been utilized in much more countries than what could be included in this reviews, such as China (34), India (35), South Africa (36), and the WHO European Region (37-41), but scientific literature reporting on the NMCR effectiveness in these countries could not be retrieved. Secondly, all included studies had an UCBA or ITS design, thus being exposed to a high risk of bias (although most studies checked for potential confounding factors, such as the case mix in the before and after phase). Most studies had low sample size which did not allow for detecting a statistically significant difference in rare outcomes such as maternal or perinatal mortality (18,20). Despite these limitations, this review collected an appreciable number of studies reporting on the impact of the NMCR cycle from different regions worldwide, and in most experiences significant gains were observed. In some cases, quality of care and/or maternal mortality could not significantly change because attainment of standards of

care were already at a good level at the baseline (13,23,27). Ideally, it will be advisable to perform large multicenter RCTs to properly document the effectiveness of NMCR. However, in practice conducting RCTSs on criterion based audit alone may be challenging, and may even be perceived as unethical, if no appropriate comparison is chosen. This is because in current practice criterion based audits are already one of the recommended strategies to improve quality of care promoted by many agencies and bodies, such as the National Institute for Clinical Excellence (NICE) (42). Notably, the review of "near-miss" cases is already recommended by WHO as a "key action to eliminate avoidable maternal and perinatal mortality and morbidity and improve the quality of care" (43) and as such it is already implemented in several countries.

The audit of maternal near miss cases is an approach utilised also in several high-income settings: UK has a well-established programme of confidential enquiries into maternal deaths and a national system for research on maternal near-miss-the UK Obstetric Surveillance System (UKOSS) (44,45); New Zealand established a national system for severe maternal morbidity review (46); several countries within the International Network of Obstetric Survey Systems (INOSS) are collecting data on severe maternal morbidities for study purposes (47), while other countries such as Italy (ITOSS) are starting implementing near-miss audits (48,49). Despite there are some differences in the type of interventions applied (eg not all of these approaches are facility based) still the existence of these large networks on maternal near miss case reviews and the amount of resources devoted to them somehow testify the importance recognized in reviewing near miss cases.

In the future, rather than investing resources in exploring whether near miss audits or criterion base audits in general are overall effective, it will be more interesting to explore which characteristics make them effective and sustainable. Available literature does not allow for directly comparing the effectiveness of different methodologies on how practically performing the audits, but at least it does provide some useful starting point for discussion and for future research. First, with regards to the number of cases audited, this varied largely in the included studies from a minimum of less than 10 cases per year (18,20) to a maximum of several hundred cases in few months (14,29), with a third approach consisting in performing a large retrospective review of past cases at the baseline, and then collecting fewer new cases prospectively. When many cases were reviewed, this allowed for an in depth description of the gaps in care. However, the analysis of a large number of cases does not necessarily ensure the development of good recommendations for quality improvement, neither their implementation. Additionally, the sustainability of auditing on a large number of cases, outside a research setting, is questionable. Studies included in this review suggest that even the periodic review of few cases may help identifying gaps in routine care, and developing SMART recommendations (ie Specific, Measurable, Achievable, Realistic,

Time-bound (50)), and improving quality of care significantly (18,20).

Second, the study screening revealed that many audit experiences focused on the description of the findings of the audits, while only a minority get to the point of developing recommendations for improving quality of care. Studies from both the European and the African region (18,51,52) confirm this finding highlighting that the second part of the audit cycle (ie developing recommendations, implementing them, checking on progress) is in general more problematic and usually less well conducted compared to the first part of the audit cycle. The attitude of openly discussing cases within a multidisciplinary team and agreeing solutions was described as challenging in different settings, especially for mid-level staff (midwifes, nurses) who may not used at discussing their views together with doctors and managers (18,20). Hospital staff, managers included, often do not receive any formal training in quality improvement methods and in how correctly performing an audit cycle. Studies included in this review revealed that most experiences of implementation of NMCR cycle were externally supported, either by the WHO, academia, and/or other development partners (15,18,20-24,26-28). The need for external support, and for establishing a functional quality assurance mechanism are recognised by WHO crucial for ensuring an effective NMCR implementation (5).

Third, in regards to who performed the review, in most cases these were performed by a hospital multidisciplinary team, while in few cases (18,10,25,29) a single person (clinician or researcher) performed the audit and later presented results to hospital staff. Although having a single person appointed to perform the case-review may increase feasibility, this actually largely reduces ownership of the process, together with minimizing occasions for discussion and team building among staff. Studies noted that involvement of all health care providers in the audit process promoted successful implementation, ownership and sustainability of the process (14,20,28). The involvement of mid level staff such as nurses and midwives was reported to result in improved staff autonomy and team work (14,21,27). Currently the WHO approach (5) recommends the NMCR to be performed by the staff who managed the cases, including nurses, midwives, and any other staff directly or indirectly involved in case management. In regards to the participation of the senior management, different studies observed that this promoted the implementation of recommendations that required allocation of resources and changes in policies and organisation of care (26,28).

Forth, in relation to the patient's experience of care, this was collected for auditing purposes only in very few of the existing studies, and yet not fully taken into account. For example a study conducted in Moldova (18) revealed that the language used to interview women was rather medical and no account of the woman's feelings was actually reported. All women appeared

satisfied with the care provided and praised the staff, very few women made suggestions for improvements, and very few recommendations developed from the audit related to women's views (18). Possible explanations for these findings according to authors included: women's low expectations, lack of women's empowerment, women's reluctance to discuss dissatisfaction and staff 's actions openly, interviewers' lack of capacity and willingness, and paternalists attitude towards patients (18). Authors of the study concluded that there was a need for a shift in mentality, along with a need for providing better training for interviewers (18). In the last years, WHO has given increasing importance to patient's experience of care (1). Listening to women's views may provide important information, as testified by studies in Brazil, Rwanda and UK (53-55) and by a study in Iran where women's views were successfully used to improve quality of care (56). Currently WHO recommends to always interview women and their families and to use their inputs for improving care (5).

Finally, as pointed out by authors of the included studies, interventions aiming at improving quality of care without strengthening the health systems and improving community awareness may have minimal success (15,22). A study in Malawi reported that availability of essential supplies, such as blood for transfusions, remained low even after the NMCR due to health system failures and this clearly was a barrier for improving case management (22). Qualitative findings collected through focus group in a study in Uganda (15) pointed out among factors that may have hampered the effectiveness of NMCR health facility factors such as: stock-out of essential supplies, shortage of human resources, lack of task allocation, inadequate supervision. Importantly, in most studies, the number of staff and available resources remained stable in the before and after phase, while, as a result of the audit, there was a reorganization of staff activities, such as better specification of roles and responsibilities, task shifting, and improved communication (14,16,17,20,28).

Cost of the NMCR approach in improving health outcomes and quality of care was not formally evaluated in the retrieved studies. However, several papers stated that the NMCR was an inexpensive and simple intervention, requiring little technology (24,26-28). A study involving 12 health centres in Malawi reported that each audit meeting cost about 150 US $, including foods and transport of participants to the District Hospital (27). Another study in Uganda stated that "the audit process had challenged the assumption that all quality improvements need to be externally provided and are expensive" (28). These findings are in line with a systematic review of barriers and facilitators for effective NMCR implementation, reporting that a relatively low budget is needed to facilitate activities (37). In some experiences, the NMCR improved use or availability of existing economic resources: in Malawi, it "promoted a wiser allocation of resources for maternity care at the district level" (27); in Uganda a fundraising committee was established to raise funds for the drugs and equipment needed according to the recommendations (28).

CONCLUSIONS

Implication for policy and research

Among other strategies to reduce maternal mortality and morbidity and for improving the quality of maternal and perinatal care, policy makers should consider the implementation of the maternal NMCR cycle approach.

Researchers should aim at generating more evidence on how effectively implementing the NMCR cycle, how improving its impact on newborn outcomes and on outcomes reflecting patients' centrality, such as patients' satisfaction and/or perception of quality of care received, together with documenting the cost effectiveness of the NMCR approach.

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Conflict of interest

None

Role of authors

ML conceived the papers, screened the study, extracted data, drafted the paper and finalised the paper. SR, VC, AE screened the study, extracted data and revised the first draft.

Data Sharing statement

All details of the analyses conducted are provided within the manuscript

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Table 1. Study settings, designs and duration

Author	Design °	Duration	Years	Country	WB classification *	Setting	N Hospital	Hospital type involved §
Lumala 2017 [13]	ITS	10 months	2014-2015	Uganda	L	Urban	1	tertiary specialist hospital, Catholic funded private non profit
Mgaya 2017 [14]	NCBA	25 months	2013-2015	Tanzania	L	Urban	1	tertiary specialist hospital
Kayiga 2016 [15]	NCBA	7 months	2013	Uganda	L	Urban	1	tertiary specialist hospital
Mohd Azri 2015 [16]	NCBA	2 years	2012-2014	Malaysia	UM	Urban	1	tertiary specialist hospital
Gebrehiwot 2014 [17]	NCBA	18 months	2011-2012	Ethiopia	L	Urban	10	public hospitals
Baltag 2012 [18]	NCBA	13 moths	2005-2006	Moldova	LM	Mixed	3	mixed (referral-level facilities at municipal, national and district levels)
Kidanto 2012 [19]	NCBA	3 years	2006-2009	Tanzania	L	Urban	1	teaching hospital
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	NCBA	2 years	2009-2011	Kazakhstan	UM	Urban	6	national research centre, regional and city hospitals)
Van den Akker 2011 [22]	ITS	2 years	2007-2009	Malawi	L	Rural	29	mixed (1 referral hospital and 28 government, private and mission smaller facilities)
Bailey 2010 [23]	NCBA	2 years	2003-2004	Vietnam	L §§	Mixed	5	mixed (provincial, area and district)
Van den Akker 2009 [24]	NCBA	1 year	2007-2008	Malawi	L	Rural	1 + undefined numbers of health centers	mixed (referral hospital, health centers)

Hunyinbo 2008 [25]	NCBA	13 months	2002-2003	Nigeria	L §§	Urban	1	tertiary specialist hospital
Kongnyuy 2008 [26]	NCBA	2 years	2005-2007	Malawi	L	Mixed	73	mixed (hospitals, health centers)
Kongnyuy 2008 [27]	NCBA	6 months	2006-2007	Malawi	L	Rural	1 hospital +12 health centers	one district hospital, plus satellite health centers
Weeks 2005 [28]	NCBA	20 months	2001-2002	Uganda	L	Urban	1	teaching hospital
Wagaarachchi 2001 [29]	NCBA	26 months	1997-2000	Ghana and Jamaica	L §§	Urban	4	district hospitals

° NCBA= non controlled before and fater study, ITS= Intermittent time series

§ L=Low income; LM=Lower middle income; UM=Upper middle income

§§ Ghana, Jamaica, Nigeria and Vietnam were classified as low income countries during the time of the study, while they were upgraded to lower middle income in 2010, 2007 2008, and 2009 respectively.

Table 2. Characteristics of the interventions

Author	Characteristics of the audit	Who performed the audit *	Who developed the recommendations **	Type of cases audited §	Selection criteria	N Case audited (before / after)	Woman Interview	Associated interventions °
Lumala 2017 [13]	two phases, retrospective	A medical doctor, using WHO guidelines as source of standard	facility staff	PPH and severe pre-eclampsia, eclampsia	All in-patient cases in the study period, not referred and not receiving hydralazine or magnesium sulphate from the referring unit	238 (125 before, 133 after)	no	G, T
Mgaya 2017 [14]	two phases, retrospective	Trained postnatal ward nurses, using a pre-piloted form, and predefined standards (a consultant, a specialist and a midwife were also available for consultation)	facility staff (AN, L, MO, MW, P)	obstructed labour	All cases of obstructed labour with a single foestus in cephalic presentation, and no other severe medical conditions or PROM	510 (260 before, 250 after)	Yes, when necessary to integrate info from medical files	G, S, T
Kayiga 2016 [15]	two phases, prospective	NR	facility staff (MO, MW, M)	obstructed labour	all cases occurring in the study period	360 (180 before, 180 after)	yes	G, T
Mohd Azri 2015 [16]	First phase retrospective, second regular prospective	NR	facility staff (members of the obstetric department)	eclampsia	all cases occurring in the study period	51 (42 before, 9 after)	no	T, P, PA
Gebrehiwot 2014 [17]	prospective	facility staff (MO, MW and other hospital staff + focal	facility staff	all NM + MD	all cases occurring in the study period	2568	no	P

		person)						
Baltag 2012 [18]	prospective	facility staff involved in case management (MO, MD + occasionally L, T, PHC)	facility staff involved in case management (MO, MD + occasionally L, T, PHC)	NM	not pre-defined criteria, cases were chosen by director. In one hospital a tendency to choose cases more likely to lead to praises for the maternity team was noted	30 approx (1 case per month in each hospital)	yes	G, P, S
Kidanto 2012 [19]	first phase retrospective, second prospective	1 senior doctor	facility staff	eclampsia and pre-eclampsia	all cases occurring in the study period	477 (389 before, 88 after)	no	G, T, S
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	prospective	facility staff	facility staff	PPH and severe pre-eclampsia	NR	Not more than 10 each hospital each year (total unspecified)	yes	P,S
Van den Akker 2011 [22]	prospective every 2 to 3 weeks; quarterly evaluation of outcomes	facility staff, occasionally external obs gyn	facility staff	infection, PPH, uterine rupture, preeclampsia, others) + MD	all cases occurring in the study period	45 (24 deaths; 21 SOC)	no	P,S

Bailey 2010 [23]	first phase retrospective, than regular prospective	facility staff (MO, N, M)	facility staff (MO, N, M)	severe preeclampsia, postpartum infection, prolonged/obstructed labour, PPH, organisation of emergency service	all cases occurring in the study period	558 (312 before, 246 after)	no	T,P,S
Van den Akker 2009 [24]	prospective every 2- 3 weeks for 3 months than extended audit with 2 external obstetricians	facility staff (M,MA, MO, MW,N)	facility staff (MO, N, M)	uterine rupture	cases that appeared to be of particular educational value to the PI or any other hospital staff	35	no	T (TBA also involved in training)
Hunyinbo 2008 [25]	two phases, prospective	Study investigator/s	facility staff (M,MA, MO, N,P, L)	PPH, uterine rupture, eclampsia, obstructed labour, sepsis	all cases occurring in the study period	130 (65 before, 65 after)	no	A, P,S
Kongnyuy 2008 [26]	two phases, prospective	facility staff (AN,M,MO,MW, L,T)	facility staff (quality improvement team)	PPH, obstructed labour, sepsis, preeclampsia/ eclampsia, neonatal care, CS , women-friendly care+ MD	NR	NR	no	T, P,S
Kongnyuy 2008 [27]	two phases, retrospective	district team (N, MW, CO,AN,T)	hospital staff (quality improvement team)	pre-eclampsia/ eclampsia, PPH, prolonged/ obstructed labour, retained placenta, sepsis, complications of	all cases occurring in the study period	122 (60 before, 62 after)	no	T,S,P

				abortion, ectopic pregnancy				
Weeks 2005 [28]	first phase retrospective, second prospective	facility staff (including low grade staff)	facility staff	severe pre-eclampsia	all cases occurring in the study period	86 (43 before, 43 after)	no	S
Wagaarachchi 2001 [29]	first phase retrospective, second prospective	non-medical assistants (10% of cases validated by independent re-review)	facility staff (M,MO, M + all relevant staff)	PPH, eclampsia, infection, obstructed labor, uterine rupture	all cases occurring in the study period	889 (551 before, 338 after)	no	S,T,P

*NR= not reported

** AN= anesthetist of anesthetic technician, CO=clinical officer, L= Laboratory, M= manager, MA=medical assistant, MO=medical officer, MW=midwife, N=nurse, P=Pharmacy, PHC= primary health care staff , T= technician

° A= advocacy with stakeholders G= guidelines, P=Protocols, PA= information for patients, S=standards, T=training, TBA= traditional birth attendants §

CS= caesarian section, MD= maternal deaths, ND= neonatal deaths, NM=Near miss, PPH= post-partum hemorrhage, PROM= premature rupture of membranes, SOC= all severe obstetric cases, SEL= selected obstetric cases

Table 3. Type of outcomes evaluated in the studies

Author	Patient centrality and acceptability	Accessibility Timely care	Efficiency and equity	Safety	Effectiveness
Lumala 2017 [13]	—	yes	—	—	yes
Mgaya 2017 [14]	—	yes	—	—	yes
Kayiga 2016 [15]	—	—	—	—	yes
Mohd Azri 2015 [16]	—	—	—	—	yes
Gebrehiwot 2014 [17]	—	yes	—	—	yes
Baltag 2012 [18]	yes	—	—	—	yes
Kidanto 2012 [19]	—	yes	—	—	yes
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	yes	yes	—	—	yes
Van den Akker 2011 [22]	—	yes	—	—	yes
Bailey 2010 [23]	—	yes	—	—	yes
Van den Akker 2009 [24]	—	yes	—	—	yes
Hunyinbo 2008 [25]	—	yes	—	—	yes
Kongnyuy 2008 [26]	—	yes	—	—	yes

Kongnyuy 2008 [27]	—	yes	—	—	yes
Weeks 2005 [28]	—	yes	—	—	yes
Wagaarachchi 2001 [29]	—	yes	—	—	yes

Table 4. Effectiveness of the NMCR cycle on health outcomes

Author	Maternal Mortality (MM)	Neonatal mortality (NM)	Morbidity and other outcomes
Lumala 2017 [13]	_	_	_
Mgaya 2017 [14]	-	-	SAMM (incidence: 9.0% vs. 8.8% (p = 0.98). Uterine rupture (incidence): 1/260 vs 0/250 (p=0.49) Perinatal severe morbidities and deaths and fresh stillbirths: 16% vs. 8.8% (p = 0.01)
Kayiga 2016 [15]	-	NM: 27/180 vs 27/180	Uterine rupture (Incidence): 8/180 vs 2/180 (p=0.04) Maternal sepsis (Incidence): 10/180 vs 2/180 (p=0.02) Post-spinal headache (incidence): 0/180 vs 13/180 (p<0.001) Baby admitted to intensive care: 27/180 vs 31/180 (p=0.61)
Mohd Azri 2015 [16]	MM: 2/49 vs 1/9	NM: 4/49 vs 3/9	Eclampsia (incidence): 42/44818 vs 9/10784 (p> 0.05) Recurrent eclamptic fits: 8/42 vs 1/9 (p> 0.05) Newborn babies with Apgar score (< 7) at 5 minutes after birth: 8/42 vs 3/9 (p> 0.05) Birth weight less than 2500g 22/42 vs 5/9 (p> 0.05)
Gebrehiwot 2014 [17]	-	-	-
Baltag 2012 [18]	-	-	-
Kidanto 2012 [19]	MM 30/389 vs 0/88	PM: 161/389 vs 32/88	-
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	-	-	Improved patients satisfaction (NR)
Van den Akker 2011 [22]	MM 6/2295 vs 4/5291	-	SAMM (Incidence): 33/2295 vs 49/5291 (p=0.08) Major PPH (incidence): 17/2295 vs 15/5291 (p=0.006) Uterine rupture (Incidence): 14/2295 vs 4/5291 (p=0.03) Severe pre-eclampsia (Incidence): 6/2295 vs 16/5291 (p=0.3)

			Maternal infections (Incidence): 10/2295 vs 14/5291 (p=0.6)
Bailey 2010 [23]	-	-	-
Van den Akker 2009 [24]	-	-	Uterine rupture (incidence): 16/833 vs 19/3099 (OR 0.32; 95% CI, 0.16–0.63)
Hunyinbo 2008 [25]	MM: 2/65 vs 2/65	-	
Kongnyuy 2008 [26]	MM: 104/2618685 vs 93/2944360		-
Kongnyuy 2008 [27]	MM 3/60 vs 2/62	PM: 5/60 vs 3/62	-
Weeks 2005 [28]	MM: 4/43 vs 0/43	-	Eclampsia (incidence): 5/43 vs 5/43 (p> 0.05)
Wagaarachchi 2001 [29]	MM: 18/551 vs 17/338	-	-

Abbreviations: CFR= case fatality rate; MM= maternal mortality; MMO= maternal morbidity; NM= neonatal mortality; NR= not further specified; PM: perinatal mortality; PPH= post partum hemorrhage; SAMM: severe acute maternal morbidity

Table 5. Effectiveness of the NMCR cycle on the process of care

Author	Statistically significant improvement in pre-defined standards	Other improvements
Lumala 2017 [13]	Eclampsia and pre-eclampsia: 7/10 standards PPH: 3/4 standards	-
Mgaya 2017 [14]	Obstructed labour: 6/10 standards on diagnosis, 6/10 standards on case management	Improved timeliness: significant reduction of time needed from decision to perform a caesarian section to delivery (mean difference:-30 minutes, p< 0.001)
Kayiga 2016 [15]	Obstructed labour: 2/6 standards, 4/13 measures of standards	-
Mohd Azri 2015 [16]	Improved adherence to 2/2 audit criteria that where substandard in the first phase (all other 10 criteria were already according to standards at baseline)	-
Gebrehiwot 2014 [17]	-	Almost all piloted hospitals and some health centers use partograph to follow uterine contraction during labor Improved documentation and reporting Improved referral linkage and communication to and from satellite health centers Reducing waiting time
Baltag 2012 [18]	-	Improved clinical practice (NS) Improved medical records Improved attitude towards patients
Kidanto 2012 [19]	Eclampsia and pre-eclampsia: 10/16 standards	-
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	-	Improved case management and monitoring (eg weighing of blood losses and documenting systematically) eliminating obvious mistakes Improved acceptance and the utilization and integration of

		technologies promoted and evidenced-based practices by the national guidelines
Van den Akker 2011 [22]	-	Improved patients monitoring
Bailey 2010 [23]	Eclampsia: 12/18 standards Infections: 11/23 standards Obstructed labour: 1/1 standards PPH: 3/3 standards	-
Van den Akker 2009 [24]	-	-
Hunyinbo 2008 [25]	SAMM: 8/31 standards	-
Kongnyuy 2008 [26]	-	Significant increase in the met need for EmOC (15.2% for 2005, 17.0% for 2006 and 18.8% for 2007, p for trend < 0.001).
Kongnyuy 2008 [27]	SAMM: 4 /7 standards (other criteria were already according to standards at baseline)	-
Weeks 2005 [28]	Severe pre-eclampsia: 5/9 standards	-
Wagaarachchi 2001 [29]	SA: 8/31 standards	-

Abbreviations: SAMM=Severe acute maternal morbidity

Table 6. Effectiveness of the NMCR cycle on the structure

Author	Physical structure	Staffing	Equipment and supplies	Training, monitoring and supervision	Local policies and organization of services
Lumala 2017 [13]				Training sessions, drills and simulations	Improved displaying of national guidelines
Mgaya 2017 [14]				Training and supervision	Introduction and dissemination of guidelines, Improved team work and internal communication among hospital staff
Kayiga 2016 [15]					Re-engineering hospital Red Alert System: list of responsible person to be contacted during Red Alert activation was put up in all obstetrics facilities; Information on the importance of activating the Red Alert in eclampsia cases was disseminated to all staff; hospital telephone operator was informed regarding existence of this system and how it functions.
Mohd Azri 2015 [16]		Better specification of roles and responsibilities			
Gebrehiwot 2014 [17]	Some hospitals expanded accommodate more cases	Staff organization: duties assignment; staff rotation every 12 h to avoid tiredness	Contribution of resources (stationery, transport)	Provision of training and feedback to health centers	Protocols, improved coordination with health centers
Baltag 2012 [18]			Improved equipment and supplies		Protocols, organization of care and management
Kidanto 2012 [19]		Improved doctor availability			Reorganization of daily routine and setting of priorities, doctors assigned to manage cases of eclampsia

Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]		Rational use of staff by internal redistribution, optimization of human resources by reducing the working hours, increased role of mid-level staff (midwives and nurses);	Mobile devices for timely alert and warning, drugs and blood components, prostaglandins and uterotonics	Training on protocols and standards, periodic drills, improving time management skills	Developing new protocols, developing emergency care algorithms and conditions for transportation from remote areas, identifying the responsible person for the readiness of the emergency kit, monitoring forms, weighing of blood losses and documenting systematically
Van den Akker 2011 [22]				Training, regular on job coaching, improved supervision, monitoring of ambulance use	Protocols and use of partograph
Bailey 2010 [23]			Purchase of equipment (lab, car for oncall, telephone for emergency), wall flow charts	Training, supervision	Leadership on implementing changes, standardization of treatment with protocols and checklists, team work record keeping
Van den Akker 2009 [24]			More ambulance	Training, supervision, follow up visits in health centers	Protocols, transport organization, organize session for theater staff with the intention to reduce delay in surgical care
Hunyinbo 2008 [25]			Pharmacy supply including oxytocins, MgSO4, blood and coagulation tests		Protocols, clinical meetings, observational and fluid balance charts
Kongnyuy 2008 [26]	The number of comprehensive and basic EmOC facilities did not change over the 3-year				

Kongnyuy 2008 [27]		Autonomy in decision making in MW-N	Better equipment and set up of service	Training	Reorganization of emergency care service, including use of ambulances,
Weeks 2005 [28]		Staff in the labour room reorganised iving each member a specific role in the management of emergencies; two extra midwives	Equipment (urine dipstick, BP machines)		Triage established, leadership (direct of labour appointed), protocol and chart, commitment to improve medical files, departmental meetings, fundraising (a fundraising committee was established to raise funds for the drugs and equipment in recommendations)
Wagaarachchi 2001 [29]			Record storage, blood cultures, structured patient records		Protocols, reviewing supervisory responsibilities, organization of regular clinical meetings

Abbreviations: BP= Blood pressure; EmOC= Emergency Obstetric Care; N= Nurses; M=Midwives

Figure 1. Study Flow Diagram

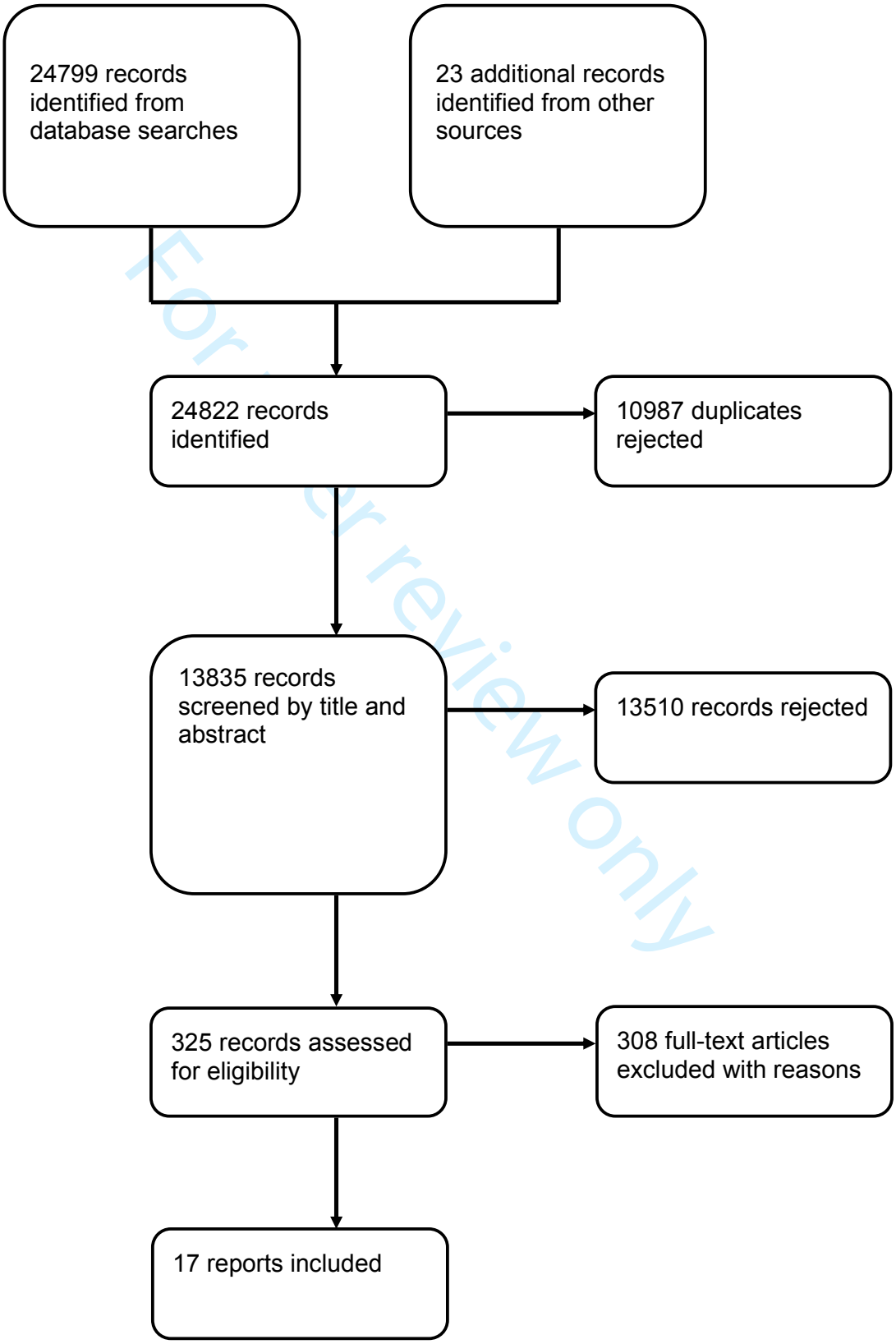


Figure 2. Pooled effect of the NMCR on maternal mortality

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mohd Azri 2015 (16) Malaysia	1	9	2	49	0.4%	2.94 [0.24, 36.32]
Hunyinbo 2008 (25) Nigeria	2	65	2	65	1.3%	1.00 [0.14, 7.32]
Kongnyuy 2008 (27) Malawi	2	62	3	60	1.9%	0.63 [0.10, 3.93]
Weeks 2005 (28) Uganda	0	43	4	43	2.9%	0.10 [0.01, 1.93]
Van den Akker 2011 (22) Malawi	4	5241	6	2995	5.0%	0.38 [0.11, 1.35]
Kidanto 2012 (19) Tanzania	0	88	30	389	7.4%	0.07 [0.00, 1.10]
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.6%	1.57 [0.80, 3.09]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	72.5%	0.80 [0.60, 1.05]
Total (95% CI)		**2950206**		**2622837**	**100.0%**	**0.77 [0.61, 0.98]**
Total events	119		169			

Heterogeneity: Chi² = 11.39, df = 7 (P = 0.12); I² = 39%

Test for overall effect: Z = 2.09 (P = 0.04)

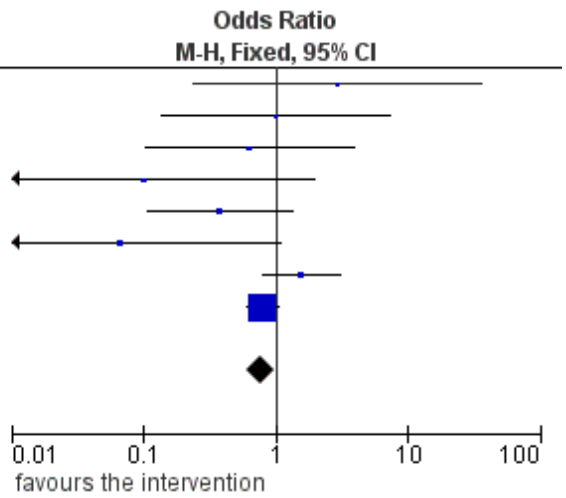


Figure 3. Pooled effect of the NMCR on perinatal or neonatal mortality

Study or Subgroup	favours the intervention Events	favours the intervention Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mohd Azri 2015 (16) Malaysia	3	9	4	49	1.2%	5.63 [1.00, 31.49]
Kongnyuy 2008 (27) Malawi	3	62	5	60	7.3%	0.56 [0.13, 2.45]
Kayinga 2016 (15) Uganda	27	180	27	180	34.6%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	56.9%	0.81 [0.50, 1.31]
Total (95% CI)		**339**		**678**	**100.0%**	**0.92 [0.65, 1.30]**
Total events	65		197			

Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 40%

Test for overall effect: Z = 0.49 (P = 0.63)

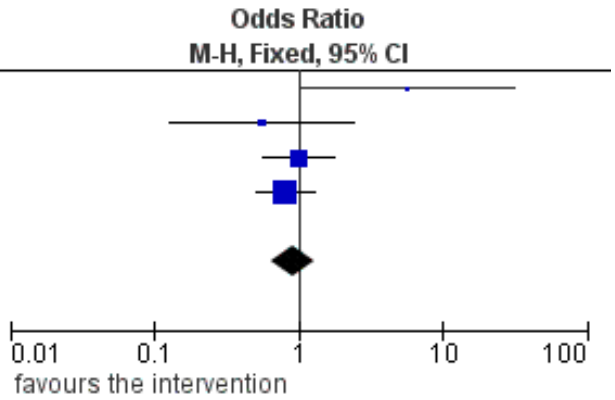


Table S1. Risk of bias

Author	Study design	Risk of bias criteria for RCTs, CCTs, CBAs, UCBAs					Additive risk of bias criteria for ITS		
		Random sequence generation	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective reporting*	*Intervention independent of other changes?*	*Shape of the intervention effect prespecified?*	*Intervention unlikely to affect data collection?*
Lumala 2017 [13]	ITS	high	high	high	low	unclear	high	low	high
Mgaya 2017 [14]	NCBA	high	high	high	low	unclear			
Kayiga 2016 [15]	NCBA	high	high	high	low	unclear			
Mohd Azri 2015 [16]	NCBA	high	high	high	low	unclear			
Gebrehiwot 2014 [17]	NCBA	high	high	high	low	unclear			
Baltag 2012 [18]	NCBA	high	high	high	low	unclear			
Kidanto 2012 [19]	NCBA	high	high	high	low	unclear			
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	NCBA	high	high	high	low	unclear			
Van den Akker 2011 [22]	ITS	high	high	high	low	unclear	high	low	high
Bailey 2010 [23]	NCBA	high	high	high	low	unclear			
Van den Akker 2009 [24]	NCBA	high	high	high	low	unclear			

Hunyinbo 2008 [25]	NCBA	high	high	high	low	unclear			
Kongnyuy 2008 [26]	NCBA	high	high	high	low	unclear			
Kongnyuy 2008 [27]	NCBA	high	high	high	low	unclear			
Weeks 2005 [28]	NCBA	high	high	high	low	unclear			
Wagaarachchi 2001 [29]	NCBA	high	high	high	low	unclear			

Figure S1. Sensitivity analysis : Pooled effect of the NMCR on maternal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Studies with at least 300 cases and 30 events						
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.5%	1.57 [0.80, 3.09]
Kidanto 2012 (19) Tanzania	0	88	30	88	19.8%	0.01 [0.00, 0.18]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	71.8%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Test for subgroup differences: Not applicable						

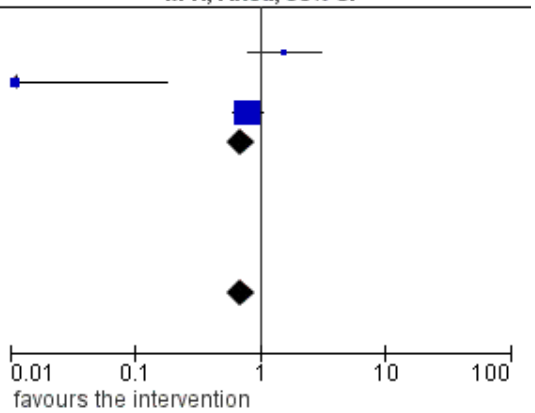


Figure S2. Sensitivity analysis : Pooled effect of the NMCR on perinatal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Studies with at least 300 cases and 30 events						
Kayinga 2016 (15) Uganda	27	180	27	180	37.8%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	62.2%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						

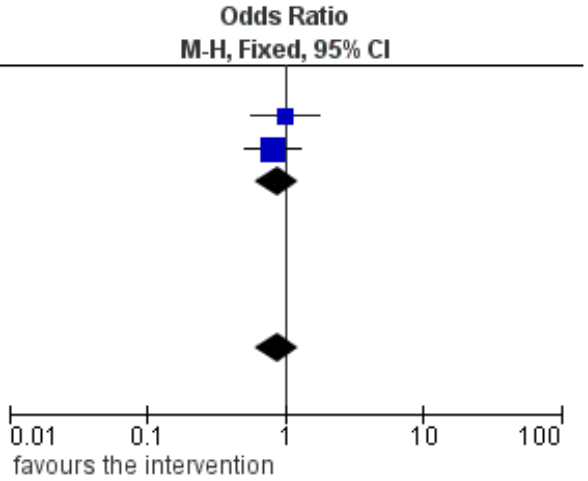


Figure S3. Subgroup analysis : Pooled effect of the NMCR audit on maternal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Studies with at least 300 cases and 30 events						
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	7.6%	1.57 [0.80, 3.09]
Kidanto 2012 (19) Tanzania	0	88	30	88	17.7%	0.01 [0.00, 0.18]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	64.4%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2944786**		**2619324**	**89.8%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
1.5.2 Studies with less than 300 cases and 30 events						
Mohd Azri 2015 (16) Malaysia	1	9	2	49	0.3%	2.94 [0.24, 36.32]
Hunyinbo 2008 (25) Nigeria	2	65	2	65	1.1%	1.00 [0.14, 7.32]
Kongnyuy 2008 (27) Malawi	2	62	3	60	1.7%	0.63 [0.10, 3.93]
Weeks 2005 (28) Uganda	0	43	4	43	2.6%	0.10 [0.01, 1.93]
Van den Akker 2011 (22) Malawi	4	5241	6	2995	4.5%	0.38 [0.11, 1.35]
Subtotal (95% CI)		**5420**		**3212**	**10.2%**	**0.50 [0.22, 1.12]**
Total events	9		17			
Heterogeneity: Chi² = 3.74, df = 4 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
Total (95% CI)		**2950206**		**2622536**	**100.0%**	**0.68 [0.54, 0.87]**
Total events	119		169			
Heterogeneity: Chi² = 19.07, df = 7 (P = 0.008); I² = 63%						
Test for overall effect: Z = 3.17 (P = 0.002)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%						

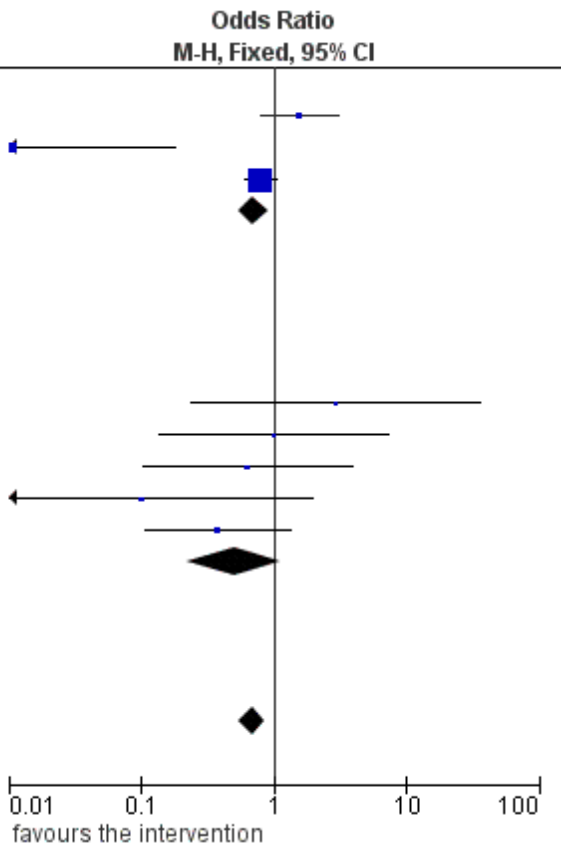


Figure S4. Subgroup analysis : Pooled effect of the NMCR on perinatal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Studies with at least 300 cases and 30 events						
Kayinga 2016 (15) Uganda	27	180	27	180	34.6%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	56.9%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**268**		**569**	**91.5%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.6.2 Studies with less than 300 cases and 30 events						
Mohd Azri 2015 (16) Malaysia	3	9	4	49	1.2%	5.63 [1.00, 31.49]
Kongnyuy 2008 (27) Malawi	3	62	5	60	7.3%	0.56 [0.13, 2.45]
Subtotal (95% CI)		**71**		**109**	**8.5%**	**1.30 [0.44, 3.82]**
Total events	6		9			
Heterogeneity: Chi² = 4.03, df = 1 (P = 0.04); I² = 75%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**339**		**678**	**100.0%**	**0.92 [0.65, 1.30]**
Total events	65		197			
Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.49 (P = 0.63)						
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%						

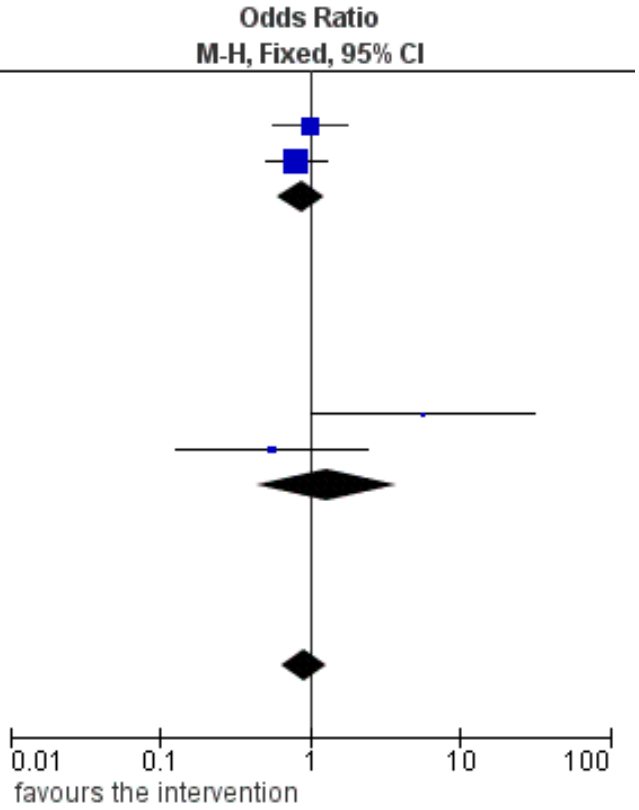


Figure S5. Funnel plot: effect of the NMCR on maternal mortality

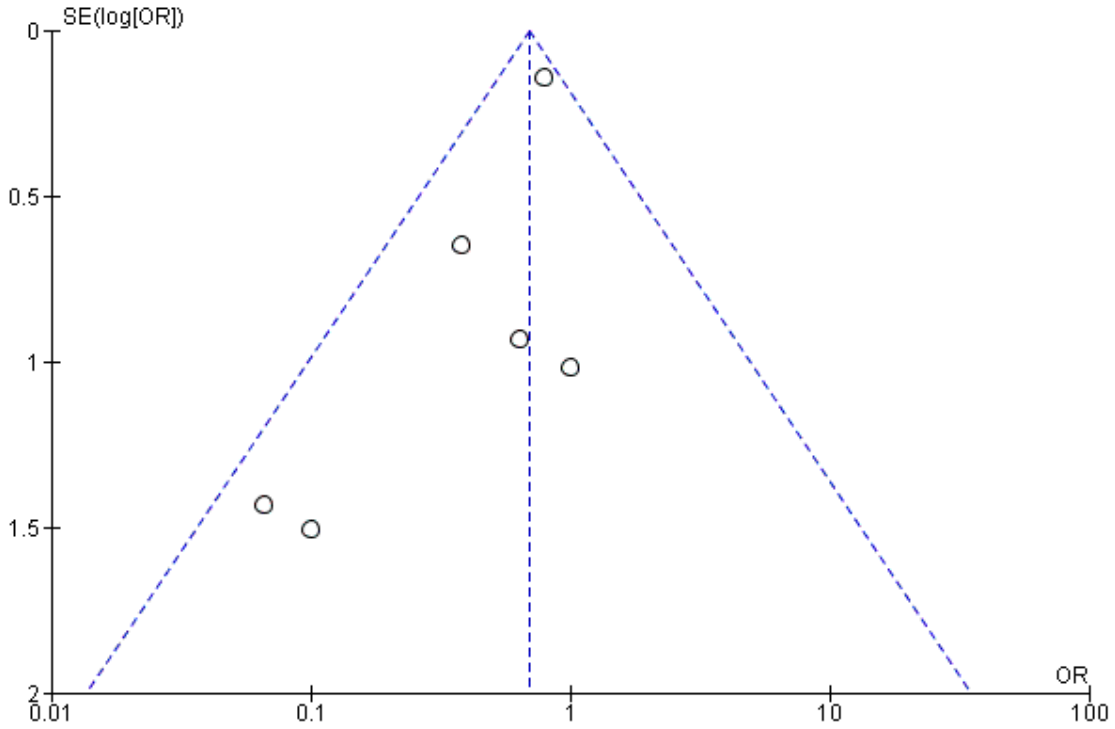
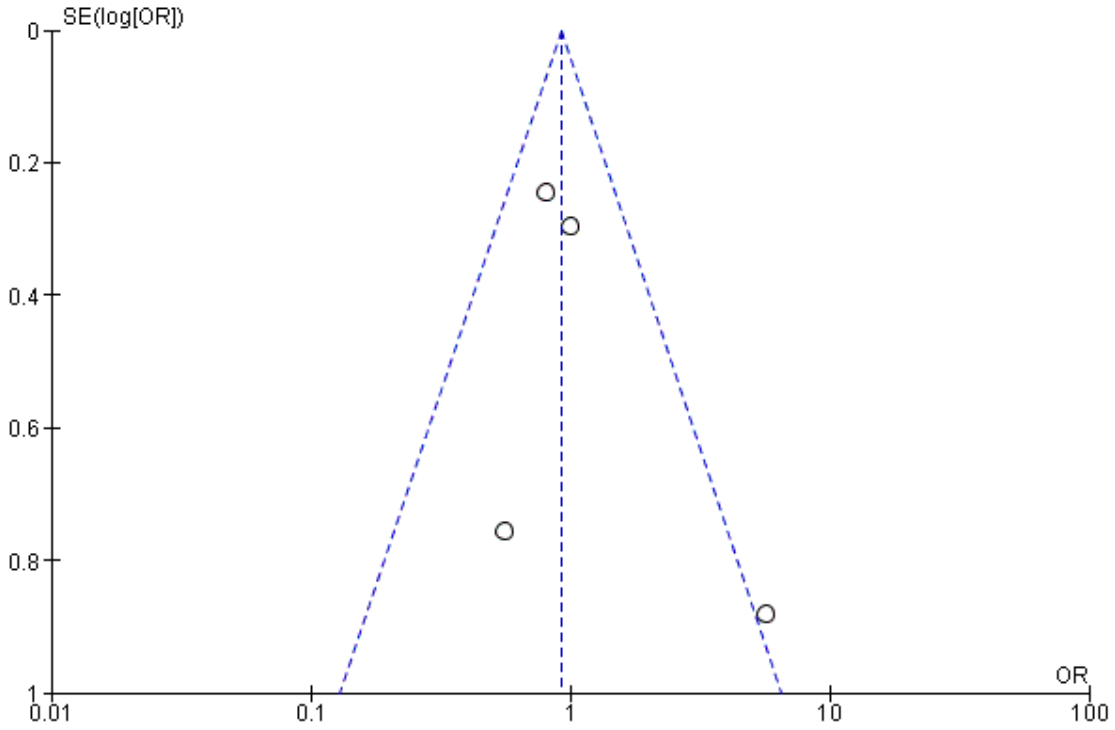


Figure S6. Funnel plot: effect of the NMCR on perinatal mortality



Box 1. Search strategy

PubMed **Date: Sept 15, 2017** **Total retrieved: 5578**

"near miss" OR (audit AND (obstetric* OR matern* OR pregnan* OR woman OR women))

Lilacs **Date: Sept 15, 2017** **Total retrieved: 227**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Global Idex Medicus **Date: Sept 15, 2017** **Total retrieved: 7806**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Web of Science **Date: Sept 18, 2017** **Total retrieved: 4850**

TS= "near miss" OR (TS=audit AND TS=(gravid* OR pregnan* OR obstetr* OR woman OR women OR matern*))

Cochrane Library **Date: Sept 15, 2017** **Total retrieved: :411**

"near miss" OR (audit AND (gravid* or pregnan* or obstetr* or woman or women or matern*))

EMBASE **Date: Sept 15, 2017** **Total retrieved: 5927**

1 ("near miss" or audit).ab. (34259)
2 (obstetric* or matern* or pregnan* or woman or women).ab. (1057153)
3 1 and 2 (4764)
4 ("near miss" or audit).ti. (13725)
5 (obstetric* or matern* or pregnan* or woman or women).ti. (325314)
6 4 and 5 (724)
7 3 or 6 (4962)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	42 (box 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-6 Figure 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 Figure 1-2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 Table S1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 Figure S1-S6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-13
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Effectiveness of the facility based maternal near-miss case reviews in improving maternal and newborn quality of care in low and middle income countries: systematic review

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Date Submitted by the Author:	18-Dec-2017
Complete List of Authors:	Lazzerini, Marzia; Institute for Maternal and Child Health IRCCS Burlo Garofolo, WHO Collaborating Centre Richardson, Sonia ; Institute for Maternal and Child Health IRCCS Burlo Garofolo, WHO Collaborating Centre Ciardelli, Valentina ; Department of obstetrics and gynaecology, Bentivoglio Hospital Erenbourg, Anna ; Institute for Maternal and Child Health IRCCS Burlo Garofolo, WHO Collaborating Centre
Primary Subject Heading:	Global health
Secondary Subject Heading:	Health services research
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical audit < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS

Effectiveness of the facility based maternal near-miss case reviews in improving maternal and newborn quality of care in low and middle income countries: a systematic review

Running title: Effectiveness of NMCR on maternal and newborn quality of care in LMIC

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Abstract word count: 292

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ABSTRACT

Objectives

The maternal near-miss case review (NMCR) has been promoted by WHO as an approach to improve quality of care (QoC) at facility level. This systematic review synthesizes evidence on the effectiveness of the NMCR on QoC and maternal and perinatal health outcomes in low and middle-income countries (LMIC).

Methods

Studies were searched for in six electronic databases (MEDLINE, Index Medicus, Web of Science, the Cochrane library, Embase, LILACS), with no language restrictions. Two authors independently screened papers and selected them for inclusion and independently extracted data. Maternal mortality was the primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care: efficacy, safety, efficiency, equity, accessibility and timely care, acceptability and patient-centered care.

Results

Out of 24,822 papers retrieved, 17 studies from 11 countries were included. Maternal mortality measured before and after the implementation of the NMCR cycle significantly decreased (odd ratio (OR) 0.77, 95%CI 0.61 to 0.98, eight studies, 5,5573,043 women; I^2= 39%). A statistically significant reduction in the incidence of uterine rupture, post-partum haemorrhage, and maternal sepsis was observed in three out of six studies. Ten studies reporting on maternal care process all showed some significant improvement when measured against pre-defined standards. All studies reported that the NMCR resulted in some amelioration of the facility structure (physical structure, staffing, equipment, training, organization of care). Newborn outcomes were overall poorly reported; four studies showed no significant difference in perinatal mortality. Patient satisfaction and equity were also poorly reported.

Conclusions

Policy makers may consider implementing the maternal NMCR cycle approach among strategies aiming at improving QoC and reducing maternal mortality and morbidity in LMIC. Future studies should better document the effectiveness of the NMCR cycle particularly on outcomes reflecting patient-centered care and cost-effectiveness.

Article summary: strengths and limitations of this study

- The maternal near-miss case review (NMCR) approach has been used in different settings; however, so far no systematic review has ever reported on its effectiveness. The present review fills an existing gap in evidence synthesis by reporting latest evidence on the effectiveness of NMCR cycle as a type of criterion base audit in low and middle-income countries (LMIC).
- Findings of this review are limited by the paucity of existing scientific literature: despite the NMCR approach has been utilised in many countries, such as China, India, South Africa and the WHO European Region, scientific literature reporting on the NMCR effectiveness is relatively scarce.
- Despite the above described limitations, this review collected an appreciable number of studies reporting on the impact of the NMCR cycle from different regions worldwide, including Africa, Central Asia, South East Asia, Latin America and Caribbean- and adds as a new knowledge that this approach may be effective in reducing maternal mortality, and in improving quality of maternal and newborn health care at facility level.

Keywords

Near miss case review; quality of care; maternal health; perinatal health; low and middle income countries

Disclosure of interests

No competing interest

List of abbreviations

CBAs= controlled before-and after studies
CCTs= controlled clinical trials
ITSs= and intermittent time series
LMIC = low and middle-income countries
NMCR= Near miss cases review
OR= odds ratio
QoC= Quality of care
RCTs= randomised controlled trials (RCTs)
UCBAs=uncontrolled before and after studies
WHO = World Health Organization

BACKGROUND

Ensuring adequate quality of health care is a primary objective of the World Health Organization (WHO) Global Strategy for Women's, Children's and Adolescent's Health 2016-2030 (1,2). Quality in health care is recognized by WHO as essential for the health and well-being of the population, and as a basic aspect of human rights (2,3).

Among different approaches aiming at improving quality of care in maternity services, the maternal near-miss cases review (NMCR) approach was promoted by WHO and partners since 2004 within the strategy Beyond the Numbers (4). The facility-based individual NMCR cycle is defined as a type of criterion-based audit seeking to improve maternal and perinatal health care and outcomes by conducting a review, g, at hospital level, of the care provided to maternal near-miss cases (5). A maternal near miss case is defined as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within six weeks after pregnancy (5).

In the last 20 years, NMCR have been promoted as an alternative way to audit case management, more acceptable for health workers than mortality audits, which have been in use for many years (4,5). As a matter of fact, in low mortality settings or at the health service level, the number of maternal deaths is usually insufficient or not representative enough to allow reliable policy guidance (4). Moreover, discussing cases of deaths may have legal implication and may be perceived as challenging by hospital staff (4). Near-miss cases occur more frequently than maternal deaths, their review can directly inform on both strengths and weakness in the process of care, and it is usually perceived by staff as easier to perform than mortality audits (5,6).

The objective of the NMCR cycle is to identify areas amenable of improving quality of care, and finding and implementing solutions to the problems identified. Actions for improving quality of care are proposed and agreed by hospital staff, and subsequently monitored to check their implementation (5). This bottom-up approach aims at ensuring local ownership and facilitating team-building dynamics (5). Beside reviewing clinical management the NMCR can cover other domains involved with delivery of care, including availability of essential equipment, staffing, training, policies and organization of services (5). According to the WHO guidance (5) patients' experience of care should be collected through interviews and taken into account in developing recommendations aiming at improving quality of care.

The NMCR approach has been used in different settings (5); however, so far no systematic review has ever reported on its effectiveness. The objective of this review is to systematically evaluate and synthesise the evidence on the effectiveness of the NMCR cycle on the quality of care and on

maternal and perinatal health outcomes in low and middle-income countries (LMICs).

METHODS

Search strategy and eligibility criteria

In conducting this review we followed the guidelines reported in the PRISMA (Preferred Reporting Items for systematic reviews and meta-analyses) (7). A protocol including detailed methods of the review was developed before starting the review.

We searched up to September 2017 the following databases: MEDLINE through Pubmed (from 1956); LILACS (no date restrictions); Global Index Medicus (no date restrictions); Science Citation Index Expanded (SCI-EXPANDED) through Web of Science (no date restrictions); Social Sciences Citation Index (SSCI) through Web of Science (no date restrictions); Cochrane library (no date restrictions); Embase through OVID (from 1996). The search strategy is reported in **Box 1**. Manual searches of reference lists were also performed. We did not apply any language restrictions.

Studies were eligible for inclusion if they reported on the effectiveness (outcome) on maternal and perinatal health care (population) of the individual NMCR cycle at facility level (intervention), in a LMIC (setting), defined as for the World Bank definition at the time of the study (8). Given the paucity of randomised controlled trials (RCTs) on the subject, we also opted to include in this review in this review non randomized controlled clinical trials (CCTs), controlled before-and after studies (CBAs), uncontrolled before and after studies (UCBAs) and intermittent time series (ITSs). Qualitative studies were excluded. Both studies using the WHO definition of a maternal near-miss case published in year 2011 (9) or previous/locally adapted definitions, such as locally developed disease-specific definitions, were included. Studies reporting on interventions where the full audit cycle was implemented (ie including implementation of changes) were included, while studies only reporting descriptive findings of the case review (ie identifications of gaps in case management without developing and implementing recommendations) were not eligible. Abstracts and unpublished reports were also not eligible for inclusion.

Maternal mortality was predefined as our primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care (10), namely: efficacy (eg maternal morbidity), safety (eg adverse events), efficiency (cost), equity (eg equitable care), accessibility and timely care (eg access to care), acceptability and patient-centered care (eg patients' satisfaction). Effectiveness on the quality of care is reported according the Donabedian model of quality improvement, which differentiate in between: i) outcomes of care (eg health

outcomes, costs, satisfaction), ii) process of care (eg diagnosis and treatment); iii) and inputs/structure (eg physical structure, staffing, equipment and supplies, training, policies and organization of care) (11).

Data collection and analysis

Studies were selected for inclusion by two independent authors in two teams (VC and AE, ML and SR). Any disagreement was resolved through discussion. The full text of all eligible citations was examined in detail. Two authors (ML, SR) extracted data from included studies, using a pre-piloted data-extraction form. Disagreements were resolved by discussion between the two authors and consensus with a third author.

We extracted information regarding: study setting, design and duration; characteristics of the intervention; type of outcomes evaluated; effectiveness of the NMCR on the outcomes. For the study with ITS design we included in the metanalysis of maternal mortality the first and the last time point reported. Data on effectiveness were extracted as crude numbers or percentages. Data on maternal mortality were extracted as disease-specific maternal mortality when case reviews focused only on specific diseases, and as total maternal mortality when case reviews included all major obstetric emergencies.

When meta-analysis was possible and appropriate, for each outcome factor we generated a pooled odds ratio (OR) using the Mantel-Haenszwel weighting method (12). Pooled data were presented in forest plots; data that could not be meta-analyzed was presented in tables and text. We tested the null hypothesis that all studies evaluate the same true effect by the Cochran's Q test, with two-sided $p<0.05$ considered statistically significant. The degree of heterogeneity between studies was assessed by visual inspection of the forest plots and I-squared (I2) statistic with its 95% confidence intervals, and interpreted according to the Cochrane manual (12).

The Cochrane 'Risk of bias' tool modified with the Cochrane Effective Practice and Organization of Care Group (EPOC) criteria for ITSs (12) was used to assess the risk of bias in included studies. We aimed at performing the following sensitivity analyses: i) removing the studies with high risk of bias; ii) removing studies including less than 300 cases and less than 30 events (ie cases of maternal death or perinatal death). We performed a subgroup analysis exploring the effect of NMCR in low income countries (defined as for the World Bank definition at the time of the study (8)) compared to middle income countries.

RESULTS

Characteristics of the studies

The search yielded overall 24,822 records (**Figure 1**). Overall 17 papers (13-29) from Africa (Ghana, Ethiopia Malawi, Nigeria, Tanzania, Uganda), Europe and Central Asia (Kazakhstan, Moldova), South East Asia (Malaysia, Vietnam) and Latin America and Caribbean (Jamaica) met the inclusion criteria.

Characteristics of the study settings and design are summarized in **Table 1**. All except one study (23) were published during the last 15 years. Two papers referred to the same experience (20, 21); findings from these studies are jointly reported in the tables, and we used the most recent reference (20) to identify them. All studies were uncontrolled before and after-studies (UCBAs), describing the effectiveness of the NMCR cycle with a before and after analysis, except for two studies with ITS design (13, 22). Studies duration ranged from a minimum of 6 months (27) to a maximum of 26 months (29). Ten studies were held in an urban setting (13-17,19,20,25,28,29), three in a rural setting (22,24,27), and three in a mixed setting (18,23,26). One study was multi-centered (Ghana and Jamaica) (29). Among the 16 experiences reported, nine were of large size: one very large study In Malawi included 73 facilities in three districts (26); another three studies in Malawi enrolled respectively 29 and 13 facilities of different level and type (22,27), while one was conducted in one referral hospital plus several (number not further specified) health centres (24); a study in Ethiopia involved 10 public hospitals (17); studies in Kazakhstan, Vietnam, Ghana, Jamaica and Moldova involved six, five, four and three hospitals respectively (20,23,29,18). The remaining seven studies where single-center studies and took place in one teaching/tertiary level care hospital each.

Characteristics of the intervention are summarized in **Table 2**. In about half of studies cases were audited prospectively (15,17,18,20,22,24-26), while in the other studies audits were either conducted retrospectively (12,13,27), or retrospectively in a first phase then prospectively in the second phase (16,19,23,28,29). While in all cases the internal staff within the facility was involved in developing the recommendations, studies differed by who performed the case reviews: in most experiences audits were conducted by internal staff within the facility/ies, with the exception of four cases where a study investigator/physician audited the cases against pre-defined criteria and later presented it to hospital staff (13,19,25,29) and two cases where this information was not specified (15,16). Type of obstetric complications selected for audit included: severe pre-eclampsia/eclampsia (13,16,19,22,23,25-29), post-partum haemorrhage (13,20,22,23,25-27,29), obstructed labour (14,15,23,26,27,29), uterine rupture (24,25,29), infections (23,25,27),

complications of abortion (27). Five studies focused on one complication only (14-16,24,28) while in all other studies more than one condition was audited. In three studies cases of maternal mortality were audited together with cases of near-miss (17,22,26). The criteria for case selection was "all cases occurring in the study period", except in one experience in Malawi where cases of particular educational interest were selected (24), and a study in Moldova were, despite no pre-defined criteria, it was observed that cases "more likely to lead to praises for the maternity team" were selected (18). Number of total cases audited in each study ranged widely, from 30 cases (18) to 2568 cases (17).

Only in four experiences women were interviewed (14,15,18,20), but in one of them this was explicitly merely for recording bureaucratic details (15), rather than for the purpose of collecting women views and perspectives on quality of care received. All studies associated the audits with the development or implementation of standards of care (used also in most cases to perform the audits), while few studies also associated additional interventions for the hospital staff, such as development/dissemination of guidelines, and training on case management (13,15, 23).

As reported in **Table S1**, types of outcomes evaluated in the studies reported mostly on two dimensions of quality of care (10): effectiveness and accessibility and timely care. Outcomes related to the other dimension of quality of care, such as patient centrality and acceptability (eg patient satisfaction), efficiency and equity, safety (eg rate of adverse events, incident reporting) were not explored, with the exception of one study in Kazakhstan reporting on improved patients satisfaction (20) and one in Moldova reporting improved attitude towards patients (18).

Effectiveness of the NMCR cycle

Effectiveness on health outcomes

In a meta-analysis including eight studies maternal mortality measured before and after the implementation of the NMCR cycle significantly decreased (OR 0.77, 95%CI 0.61 to 0.98, 5,5573,043 women, **Figure 2**), with relatively low heterogeneity between studies (I^2= 39%). An additional study from Uganda reported to have observed a reduction in maternal mortality, but data were not further made explicit (15).

Three out of six studies reported a statistically significant reduction in the incidence of the following preventable obstetric complications: uterine rupture, major post-partum haemorrhage, and maternal sepsis (**Table 3**).

Newborn outcomes were overall poorly reported. Of five studies documenting perinatal mortality,

fours could be included in the meta-analysis, showing no significant differences in perinatal deaths in the before and after period (OR 0.92, 95%CI 0.65, 1.30, **Figure 3**) with low heterogeneity between studies (I^2= 40%). The fifth study (14), conducted in Uganda, reported a significant reduction in the incidence of a combined outcome including perinatal severe morbidities, deaths and stillbirths (**Table 3**). Only one study reported on number of newborns admitted to ICU, without statistical difference in the before and after NCMR period (15). Another single study reported on Apgar score birth weight, without changes in the before and after period (16).

One study reported increased patient satisfaction after the implementation of the NMRC cycle (20).

Effectiveness on process outcomes

The effectiveness of the NMCR on the process of care is synthetized in **Table 3.** Ten studies reported on the process of care when measured quantitatively against pre-defined standards and all showed some significant improvements (13-16,19,23,25,27,28,29). Six studies reported other findings, such as improved case documentation, referral, use of partograph, monitoring and teamwork (14,17,18,20,22,26).

Effectiveness on structure outcomes

Effectiveness on the structure is detailed in **Table 4**. All studies reported some improvements in one or more domains. Overall most frequent changes relate to: purchasing of essential equipment and supplies; additional training, monitoring and supervision; policies and organization of care including reorganisation of staff and their duties, implementation of systems aiming at standardising case management through disseminating of guidelines, checklists and monitoring forms, better coordination among different services.

Risk of bias and other analyses

All studies were rated as a high risk of bias based on the Cochrane and EPOC criteria (**Table S2**), mostly due to the study design (NCBA or ITS studies).

The sensitivity analysis showed that when studies with a very small sample size were excluded, the effect of the NMCR on maternal mortality becomes stronger than when all studies were included (OR 0.71, 95%CI 0.55 to 0.90, three studies I^2=86% **Figure S1).** The effect of NMCR on perinatal mortality did not significantly changed in the sensitivity analysis (**Figure S2**).

Thirteen studies were held in low-income countries (13-15,17,19,22-27,28,29), two in upper middle-income countries (16,20), and one in a lower middle-income country (18) (**Table S3**). In the subgroup analysis, the effect of NMCR on maternal mortality was statistically significant in low

income countries (R 0.77, 95%CI 0.60 to 0.98, 7 studies), while only one small study could be included in the category of middle income countries, without statistical significance (**Figure S3).** The effect of NMCR on perinatal mortality was not affected by subgroup analysis (**Figure S4).** Funnel plots did not suggest publication bias (**Figure S5 and S6**).

DISCUSSION

This review suggests that the facility based individual maternal NMCR cycle may be an effective strategy for reducing maternal mortality in high burden countries, and for improving overall quality of maternal care in LMIC. Results of a pooled analysis of findings from eight studies showed that the NMCR cycle significantly reduced maternal mortality (OR 0.77, 95%CI 0.61 to 0.98, **Figure 2**), with relatively low heterogeneity of results (I^2=39%). Three out of six studies reported a significant reduction in the incidence of preventable obstetric complications such as uterine rupture, major post-partum haemorrhage, and maternal sepsis. Out of ten studies reporting on the process of care when measured against pre-defined standards all showed some statistically significant improvement. Additionally, in all studies the implementation of the NMCR cycle resulted in some amelioration in the structure of the hospital, such as an increased availability of essential equipment and supplies, additional training, monitoring and supervision, and the implementation of new policies and better organization of services.

Previous systematic reviews had observed a benefit of criterion-base audits in improving the quality of obstetric care (30-32). However, a review on the effectiveness of criterion-base audits in LMIC published some years ago concluded that, despite criterion-base audits being increasingly used, few studies had reported on their effectiveness (33). The present review retrieved all latest evidence on the effectiveness of NMCR cycle as a type of criterion base audit, synthesized studies from LMIC in different geographical regions- including Africa, Central Asia, South East Asia, Latin America and Caribbean- and adds as a new knowledge that this approach may be effective in reducing maternal mortality and in improving quality of health care provided.

Findings of this review are limited by the paucity of existing scientific literature: the NMCR approach has been utilized in many more countries than what could be included in this reviews, such as China (34), India (35), South Africa (36), and the WHO European Region (37-41), but scientific literature reporting on the NMCR effectiveness in these countries could not be retrieved. Secondly, all included studies had an UCBA or ITS design, thus being exposed to a high risk of bias (although most studies checked for potential confounding factors, such as the case mix in the before and after phase). Several studies had a low sample size which did not allow for detecting a statistically significant difference in rare outcomes such as maternal or perinatal mortality (18,20),

Despite these limitations, this review collected an appreciable number of studies, including also some very large studies (17,22,26,27), reporting on the impact of the NMCR cycle from different regions worldwide, and in most experiences significant gains were observed. In some cases, a significant benefit in the study outcomes could not be detected because in-hospital maternal mortality was too low or because standards of care were already good at the baseline (13,23,27 . Ideally, it will be advisable to perform large multicenter RCTs to properly document NMCR effectiveness. However, in practice conducting a RCT on criterion based audit alone may be challenging, and may even be perceived as unethical, if no appropriate comparison is chosen. This is because in current practice criterion based audits are already one of the recommended strategies to improve quality of care promoted by many agencies and bodies, such as the National Institute for Clinical Excellence (NICE) (42). Notably, the review of "near-miss" cases is already recommended by WHO as a "key action to eliminate avoidable maternal and perinatal mortality and morbidity and improve the quality of care" (43) and as such it is already implemented in several countries.

The audit of maternal near miss cases is an approach also utilized in several high-income settings: UK has a well-established programme of confidential enquiries into maternal deaths and a national system for research on maternal near-miss-the UK Obstetric Surveillance System (UKOSS) (44,45); New Zealand established a national system for severe maternal morbidity review (46); several countries within the International Network of Obstetric Survey Systems (INOSS) are collecting data on severe maternal morbidities for study purposes (47), while other countries such as Italy (ITOSS) are starting implementing near-miss audits (48,49). Although there are some differences in the type of interventions applied (eg not all of these approaches are facility based), still the existence of these large networks on maternal near miss case reviews and the amount of resources devoted to them somehow testify the importance recognized in reviewing near miss cases.

In the future, rather than investing resources in exploring whether near miss audits or criterion base audits in general are overall effective, it will be more interesting to explore which characteristics make them effective and sustainable. Available literature synthesised in this review does not allow for directly comparing the effectiveness of different methodologies on how to perform audits in practice, but at least it does provide some useful starting point for discussion and for future research. First, with regards to the number of cases audited, this varied largely in the included studies from a minimum of less than 10 cases per year (18,20) to a maximum of several hundred cases in few months (14,29), with a third approach consisting in performing a large retrospective review of past cases at the baseline, and then collecting fewer new cases prospectively. When many cases were reviewed, this allowed for an in depth description of the

gaps in care. However, the analysis of a large number of cases does not necessarily ensure the development of good recommendations for quality improvement, neither their implementation. Additionally, the sustainability of auditing on a large number of cases, outside a research setting, is questionable. Studies included in this review suggest that even the periodic review of few cases may help identifying gaps in routine care, developing SMART recommendations (ie Specific, Measurable, Achievable, Realistic, Time-bound (50)), and improving quality of care significantly (18,20). This is the approach also recommended by WHO (5).

Secondly, studies included in this review revealed that most experiences of implementation of NMCR cycles were externally supported, either by the WHO, academia, and/or other development partners (15,18,20-24,26-28). This is in line with other existing literature (,51,52) highlighting that in particular the second part of the audit cycle (ie developing recommendations, implementing them, checking on progress) is in general problematic and usually less well conducted compared to the first part of the audit cycle. The attitude to openly discuss cases within a multidisciplinary team and agreeing solutions was described as challenging in different settings, especially for mid-level staff (midwives, nurses) who may not be used to voice their views in the presence of doctors and managers (18,20). Hospital staff, managers included, often do not receive any formal training in quality improvement methods or any guidance in correctly performing an audit cycle. The need for ensuring sustained external support, and for establishing a functional quality assurance mechanism are recognised by WHO crucial for ensuring an effective NMCR implementation (5).

Thirdly, although having a single person appointed to perform the case-review - as performed in some studies included in this review (18,10,25,29)- may increase feasibility, this actually largely reduces ownership of the process, together with minimizing occasions for discussion and team building among staff. Studies noted that involvement of all health care providers in the audit process promoted successful implementation, ownership and sustainability of the process (14,20,28). The involvement of mid level staff such as nurses and midwives was reported to result in improved staff autonomy and team work (14,21,27). Some studies observed that participation of the senior management promoted the implementation of recommendations that required allocation of resources and changes in policies and organisation of care (26,28). Currently the WHO approach (5) recommends the NMCR to be performed by the staff who managed the cases, including nurses, midwives, and any other staff directly or indirectly involved in case management.

Fourthly, the patient's experience of care was assessed only in very few of the existing studies, and yet not fully taken into account. In the last few years, WHO has given increasing importance to patient's experience of care (1). Listening to women's views may provide important information, as testified by studies in Brazil, Rwanda and UK (53-55) and by a study in Iran where women's

views were successfully used to improve quality of care (56). Currently WHO recommends to always interview women and their families and to use their inputs for improving care (5).

Finally, as pointed out by authors of the included studies, interventions aiming at improving quality of care without strengthening the health systems and improving community awareness may have minimal success (15,22). A study in Malawi reported that availability of essential supplies, such as blood for transfusions, remained low even after the NMCR due to health system failures and this clearly was a barrier for improving case management (22). Qualitative findings collected through focus group in a study in Uganda (15) pointed out among issues that may have hampered the effectiveness of NMCR health facility factors such as: stock-out of essential supplies, shortage of human resources, lack of task allocation, inadequate supervision. However, in most studies, even if the number of staff and available resources remained stable in the before and after phase, as a result of the audit there was a reorganization of staff activities, such as better specification of roles and responsibilities, task shifting, and improved communication (14,16,17,20,28).

Cost of the NMCR approach in improving health outcomes and quality of care was not formally evaluated in the retrieved studies. However, several papers stated that the NMCR was an inexpensive and simple intervention, requiring little technology (24,26-28). A study involving 12 health centres in Malawi reported that each audit meeting cost about 150 US $, including foods and transport of participants to the District Hospital (27). Another study in Uganda stated that “the audit process had challenged the assumption that all quality improvements need to be externally provided and are expensive” (28). These findings are in line with a systematic review of barriers and facilitators for effective NMCR implementation, reporting that a relatively low budget is needed to facilitate activities (37). In some experiences, the NMCR improved use or availability of existing economic resources: in Malawi, it “promoted a wiser allocation of resources for maternity care at the district level” (27); in Uganda a fundraising committee was established to raise funds for drugs and equipment needed according to the recommendations (28).

CONCLUSIONS

Implication for policy and research

Among other strategies to reduce maternal mortality and morbidity and for improving the quality of maternal and perinatal care, policy makers may consider the implementation of the maternal NMCR cycle approach.

Researchers should aim at generating more evidence on how to effectively implement the NMCR cycle, how to improve its impact on newborn outcomes and on outcomes reflecting patients' centrality (such as patients' satisfaction and/or perception of quality of care received), together with documenting the cost effectiveness of the NMCR approach.

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Conflict of interest

None

Role of authors

ML conceived the papers, screened the study, extracted data, drafted the paper and finalised the paper. SR, VC, AE screened the study, extracted data and revised the first draft.

Data Sharing statement

All details of the analyses conducted are provided within the manuscript

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TABLES

Box 1. Search strategy

PubMed **Date: Sept 15, 2017** **Total retrieved: 5578**

"near miss" OR (audit AND (obstetric* OR matern* OR pregnan* OR woman OR women))

Lilacs **Date: Sept 15, 2017** **Total retrieved: 227**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Global Idex Medicus **Date: Sept 15, 2017** **Total retrieved: 7806**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Web of Science **Date: Sept 18, 2017** **Total retrieved: 4850**

TS= "near miss" OR (TS=audit AND TS=(gravid* OR pregnan* OR obstetr* OR woman OR women OR matern*))

Cochrane Library **Date: Sept 15, 2017** **Total retrieved: :411**

"near miss" OR (audit AND (gravid* or pregnan* or obstetr* or woman or women or matern*))

EMBASE **Date: Sept 15, 2017** **Total retrieved: 5927**

1 ("near miss" or audit).ab. (34259)
2 (obstetric* or matern* or pregnan* or woman or women).ab. (1057153)
3 1 and 2 (4764)
4 ("near miss" or audit).ti. (13725)
5 (obstetric* or matern* or pregnan* or woman or women).ti. (325314)
6 4 and 5 (724)
7 3 or 6 (4962)

Table 1. Study settings, designs and sample sizes

Author	Design	Duration	Country	Setting	Number and type of hospitals §
Lumala 2017 [13]	ITS	10 months	Uganda	Urban	1 tertiary specialist hospital, catholic funded private non profit
Mgaya 2017 [14]	NCBA	25 months	Tanzania	Urban	1 tertiary specialist hospital
Kayiga 2016 [15]	NCBA	7 months	Uganda	Urban	1 tertiary specialist hospital
Mohd Azri 2015 [16]	NCBA	2 years	Malaysia	Urban	1 tertiary specialist hospital
Gebrehiwot 2014 [17]	NCBA	18 months	Ethiopia	Urban	10 public hospitals
Baltag 2012 [18]	NCBA	13 moths	Moldova	Mixed	3 mixed (referral-level facilities at municipal, national and district levels)
Kidanto 2012 [19]	NCBA	3 years	Tanzania	Urban	1 teaching hospital
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	NCBA	2 years	Kazakhstan	Urban	6 mixed (national research centre, regional and city hospitals)
Van den Akker 2011 [22]	ITS	2 years	Malawi	Rural	29 mixed (1 referral hospital and 28 government, private and mission smaller facilities)
Bailey 2010 [23]	NCBA	2 years	Vietnam	Mixed	5 mixed (provincial, area and district)
Van den Akker 2009 [24]	NCBA	1 year	Malawi	Rural	1 referral hospital + undefined numbers of health centers
Hunyinbo 2008 [25]	NCBA	13 months	Nigeria	Urban	1 tertiary specialist hospital
Kongnyuy 2008 [26]	NCBA	2 years	Malawi	Mixed	73 mixed (hospitals, health centers)

Kongnyuy 2008 [27]	NCBA	6 months	Malawi	Rural	1 one district hospital, 12 satellite health centers
Weeks 2005 [28]	NCBA	20 months	Uganda	Urban	1 teaching hospital
Wagaarachchi 2001 [29]	NCBA	26 months	Ghana and Jamaica	Urban	4 district hospitals

Abbreviations: NCBA= non controlled before and fater study, ITS= Intermittent time series

Table 2. Characteristics of the interventions

Author	Characteristics of the audit	Who performed the audit	Who developed the recommendations	Type of cases audited	Selection criteria	N Case audited (before / after)	Woman Interview
Lumala 2017 [13]	two phases, retrospective	medical doctor	facility staff	PPH and severe pre-eclampsia, eclampsia	All in-patient cases in the study period, not referred and not receiving hydralazine or magnesium sulphate from the referring unit	238 (125 before, 133 after)	no
Mgaya 2017 [14]	two phases, retrospective	trained postnatal ward nurses, s (a consultant, a specialist and a midwife were also available for consultation)	facility staff (AN, L, MO, MW, P)	obstructed labour	All cases of obstructed labour with a single foestus in cephalic presentation, and no other severe medical conditions or PROM	510 (260 before, 250 after)	Yes
Kayiga 2016 [15]	two phases, prospective	NR	facility staff (MO, MW, M)	obstructed labour	all cases occurring in the study period	360 (180 before, 180 after)	yes
Mohd Azri 2015 [16]	first phase retrospective, second regular prospective	NR	facility staff (members of the obstetric department)	eclampsia	all cases occurring in the study period	51 (42 before, 9 after)	no
Gebrehiwot 2014 [17]	prospective	facility staff (MO, MW and other hospital staff + focal person)	facility staff	all NM + MD	all cases occurring in the study period	2568	no
Baltag 2012 [18]	prospective	facility staff involved in case management (MO, MD +	facility staff involved in case management (MO, MD +	NM	not pre-defined criteria, cases were chosen by director	30 approx (1 case per month in each hospital)	yes

		occasionally L, T, PHC)	occasionally L, T, PHC)				
Kidanto 2012 [19]	first phase retrospective, second prospective	1 senior doctor	facility staff	eclampsia and pre-eclampsia	all cases occurring in the study period	477 (389 before, 88 after)	no
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	prospective	facility staff	facility staff	PPH and severe pre-eclampsia	NR	not more than 10 in each hospital each year	yes
Van den Akker 2011 [22]	prospective every 2 to 3 weeks;	facility staff, occasionally external obs gyn	facility staff	infection, PPH, uterine rupture, preeclampsia, others) + MD	all cases occurring in the study period	45 (24 deaths; 21 SOC)	no
Bailey 2010 [23]	first phase retrospective, than regular prospective	facility staff (MO, N, M)	facility staff (MO, N, M)	severe preeclampsia, postpartum infection, prolonged/obstructed labour, PPH, organisation of emergency service	all cases occurring in the study period	558 (312 before, 246 after)	no
Van den Akker 2009 [24]	prospective every 2- 3 weeks for 3 months	facility staff (M,MA, MO, MW,N); 2 external obstetricians in the second phase	facility staff (MO, N, M)	uterine rupture	cases that appeared to be of particular educational value to the PI or any other hospital staff	35	no

Hunyinbo 2008 [25]	two phases, prospective	study investigator/s	facility staff (M,MA, MO, N,P, L)	PPH, uterine rupture, eclampsia, obstructed labour, sepsis	all cases occurring in the study period	130 (65 before, 65 after)	no
Kongnyuy 2008 [26]	two phases, prospective	facility staff (AN,M,MO,MW, L,T)	facility staff (quality improvement team)	PPH, obstructed labour, sepsis, preeclampsia/ eclampsia, neonatal care, CS , women-friendly care+ MD	NR	NR	no
Kongnyuy 2008 [27]	two phases, retrospective	district team (N, MW, CO,AN,T)	hospital staff (quality improvement team)	pre-eclampsia/ eclampsia, PPH, prolonged/ obstructed labour, retained placenta, sepsis, complications of abortion, ectopic pregnancy	all cases occurring in the study period	122 (60 before, 62 after)	no
Weeks 2005 [28]	first phase retrospective, second prospective	facility staff (including low grade staff)	facility staff	severe pre-eclampsia	all cases occurring in the study period	86 (43 before, 43 after)	no
Wagaarachchi 2001 [29]	first phase retrospective, second prospective	non-medical assistants (10% of cases validated by independent re-review)	facility staff (M,MO, M + all relevant staff)	PPH, eclampsia, infection, obstructed labor, uterine rupture	all cases occurring in the study period	889 (551 before, 338 after)	no

Abbreviations: AN= anesthetist of anesthetic technician, CO=clinical officer, CS= caesarian section, L= Laboratory, M= manager, MA=medical assistant, MD= maternal deaths, MO=medical officer, MW=midwife, N=nurse, ND= neonatal deaths, NM=Near miss, NR= not reported,P=Pharmacy, PHC= primary health care staff, PPH= post-partum hemorrhage, PROM= premature rupture of membranes, SOC= all severe obstetric cases, SEL= selected obstetric cases, T= technician

Table 3. Effectiveness of the NMCR cycle on morbidity and on process outcomes

Author	Morbidity and other health outcomes	Standards of care	Other process outcomes
Lumala 2017 [13]	_	Eclampsia and pre-eclampsia: 7/10 standards PPH: 3/4 standards	-
Mgaya 2017 [14]	SAMM (incidence: 9.0% vs. 8.8% (p = 0.98). Uterine rupture (incidence): 1/260 vs 0/250 (p=0.49) Perinatal severe morbidities and deaths and fresh stillbirths: 16% vs. 8.8% (p = 0.01)	Obstructed labour: 6/10 standards on diagnosis, 6/10 standards on case management	Significant reduction of time needed from decision to perform a caesarian section to delivery (mean difference:- 30 minutes, p< 0.001)
Kayiga 2016 [15]	Uterine rupture (Incidence): 8/180 vs 2/180 (p=0.04) Maternal sepsis (Incidence): 10/180 vs 2/180 (p=0.02) Post-spinal headache (incidence): 0/180 vs 13/180 (p<0.001) Baby admitted to intensive care: 27/180 vs 31/180 (p=0.61)	Obstructed labour: 2/6 standards, 4/13 measures of standards	-
Mohd Azri 2015 [16]	Eclampsia (incidence): 42/44818 vs 9/10784 (p> 0.05) Recurrent eclamptic fits: 8/42 vs 1/9 (p> 0.05) Newborn babies with Apgar score (< 7) at 5 minutes after birth: 8/42 vs 3/9 (p> 0.05) Birth weight less than 2500g 22/42 vs 5/9 (p> 0.05)	Improved adherence to 2/2 audit criteria that where substandard in the first phase (all other 10 criteria were already according to standards at baseline)	-
Gebrehiwot 2014 [17]	-	-	Reducing waiting time
Baltag 2012 [18]	-	-	Improved medical records Improved attitude towards patients
Kidanto 2012 [19]	-	Eclampsia and pre-eclampsia: 10/16 standards	Improved records keeping
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	Improved patients satisfaction (NR)	-	Improved case management and monitoring (eg weighing of blood losses and documenting systematically)

Van den Akker 2011 [22]	SAMM (Incidence): 33/2295 vs 49/5291 (p=0.08) Major PPH (incidence): 17/2295 vs 15/5291 (p=0.006) Uterine rupture (Incidence): 14/2295 vs 4/5291 (p=0.03) Severe pre-eclampsia (Incidence): 6/2295 vs 16/5291 (p=0.3) Maternal infections (Incidence): 10/2295 vs 14/5291 (p=0.6)	-	Improved patients monitoring
Bailey 2010 [23]	-	Eclampsia: 12/18 standards Infections: 11/23 standards Obstructed labour: 1/1 standards PPH: 3/3 standards	-
Van den Akker 2009 [24]	Uterine rupture (incidence): 16/833 vs 19/3099 (OR 0.32; 95% CI, 0.16–0.63)	-	-
Hunyinbo 2008 [25]		SAMM: 8/31 standards	-
Kongnyuy 2008 [26]	-	-	Significant increase in the met need for EmOC (15.2% for 2005, 17.0% for 2006 and 18.8% for 2007, p for trend < 0.001).
Kongnyuy 2008 [27]	-	SAMM: 4 /7 standards (other criteria were already according to standards at baseline)	-
Weeks 2005 [28]	Eclampsia (incidence): 5/43 vs 5/43 (p> 0.05)	Severe pre-eclampsia: 5/9 standards	-
Wagaarachchi 2001 [29]	-	SA: 8/31 standards	-

Abbreviations: CFR= case fatality rate; MM= maternal mortality; MMO= maternal morbidity; NM= neonatal mortality; NR= not further specified; PM: perinatal mortality; PPH= post partum hemorrhage; SAMM: severe acute maternal morbidity

Table 4. Effectiveness of the NMCR cycle on the structure

Author	Physical structure	Staffing	Equipment and supplies	Training, monitoring and supervision	Local policies and organization of services
Lumala 2017 [13]					
Mgaya 2017 [14]				training on partograph, improved supervision	Improved dissemination and use of guidelines, Improved team work and internal communication among hospital staff
Kayiga 2016 [15]					Re-engineering hospital Red Alert System: list of responsible person to be contacted during Red Alert activation was put up in all obstetrics facilities; Information on the importance of activating the Red Alert in eclampsia cases was disseminated to all staff; hospital telephone operator was informed regarding existence of this system and how it functions.
Mohd Azri 2015 [16]		Better specification of roles and responsibilities		Training, improved awareness of standards, improved patient's education	Reorganization of "red alert" system
Gebrehiwot 2014 [17]	Some hospitals expanded accommodate more cases	Staff organization: duties assignment; staff rotation every 12 h to avoid tiredness	Contribution of resources (stationery, transport)	Provision of training and feedback to health centers	Improved dissemination of protocols, increased use of partograph, Improved documentation and reporting improved coordination with health centers,
Baltag 2012 [18]			Improved equipment and supplies		Improved dissemination of protocols, organization of care and management
Kidanto 2012 [19]		Improved doctor availability 24/24h	Additional equipment purchased	Training	Improved dissemination of protocols, monitoring forms, reorganization of daily routine and setting of priorities, doctors assigned to manage cases of

					eclampsia
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]		Rational use of staff by internal redistribution, optimization of human resources by reducing the working hours, increased role of mid-level staff (midwives and nurses)	Mobile devices for timely alert and warning, drugs and blood components, prostaglandins and uterotonics	Training on protocols and standards, periodic drills, improving time management skills	Developing, diffusing and use new evidenced-based protocols, developing emergency care algorithms and conditions for transportation from remote areas, identifying the responsible person for the readiness of the emergency kit, monitoring forms, weighing of blood losses and documenting systematically
Van den Akker 2011 [22]				Training, regular on job coaching, improved supervision, monitoring of ambulance use	Improved dissemination of protocols and use of partograph, doctors to visits critically ill patients at least once a day
Bailey 2010 [23]			Purchase of equipment (lab, car for oncall, telephone for emergency), wall flow charts	Training, supervision	Leadership on implementing changes, standardization of treatment with protocols and checklists, team work record keeping
Van den Akker 2009 [24]			More ambulances	Training, supervision, follow up visits in health centers	Improved dissemination of protocols, transport organization, organize session for theater staff with the intention to reduce delay in surgical care
Hunyinbo 2008 [25]			Pharmacy supply including oxytocins, MgSO4, blood and coagulation tests		Improved dissemination of protocols, clinical meetings, observational and fluid balance charts
Kongnyuy 2008 [26]	The number of comprehensive and basic EmOC facilities				

	did not change				
Kongnyuy 2008 [27]		Autonomy in decision making in MW-N	Better equipment and set up of service	Training	Reorganization of emergency care service, including use of ambulances,
Weeks 2005 [28]		Staff in the labour room reorganised giving each member a specific role in the management of emergencies; two extra midwives	Equipment (urine dipstick, BP machines)		Triage established, leadership (direct of labour appointed), protocol and chart, commitment to improve medical files, departmental meetings, fundraising (a fundraising committee was established to raise funds for the drugs and equipment in recommendations)
Wagaarachchi 2001 [29]			Record storage, blood cultures, structured patient records		Improved dissemination of protocols, reviewing supervisory responsibilities, organization of regular clinical meetings

Abbreviations: BP= Blood pressure; EmOC= Emergency Obstetric Care; N= Nurses; M=Midwives

LEGENDS

FIGURES

Figure 1. Study Flow Diagram

Figure 2. Pooled effect of the NMCR on maternal mortality

Figure 3. Pooled effect of the NMCR on perinatal or neonatal mortality

SUPPLEMENTARY TABLES

Table S1. Type of outcomes evaluated in the studies

Table S2. Risk of bias

Table S3. World bank classification of country income

SUPPLEMENTARY FIGURES

Figure S1. Sensitivity analysis : Pooled effect of the NMCR on maternal mortality in studies with at least 300 cases and 30 events

Figure S2. Sensitivity analysis : Pooled effect of the NMCR on perinatal mortality in studies with at least 300 cases and 30 events

Figure S3. Subgroup analysis : Pooled effect of the NMCR audit on maternal mortality by country income

Figure S4. Subgroup analysis : Pooled effect of the NMCR on perinatal mortality by country income

Figure S5. Funnel plot: effect of the NMCR on maternal mortality

Figure S6. Funnel plot: effect of the NMCR on perinatal mortality

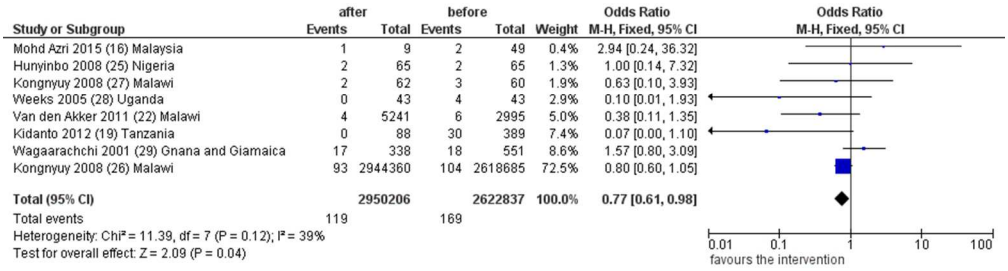


Figure 1. Study Flow Diagram

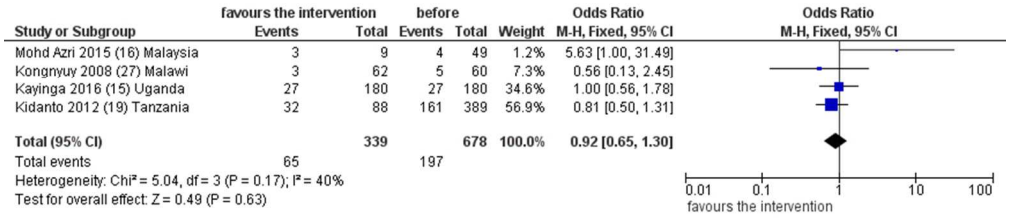


Figure 2. Pooled effect of the NMCR on maternal mortality

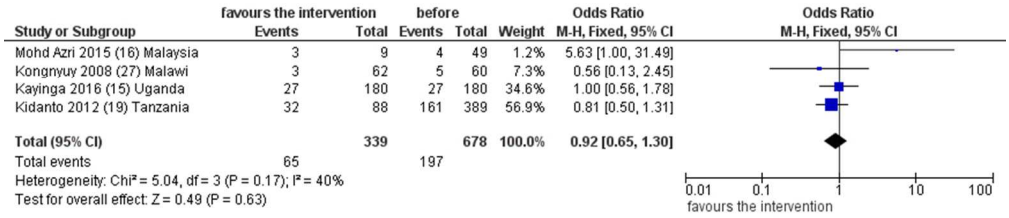


Figure 3. Pooled effect of the NMCR on perinatal or neonatal mortality

Table S1. Type of outcomes evaluated in the studies

Author	Patient centrality and acceptability	Accessibility Timely care	Efficiency and equity	Safety	Effectiveness
Lumala 2017 [13]	—	yes	—	—	yes
Mgaya 2017 [14]	—	yes	—	—	yes
Kayiga 2016 [15]	—	—	—	—	yes
Mohd Azri 2015 [16]	—	—	—	—	yes
Gebrehiwot 2014 [17]	—	yes	—	—	yes
Baltag 2012 [18]	yes	—	—	—	yes
Kidanto 2012 [19]	—	yes	—	—	yes
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	yes	yes	—	—	yes
Van den Akker 2011 [22]	—	yes	—	—	yes
Bailey 2010 [23]	—	yes	—	—	yes
Van den Akker 2009 [24]	—	yes	—	—	yes
Hunyinbo 2008 [25]	—	yes	—	—	yes
Kongnyuy 2008 [26]	—	yes	—	—	yes

Kongnyuy 2008 [27]	—	yes	—	—	yes
Weeks 2005 [28]	—	yes	—	—	yes
Wagaarachchi 2001 [29]	—	yes	—	—	yes

Table S2. Risk of bias

Author	Study design	Risk of bias criteria for RCTs, CCTs, CBAs, UCBAs					Additive risk of bias criteria for ITS		
		Random sequence generation	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective reporting*	*Intervention independent of other changes?*	*Shape of the intervention effect prespecified?*	*Intervention unlikely to affect data collection?*
Lumala 2017 [13]	ITS	high	high	high	low	unclear	high	low	high
Mgaya 2017 [14]	NCBA	high	high	high	low	unclear	-	-	-
Kayiga 2016 [15]	NCBA	high	high	high	low	unclear	-	-	-
Mohd Azri 2015 [16]	NCBA	high	high	high	low	unclear	-	-	-
Gebrehiwot 2014 [17]	NCBA	high	high	high	low	unclear	-	-	-
Baltag 2012 [18]	NCBA	high	high	high	low	unclear	-	-	-
Kidanto 2012 [19]	NCBA	high	high	high	low	unclear	-	-	-
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	NCBA	high	high	high	low	unclear	-	-	-
Van den Akker 2011 [22]	ITS	high	high	high	low	unclear	high	low	high
Bailey 2010 [23]	NCBA	high	high	high	low	unclear	-	-	-
Van den Akker 2009 [24]	NCBA	high	high	high	low	unclear	-	-	-

Hunyinbo 2008 [25]	NCBA	high	high	high	low	unclear	-	-	-
Kongnyuy 2008 [26]	NCBA	high	high	high	low	unclear	-	-	-
Kongnyuy 2008 [27]	NCBA	high	high	high	low	unclear	-	-	-
Weeks 2005 [28]	NCBA	high	high	high	low	unclear	-	-	-
Wagaarachchi 2001 [29]	NCBA	high	high	high	low	unclear	-	-	-

Table S3. World bank classification of country income

Author	Country	WB classification *
Lumala 2017 [13]	Uganda	L
Mgaya 2017 [14]	Tanzania	L
Kayiga 2016 [15]	Uganda	L
Mohd Azri 2015 [16]	Malaysia	UM
Gebrehiwot 2014 [17]	Ethiopia	L
Baltag 2012 [18]	Moldova	LM
Kidanto 2012 [19]	Tanzania	L
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	Kazakhstan	UM
Van den Akker 2011 [22]	Malawi	L
Bailey 2010 [23]	Vietnam	L §§
Van den Akker 2009 [24]	Malawi	L
Hunyinbo 2008 [25]	Nigeria	L §§
Kongnyuy 2008 [26]	Malawi	L
Kongnyuy 2008 [27]	Malawi	L
Weeks 2005 [28]	Uganda	L
Wagaarachchi 2001 [29]	Ghana and Jamaica	L §§

§ L=Low income; LM=Lower middle income; UM=Upper middle income

§§ Ghana, Jamaica, Nigeria and Vietnam were classified as low income countries during the time of the study, while they were upgraded to lower middle income in 2010, 2007 2008, and 2009 respectively.

Figure S1. Sensitivity analysis : Pooled effect of the NMCR on maternal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Studies with at least 300 cases and 30 events						
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.5%	1.57 [0.80, 3.09]
Kidanto 2012 (19) Tanzania	0	88	30	88	19.8%	0.01 [0.00, 0.18]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	71.8%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Test for subgroup differences: Not applicable						

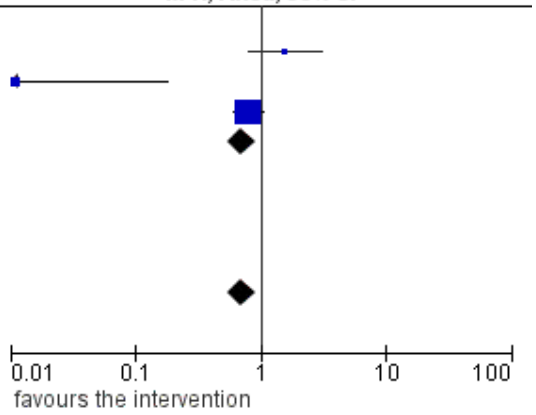


Figure S2. Sensitivity analysis : Pooled effect of the NMCR on perinatal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Studies with at least 300 cases and 30 events						
Kayinga 2016 (15) Uganda	27	180	27	180	37.8%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	62.2%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						

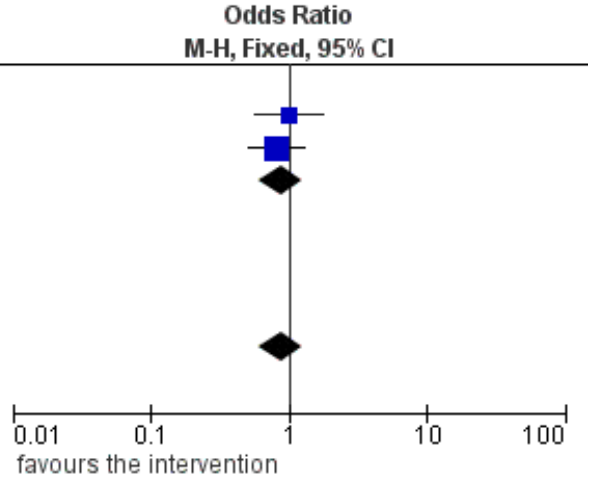


Figure S3. Subgroup analysis : Pooled effect of the NMCR audit on maternal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Studies in low income countries						
Hunyinbo 2008 (25) Nigeria	2	65	2	65	1.3%	1.00 [0.14, 7.32]
Kongnyuy 2008 (27) Malawi	2	62	3	60	1.9%	0.63 [0.10, 3.93]
Weeks 2005 (28) Uganda	0	43	4	43	2.9%	0.10 [0.01, 1.93]
Van den Akker 2011 (22) Malawi	4	5241	6	2995	5.0%	0.38 [0.11, 1.35]
Kidanto 2012 (19) Tanzania	0	88	30	389	7.4%	0.07 [0.00, 1.10]
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.6%	1.57 [0.80, 3.09]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	72.5%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2950197**		**2622788**	**99.6%**	**0.77 [0.60, 0.98]**
Total events	118		167			
Heterogeneity: Chi² = 10.38, df = 6 (P = 0.11); I² = 42%						
Test for overall effect: Z = 2.16 (P = 0.03)						
1.3.2 Studies in upper middle income countries						
Mohd Azri 2015 (16) Malaysia	1	9	2	49	0.4%	2.94 [0.24, 36.32]
Subtotal (95% CI)		**9**		**49**	**0.4%**	**2.94 [0.24, 36.32]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**2950206**		**2622837**	**100.0%**	**0.77 [0.61, 0.98]**
Total events	119		169			
Heterogeneity: Chi² = 11.39, df = 7 (P = 0.12); I² = 39%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.1%						

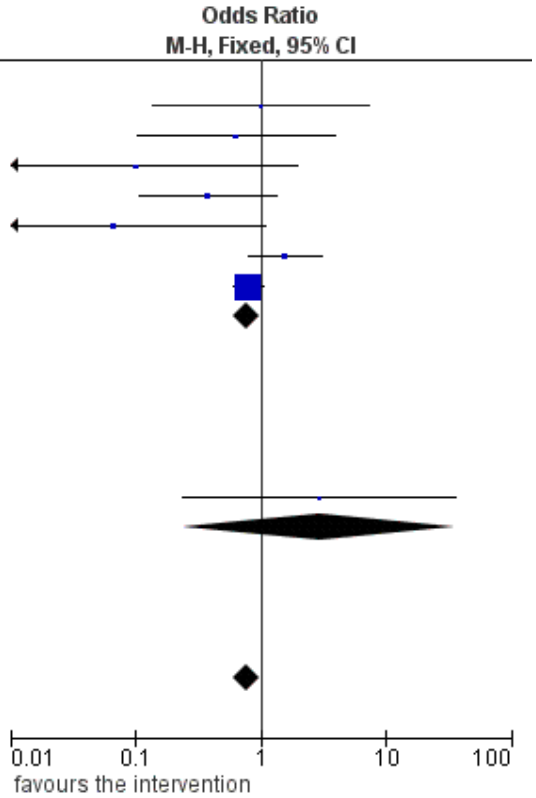


Figure S4. Subgroup analysis : Pooled effect of the NMCR on perinatal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Studies in low income countries						
Kongnyuy 2008 (27) Malawi	3	62	5	60	7.3%	0.56 [0.13, 2.45]
Kayinga 2016 (15) Uganda	27	180	27	180	34.6%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	56.9%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**330**		**629**	**98.8%**	**0.86 [0.60, 1.23]**
Total events	62		193			
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.4.2 Studies in upper middle income countries						
Mohd Azri 2015 (16) Malaysia	3	9	4	49	1.2%	5.63 [1.00, 31.49]
Subtotal (95% CI)		**9**		**49**	**1.2%**	**5.63 [1.00, 31.49]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**339**		**678**	**100.0%**	**0.92 [0.65, 1.30]**
Total events	65		197			
Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.49 (P = 0.63)						
Test for subgroup differences: Chi² = 4.39, df = 1 (P = 0.04), I² = 77.2%						

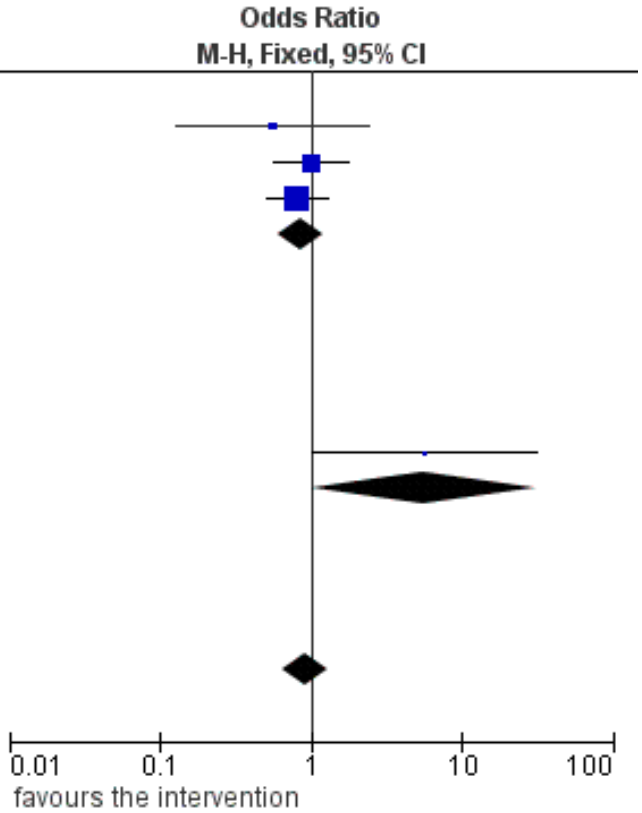


Figure S5. Funnel plot: effect of the NMCR on maternal mortality

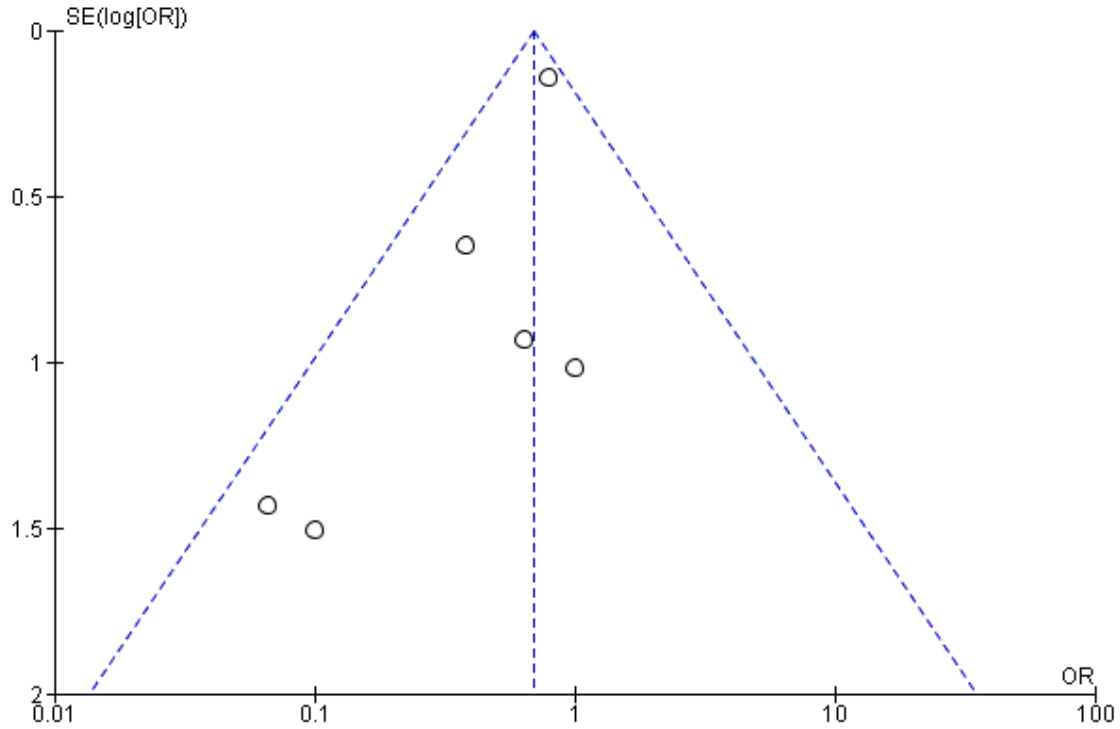
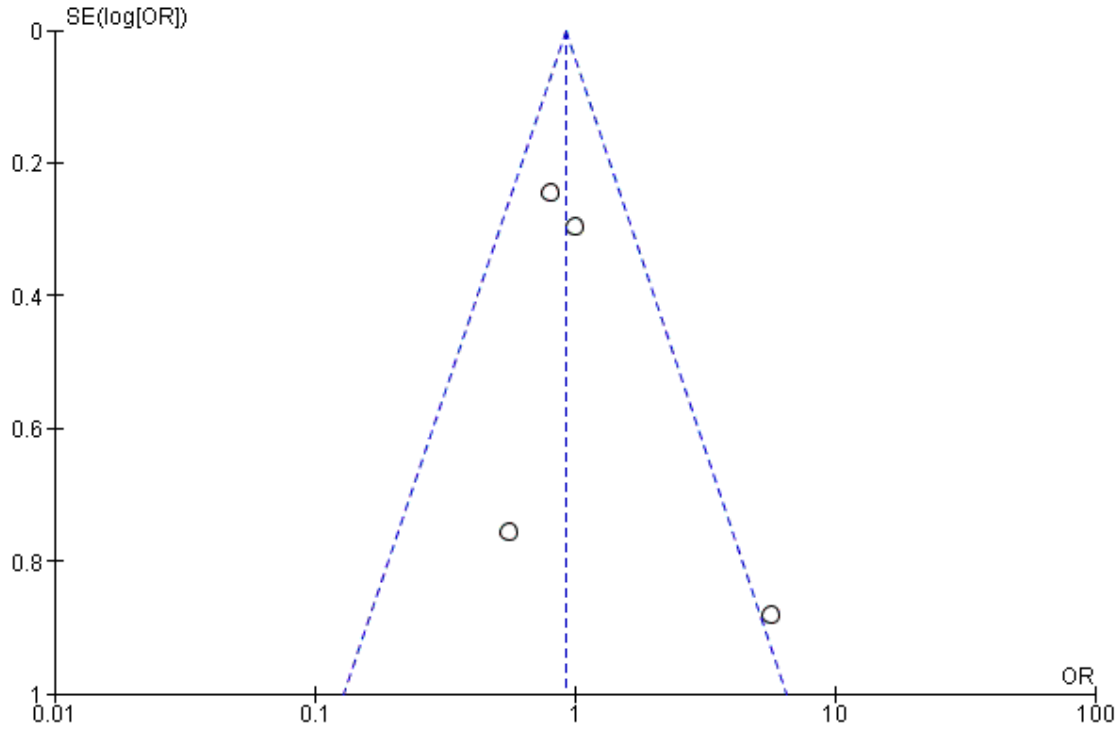


Figure S6. Funnel plot: effect of the NMCR on perinatal mortality



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	42 (box 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-4 Figure 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 Figure 1-2 e S1-S4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 Table S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 Figure S1-S6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-13

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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

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BMJ Open

Effectiveness of the facility based maternal near-miss case reviews in improving maternal and newborn quality of care in low and middle income countries: a systematic review

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Primary Subject Heading:	Global health
Secondary Subject Heading:	Health services research
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical audit < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS

Effectiveness of the facility based maternal near-miss case reviews in improving maternal and newborn quality of care in low and middle income countries: a systematic review

Running title: Effectiveness of NMCR on maternal and newborn quality of care in LMIC

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ABSTRACT

Objectives

The maternal near-miss case review (NMCR) has been promoted by WHO as an approach to improve quality of care (QoC) at facility level. This systematic review synthesizes evidence on the effectiveness of the NMCR on QoC and maternal and perinatal health outcomes in low and middle-income countries (LMIC).

Methods

Studies were searched for in six electronic databases (MEDLINE, Index Medicus, Web of Science, the Cochrane library, Embase, LILACS), with no language restrictions. Two authors independently screened papers and selected them for inclusion and independently extracted data. Maternal mortality was the primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care: efficacy, safety, efficiency, equity, accessibility and timely care, acceptability and patient-centered care.

Results

Out of 24,822 papers retrieved, 17 studies from 11 countries were included. Maternal mortality measured before and after the implementation of the NMCR cycle significantly decreased (odd ratio (OR) 0.77, 95%CI 0.61 to 0.98, eight studies, 5,5573,043 women; I^2= 39%). A statistically significant reduction in the incidence of uterine rupture, post-partum haemorrhage, and maternal sepsis was observed in three out of six studies. Ten studies reporting on maternal care process all showed some significant improvement when measured against pre-defined standards. All studies reported that the NMCR resulted in some amelioration of the facility structure (physical structure, staffing, equipment, training, organization of care). Newborn outcomes were overall poorly reported; four studies showed no significant difference in perinatal mortality. Patient satisfaction and equity were also poorly reported.

Conclusions

Policy makers may consider implementing the maternal NMCR cycle approach among strategies aiming at improving QoC and reducing maternal mortality and morbidity in LMIC. Future studies should better document the effectiveness of the NMCR cycle particularly on outcomes reflecting patient-centered care and cost-effectiveness.

Article summary: strengths and limitations of this study

- The maternal near-miss case review (NMCR) approach has been used in different settings; however, so far no systematic review has ever reported on its effectiveness. The present review fills an existing gap in evidence synthesis by reporting latest evidence on the effectiveness of NMCR cycle as a type of criterion base audit in low and middle-income countries (LMIC).
- Findings of this review are limited by the paucity of existing scientific literature: despite the NMCR approach has been utilised in many countries, such as China, India, South Africa and the WHO European Region, scientific literature reporting on the NMCR effectiveness is relatively scarce.
- Despite the above described limitations, this review collected an appreciable number of studies reporting on the impact of the NMCR cycle from different regions worldwide, including Africa, Central Asia, South East Asia, Latin America and Caribbean- and adds as new knowledge that this approach may be effective in reducing maternal mortality, and in improving quality of maternal and newborn health care at facility level.

Keywords

Near miss case review; quality of care; maternal health; perinatal health; low and middle income countries

Disclosure of interests

No competing interest

List of abbreviations

CBAs= controlled before-and after studies

CCTs= controlled clinical trials

ITSs= and intermittent time series

LMIC = low and middle-income countries

NMCR= Near miss cases review

OR= odds ratio

QoC= Quality of care

RCTs= randomised controlled trials (RCTs)

UCBAs=uncontrolled before and after studies

WHO = World Health Organization

BACKGROUND

Ensuring adequate quality of health care is a primary objective of the World Health Organization (WHO) Global Strategy for Women's, Children's and Adolescent's Health 2016-2030 (1,2). Quality in health care is recognized by WHO as essential for the health and well-being of the population, and as a basic aspect of human rights (2,3).

Among different approaches aiming at improving quality of care in maternity services, the maternal near-miss cases review (NMCR) approach was promoted by WHO and partners since 2004 within the strategy Beyond the Numbers (4). The facility-based individual NMCR cycle is defined as a type of criterion-based audit seeking to improve maternal and perinatal health care and outcomes by conducting a review, at hospital level, of the care provided to maternal near-miss cases (5). A maternal near miss case is defined as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within six weeks after pregnancy (5).

In the last 20 years, NMCR have been promoted as an alternative way to audit case management, more acceptable for health workers than mortality audits, which have been in use for many years (4,5). As a matter of fact, in low mortality settings or at the health service level, the number of maternal deaths is usually insufficient or not representative enough to allow reliable policy guidance (4). Moreover, discussing cases of deaths may have legal implications and may be perceived as challenging by hospital staff (4). Near-miss cases occur more frequently than maternal deaths, their review can directly inform on both strengths and weakness in the process of care, and it is usually perceived by staff as easier to perform than mortality audits (5,6).

The objective of the NMCR cycle is to identify areas amenable of improving quality of care, and finding and implementing solutions to the problems identified. Actions for improving quality of care are proposed and agreed by hospital staff, and subsequently monitored to check their implementation (5). This bottom-up approach aims at ensuring local ownership and facilitating team-building dynamics (5). Beside reviewing clinical management the NMCR can cover other domains involved with delivery of care, including availability of essential equipment, staffing, training, policies and organization of services (5). According to the WHO guidance (5) patients' experience of care should be collected through interviews and taken into account in developing recommendations aiming at improving quality of care.

The NMCR approach has been used in different settings (5); however, so far no systematic review has ever reported on its effectiveness. The objective of this review is to systematically evaluate and synthesise the evidence on the effectiveness of the NMCR cycle on the quality of care and on

maternal and perinatal health outcomes in low and middle-income countries (LMICs).

METHODS

Search strategy and eligibility criteria

In conducting this review we followed the guidelines reported in the PRISMA (Preferred Reporting Items for systematic reviews and meta-analyses) (7). A protocol including detailed methods of the review was developed before starting the review.

We searched up to September 2017 the following databases: MEDLINE through Pubmed (from 1956); LILACS (no date restrictions); Global Index Medicus (no date restrictions); Science Citation Index Expanded (SCI-EXPANDED) through Web of Science (no date restrictions); Social Sciences Citation Index (SSCI) through Web of Science (no date restrictions); Cochrane library (no date restrictions); Embase through OVID (from 1996). The search strategy is reported in **Box 1**. Manual searches of reference lists were also performed. We did not apply any language restrictions.

Studies were eligible for inclusion if they reported on the effectiveness (outcome) on maternal and perinatal health care (population) of the individual NMCR cycle at facility level (intervention), in a LMIC (setting), defined as for the World Bank definition at the time of the study (8). Given the paucity of randomised controlled trials (RCTs) on the subject, we also opted to include in this review non-randomized controlled clinical trials (CCTs), controlled before-and after studies (CBAs), uncontrolled before and after studies (UCBAs) and intermittent time series (ITSs). Qualitative studies were excluded. Both studies using the WHO definition of a maternal near-miss case published in year 2011 (9) or previous/locally adapted definitions, such as locally developed disease-specific definitions, were included. Studies reporting on interventions where the full audit cycle was implemented (ie including implementation of changes) were included, while studies only reporting descriptive findings of the case review (ie identifications of gaps in case management without developing and implementing recommendations) were not eligible. Abstracts and unpublished reports were also not eligible for inclusion.

Maternal mortality was predefined as our primary outcome. Secondary outcomes included any outcome informing on any of the six dimensions of quality of care (10), namely: efficacy (eg maternal morbidity), safety (eg adverse events), efficiency (cost), equity (eg equitable care), accessibility and timely care (eg access to care), acceptability and patient-centered care (eg patient satisfaction). Effectiveness on the quality of care is reported according the Donabedian model of quality improvement, which differentiates between: i) outcomes of care (eg health

outcomes, costs, satisfaction), ii) process of care (eg diagnosis and treatment); iii) and inputs/structure (eg physical structure, staffing, equipment and supplies, training, policies and organization of care) (11).

Data collection and analysis

Studies were selected for inclusion by two independent authors in two teams (VC and AE, ML and SR). Any disagreement was resolved through discussion. The full text of all eligible citations was examined in detail. Two authors (ML, SR) extracted data from included studies, using a pre-piloted data-extraction form. Disagreements were resolved by discussion between the two authors and consensus with a third author.

We extracted information regarding: study setting, design and duration; characteristics of the intervention; type of outcomes evaluated; effectiveness of the NMCR on the outcomes. For the study with ITS design we included in the metanalysis of maternal mortality the first and the last time point reported. Data on effectiveness were extracted as crude numbers or percentages. Data on maternal mortality were extracted as disease-specific maternal mortality when case reviews focused only on specific diseases, and as total maternal mortality when case reviews included all major obstetric emergencies.

When meta-analysis was possible and appropriate, for each outcome factor we generated a pooled odds ratio (OR) using the Mantel-Haenszel weighting method (12). Pooled data were presented in forest plots; data that could not be meta-analyzed was presented in tables and text. We tested the null hypothesis that all studies evaluate the same true effect by the Cochran's Q test, with two-sided $p<0.05$ considered statistically significant. The degree of heterogeneity between studies was assessed by visual inspection of the forest plots and I-squared (I2) statistic with its 95% confidence intervals, and interpreted according to the Cochrane manual (12).

The Cochrane 'Risk of bias' tool modified with the Cochrane Effective Practice and Organization of Care Group (EPOC) criteria for ITSs (12) was used to assess the risk of bias in included studies. We aimed at performing the following sensitivity analyses: i) removing the studies with high risk of bias; ii) removing studies including less than 300 cases and less than 30 events (ie cases of maternal death or perinatal death). We performed a subgroup analysis exploring the effect of NMCR in low-income countries (defined as for the World Bank definition at the time of the study (8)) compared to middle income countries.

RESULTS

Characteristics of the studies

The search yielded overall 24,822 records (**Figure 1**). Overall 17 papers (13-29) from Africa (Ghana, Ethiopia Malawi, Nigeria, Tanzania, Uganda), Europe and Central Asia (Kazakhstan, Moldova), South East Asia (Malaysia, Vietnam) and Latin America and Caribbean (Jamaica) met the inclusion criteria.

Characteristics of the study settings and design are summarized in **Table 1**. All except one study (23) were published during the last 15 years. Two papers referred to the same experience (20, 21); findings from these studies are jointly reported in the tables, and we used the most recent reference (20) to identify them. All studies were uncontrolled before and after-studies (UCBAs), describing the effectiveness of the NMCR cycle with a before and after analysis, except for two studies with ITS design (13, 22). Studies duration ranged from a minimum of 6 months (27) to a maximum of 26 months (29). Ten studies were held in an urban setting (13-17,19,20,25,28,29), three in a rural setting (22,24,27), and three in a mixed setting (18,23,26). One study was multi-centered (Ghana and Jamaica) (29). Among the 16 experiences reported, nine were of large size: one very large study In Malawi included 73 facilities in three districts (26); another three studies in Malawi enrolled respectively 29 and 13 facilities of different level and type (22,27), while one was conducted in one referral hospital plus several (number not further specified) health centres (24); a study in Ethiopia involved 10 public hospitals (17); studies in Kazakhstan, Vietnam, Ghana, Jamaica and Moldova involved six, five, four and three hospitals respectively (20,23,29,18). The remaining seven studies where single-center studies and took place in one teaching/tertiary level care hospital each.

Characteristics of the intervention are summarized in **Table 2**. In about half of the studies, cases were audited prospectively (15,17,18,20,22,24-26), while in the other studies audits were either conducted retrospectively (12,13,27), or retrospectively in a first phase then prospectively in the second phase (16,19,23,28,29). While in all cases the internal staff within the facility was involved in developing the recommendations, studies differed by who performed the case reviews: in most experiences audits were conducted by internal staff within the facility/ies, with the exception of four cases where a study investigator/physician audited the cases against pre-defined criteria and later presented it to hospital staff (13,19,25,29) and two cases where this information was not specified (15,16). Type of obstetric complications selected for audit included: severe pre-eclampsia/eclampsia (13,16,19,22,23,25-29), post-partum haemorrhage (13,20,22,23,25-27,29), obstructed labour (14,15,23,26,27,29), uterine rupture (24,25,29), infections (23,25,27),

complications of abortion (27). Five studies focused on one complication only (14-16,24,28) while in all other studies more than one condition was audited. In three studies, cases of maternal mortality were audited together with cases of near-miss (17,22,26). The criteria for case selection was "all cases occurring in the study period", except in one experience in Malawi where cases of particular educational interest were selected (24), and a study in Moldova where, despite no pre-defined criteria, it was observed that cases "more likely to lead to praises for the maternity team" were selected (18). The number of total cases audited in each study ranged widely, from 30 cases (18) to 2568 cases (17).

Only in four experiences, women were interviewed (14,15,18,20), but in one of them this was explicitly merely for recording bureaucratic details (15), rather than for the purpose of collecting women views and perspectives on quality of care received. All studies associated the audits with the development or implementation of standards of care (used also in most cases to perform the audits), while few studies also associated additional interventions for the hospital staff, such as development/dissemination of guidelines, and training on case management (13,15, 23).

As reported in **Table S1**, types of outcomes evaluated in the studies reported mostly on two dimensions of quality of care (10): effectiveness and accessibility and timely care. Outcomes related to the other dimension of quality of care, such as patient centrality and acceptability (eg patient satisfaction), efficiency and equity, safety (eg rate of adverse events, incident reporting) were not explored, with the exception of one study in Kazakhstan reporting on improved patients satisfaction (20) and one in Moldova reporting improved attitude towards patients (18).

Effectiveness of the NMCR cycle

Effectiveness on health outcomes

In a meta-analysis including eight studies, maternal mortality, measured before and after the implementation of the NMCR cycle, significantly decreased (OR 0.77, 95%CI 0.61 to 0.98, 5,5573,043 women, **Figure 2**), with relatively low heterogeneity between studies (I^2= 39%). An additional study from Uganda reported to have observed a reduction in maternal mortality, but data were not further made explicit (15).

Three out of six studies reported a statistically significant reduction in the incidence of the following preventable obstetric complications: uterine rupture, major post-partum haemorrhage, and maternal sepsis (**Table 3**).

Newborn outcomes were overall poorly reported. Of five studies documenting perinatal mortality,

fours could be included in the meta-analysis, showing no significant differences in perinatal deaths in the before and after period (OR 0.92, 95%CI 0.65, 1.30, **Figure 3**) with low heterogeneity between studies (I^2= 40%). The fifth study (14), conducted in Uganda, reported a significant reduction in the incidence of a combined outcome including perinatal severe morbidities, deaths and stillbirths (**Table 3**). Only one study reported on number of newborns admitted to ICU, without statistical difference in the before and after NCMR period (15). Another single study reported on Apgar score birth weight, without changes in the before and after period (16).
One study reported increased patient satisfaction after the implementation of the NMRC cycle (20).

Effectiveness on process outcomes

The effectiveness of the NMCR on the process of care is synthetized in **Table 3.** Ten studies reported on the process of care when measured quantitatively against pre-defined standards and all showed some significant improvements (13-16,19,23,25,27,28,29). Six studies reported other findings, such as improved case documentation, case-referral, use of partograph, monitoring, and improved team work (14,17,18,20,22,26).

Effectiveness on structure outcomes

Effectiveness on the structure is detailed in **Table 4**. All studies reported some improvements in one or more domains. Overall most frequent changes relate to: purchasing of essential equipment and supplies; additional training, monitoring and supervision; policies and organization of care including reorganisation of staff and their duties, implementation of systems aiming at standardising case management through dissemination of guidelines, checklists and monitoring forms, better coordination among different services.

Risk of bias and other analyses

All studies were rated as a high risk of bias based on the Cochrane and EPOC criteria (**Table S2**), mostly due to the study design (NCBA or ITS studies).
The sensitivity analysis showed that when studies with a very small sample size were excluded, the effect of the NMCR on maternal mortality becomes stronger than when all studies were included (OR 0.71, 95%CI 0.55 to 0.90, three studies I^2=86% **Figure S1).** The effect of NMCR on perinatal mortality did not significantly change in the sensitivity analysis (**Figure S2**).
Thirteen studies were held in low-income countries (13-15,17,19,22-27,28,29), two in upper middle-income countries (16,20), and one in a lower middle-income country (18) (**Table S3**). In the subgroup analysis, the effect of NMCR on maternal mortality was statistically significant in low

income countries (R 0.77, 95%CI 0.60 to 0.98, 7 studies), while only one small study could be included in the category of middle income countries, without statistical significance (**Figure S3).** The effect of NMCR on perinatal mortality was not affected by subgroup analysis (**Figure S4).** Funnel plots did not suggest publication bias (**Figure S5 and S6**).

DISCUSSION

This review suggests that the facility based individual maternal NMCR cycle may be an effective strategy for reducing maternal mortality in high burden countries, and for improving overall quality of maternal care in LMIC. Results of a pooled analysis of findings from eight studies showed that the NMCR cycle significantly reduced maternal mortality (OR 0.77, 95%CI 0.61 to 0.98, **Figure 2**), with relatively low heterogeneity of results (I^2=39%). Three out of six studies reported a significant reduction in the incidence of preventable obstetric complications such as uterine rupture, major post-partum haemorrhage, and maternal sepsis. Out of ten studies reporting on the process of care when measured against pre-defined standards all showed some statistically significant improvement. Additionally, in all studies the implementation of the NMCR cycle resulted in some amelioration in the structure of the hospital, such as an increased availability of essential equipment and supplies, additional training, monitoring and supervision, and the implementation of new policies and better organization of services.

Previous systematic reviews had observed a benefit of criterion-base audits in improving the quality of obstetric care (30-32). However, a review on the effectiveness of criterion-base audits in LMIC published some years ago concluded that, despite criterion-base audits being increasingly used, few studies had reported on their effectiveness (33). The present review retrieved all latest evidence on the effectiveness of NMCR cycle as a type of criterion-based audit, synthesized studies from LMIC in different geographical regions- including Africa, Central Asia, South East Asia, Latin America and Caribbean- and adds as new knowledge that this approach may be effective in reducing maternal mortality and in improving quality of health care provided.

Findings of this review are limited by the paucity of existing scientific literature: the NMCR approach has been utilized in many more countries than could be included in this reviews, such as China (34), India (35), South Africa (36), and the WHO European Region (37-41), but scientific literature reporting on the NMCR effectiveness in these countries could not be retrieved. Secondly, all included studies had an UCBA or ITS design, thus being exposed to a high risk of bias (although most studies checked for potential confounding factors, such as the case mix in the before and after phase). Despite these limitations, this review collected an appreciable number of studies, including also some large studies (17,22,26,27), reporting on the impact of the NMCR

cycle from different regions worldwide. Although quantitative findings of the review were to some extent affected by one large study (26), it must be acknowledge that results of most studies were in the same direction (figure 1), and in all studies some significant gains, either in the standards of care or in the process outcomes, were observed. In some studies, a significant benefit in maternal mortality or in standards of care could not be detected because in-hospital maternal mortality was too low (18,20) or because standards of care were already good at the baseline (13,23,27). Ideally, it will be advisable to perform large multicenter RCTs to properly document NMCR effectiveness. However, in practice conducting a RCT on criterion-based audit alone may be challenging, and may even be perceived as unethical, if no appropriate comparison is chosen. This is because in current practice criterion based audits are already one of the recommended strategies to improve quality of care promoted by many agencies and bodies, such as the National Institute for Clinical Excellence (NICE) (42). Notably, the review of "near-miss" cases is already recommended by WHO as a "key action to eliminate avoidable maternal and perinatal mortality and morbidity and improve the quality of care" (43) and as such it is already implemented in several countries.

The audit of maternal near miss cases is an approach also utilized in several high-income settings: UK has a well-established programme of confidential enquiries into maternal deaths and a national system for research on maternal near-miss-the UK Obstetric Surveillance System (UKOSS) (44,45); New Zealand established a national system for severe maternal morbidity review (46); several countries within the International Network of Obstetric Survey Systems (INOSS) are collecting data on severe maternal morbidities for study purposes (47), while other countries such as Italy (ITOSS) are starting the implementation of near-miss audits (48,49). Although there are some differences in the type of interventions applied (eg not all of these approaches are facility based), still the existence of these large networks on maternal near miss case reviews and the amount of resources devoted to them somehow testify the importance recognized in reviewing near miss cases.

In the future, rather than investing resources in exploring whether near miss audits or criterion-based audits in general are overall effective, it will be more interesting to explore which characteristics make them effective and sustainable. Available literature synthesised in this review does not allow for directly comparing the effectiveness of different methodologies on how to perform audits in practice, but at least it does provide some useful starting point for discussion and for future research. First, with regards to the number of cases audited, this varied largely in the included studies from a minimum of less than 10 cases per year (18,20) to a maximum of several hundred cases in a few months (14,29), with a third approach consisting in performing a large retrospective review of past cases as the baseline, and then collecting fewer new cases prospectively. When many cases were reviewed, this allowed for an in depth description of the

gaps in care. However, the analysis of a large number of cases does not necessarily ensure the development of good recommendations for quality improvement, neither their implementation. Additionally, the sustainability of auditing on a large number of cases, outside a research setting with dedicated human and economic resources, is questionable. Studies included in this review suggest that even the periodic review of few cases may help identifying gaps in routine care, developing SMART recommendations (ie Specific, Measurable, Achievable, Realistic, Time-bound (50)), and improving quality of care significantly (18,20). WHO recommends to organise one session of NMCR per month, and to review in each session few cases (one or two), but pretends a high quality in the process: each session should start by checking if previous recommendations have been implemented; there should be a in depth discussion of the underlying causes of the near miss event ("why but why" approach); recommendations should be SMART; regular sessions should be organised; dissemination of results should be ensured, etc (5). At first few facilities should be selected for pilot implementation, and the NMCR approach should be further scaled up only when quality in the process has been ensured.

Secondly, studies included in this review revealed that most experiences of implementation of NMCR cycles were externally supported, either by the WHO, academia, and/or other development partners (15,18,20-24,26-28). This is in line with other existing literature (51,52) highlighting that in particular the second part of the audit cycle (ie developing recommendations, implementing them, checking on progress) is in general problematic and usually less well conducted compared to the first part of the audit cycle. The attitude to openly discuss cases within a multidisciplinary team and agreeing solutions was described as challenging in different settings, especially for mid-level staff (midwives, nurses) who may not be used to voice their views in the presence of doctors and managers (18,20). Hospital staff, managers included, often do not receive any formal training in quality improvement methods or any guidance in correctly performing an audit cycle. The need for ensuring sustained external support, and for establishing a functional quality assurance mechanism, are recognised by WHO as crucial for ensuring an effective NMCR implementation (5).

Thirdly, although having a single person appointed to perform the case-review - as performed in some studies included in this review (18,10,25,29) - may increase feasibility, this actually largely reduces ownership of the process, together with minimizing occasions for discussion and team building among staff. Studies noted that involvement of all health care providers in the audit process promoted successful implementation, ownership and sustainability of the process (14,20,28). The involvement of mid level staff such as nurses and midwives was reported to result in improved staff autonomy and team work (14,21,27). Some studies observed that participation of the senior management promoted the implementation of recommendations that required allocation

of resources and changes in policies and organisation of care (26,28). Currently the WHO approach (5) recommends the NMCR to be performed by the staff who managed the cases, including nurses, midwives, and any other staff directly or indirectly involved in case management.

Fourthly, the patient experience of care was assessed only in very few of the existing studies, and yet not fully taken into account. In the last few years, WHO has given increasing importance to patient experience of care (1). Listening to women's views may provide important information, as testified by studies in Brazil, Rwanda and the UK (53-55) and by a study in Iran where women's views were successfully used to improve quality of care (56). Currently WHO recommends to always interview women and their families and to use their inputs for improving care (5).

Finally, as pointed out by authors of the included studies, interventions aiming at improving quality of care without strengthening the health systems and improving community awareness may have minimal success (15,22). A study in Malawi reported that availability of essential supplies, such as blood for transfusions, remained low even after the NMCR due to health system failures and this clearly was a barrier for improving case management (22). Qualitative findings, collected through focus groups among staff in a study in Uganda (15), pointed out, among issues that may have hampered the effectiveness of NMCR, health facility factors such as: stock-out of essential supplies, shortage of human resources, lack of task allocation, inadequate supervision. However, in most studies, even if the number of staff and available resources remained stable in the before and after phase, as a result of the audit there was a reorganization of staff activities, such as better specification of roles and responsibilities, task shifting, and improved communication (14,16,17,20,28).

Cost of the NMCR approach in improving health outcomes and quality of care was not formally evaluated in the retrieved studies. However, several papers stated that the NMCR was an inexpensive and simple intervention, requiring little technology (24,26-28). A study involving 12 health centres in Malawi reported that each audit meeting cost about 150 US $, including foods and transport of participants to the District Hospital (27). Another study in Uganda stated "the audit process had challenged the assumption that all quality improvements need to be externally provided and are expensive" (28). These findings are in line with a systematic review of barriers and facilitators for effective NMCR implementation, reporting that a relatively low budget is needed to facilitate activities (37). In some experiences, the NMCR improved use or availability of existing economic resources: in Malawi, it "promoted a wiser allocation of resources for maternity care at the district level" (27); in Uganda a fundraising committee was established to raise funds for drugs and equipment needed according to the recommendations (28).

CONCLUSIONS

Implication for policy and research

Among other strategies to reduce maternal mortality and morbidity and for improving the quality of maternal and perinatal care, policy makers may consider the implementation of the maternal NMCR cycle approach.

Researchers should aim at generating more evidence on how to effectively implement the NMCR cycle, how to improve its impact on newborn outcomes and on outcomes reflecting patients' centrality (such as patient satisfaction and/or perception of quality of care received), together with documenting the cost effectiveness of the NMCR approach.

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Conflict of interest

None

Role of authors

ML conceived the papers, screened the study, extracted data, drafted the paper and finalised the paper. SR, VC, AE screened the study, extracted data and revised the first draft.

Data Sharing statement

All details of the analyses conducted are provided within the manuscript

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TABLES

Box 1. Search strategy

PubMed **Date: Sept 15, 2017** **Total retrieved: 5578**

"near miss" OR (audit AND (obstetric* OR matern* OR pregnan* OR woman OR women))

Lilacs **Date: Sept 15, 2017** **Total retrieved: 227**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Global Idex Medicus **Date: Sept 15, 2017** **Total retrieved: 7806**

(TW:near miss OR MH:near miss) OR ((TW:audit OR MH:audit OR TW:auditoria OR MH:auditoria OR auditoría) AND (gravid$ OR pregnan$ OR enceint$ OR embarazad$ OR obstetr$ OR mulher$ OR mujer$ OR femme$ OR woman OR women OR matern$))

Web of Science **Date: Sept 18, 2017** **Total retrieved: 4850**

TS= "near miss" OR (TS=audit AND TS=(gravid* OR pregnan* OR obstetr* OR woman OR women OR matern*))

Cochrane Library **Date: Sept 15, 2017** **Total retrieved: :411**

"near miss" OR (audit AND (gravid* or pregnan* or obstetr* or woman or women or matern*))

EMBASE **Date: Sept 15, 2017** **Total retrieved: 5927**

1 ("near miss" or audit).ab. (34259)
2 (obstetric* or matern* or pregnan* or woman or women).ab. (1057153)
3 1 and 2 (4764)
4 ("near miss" or audit).ti. (13725)
5 (obstetric* or matern* or pregnan* or woman or women).ti. (325314)
6 4 and 5 (724)
7 3 or 6 (4962)

Table 1. Study settings, designs and sample sizes

Author	Design	Duration	Country	Setting	Number and type of hospitals §
Lumala 2017 [13]	ITS	10 months	Uganda	Urban	1 tertiary specialist hospital, catholic funded private non profit
Mgaya 2017 [14]	NCBA	25 months	Tanzania	Urban	1 tertiary specialist hospital
Kayiga 2016 [15]	NCBA	7 months	Uganda	Urban	1 tertiary specialist hospital
Mohd Azri 2015 [16]	NCBA	2 years	Malaysia	Urban	1 tertiary specialist hospital
Gebrehiwot 2014 [17]	NCBA	18 months	Ethiopia	Urban	10 public hospitals
Baltag 2012 [18]	NCBA	13 moths	Moldova	Mixed	3 mixed (referral-level facilities at municipal, national and district levels)
Kidanto 2012 [19]	NCBA	3 years	Tanzania	Urban	1 teaching hospital
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	NCBA	2 years	Kazakhstan	Urban	6 mixed (national research centre, regional and city hospitals)
Van den Akker 2011 [22]	ITS	2 years	Malawi	Rural	29 mixed (1 referral hospital and 28 government, private and mission smaller facilities)
Bailey 2010 [23]	NCBA	2 years	Vietnam	Mixed	5 mixed (provincial, area and district)
Van den Akker 2009 [24]	NCBA	1 year	Malawi	Rural	1 referral hospital + undefined numbers of health centers
Hunyinbo 2008 [25]	NCBA	13 months	Nigeria	Urban	1 tertiary specialist hospital
Kongnyuy 2008 [26]	NCBA	2 years	Malawi	Mixed	73 mixed (hospitals, health centers)

Kongnyuy 2008 [27]	NCBA	6 months	Malawi	Rural	1 one district hospital, 12 satellite health centers
Weeks 2005 [28]	NCBA	20 months	Uganda	Urban	1 teaching hospital
Wagaarachchi 2001 [29]	NCBA	26 months	Ghana and Jamaica	Urban	4 district hospitals

Abbreviations: NCBA= non controlled before and fater study, ITS= Intermittent time series

Table 2. Characteristics of the interventions

Author	Characteristics of the audit	Who performed the audit	Who developed the recommendations	Type of cases audited	Selection criteria	N Case audited (before / after)	Woman Interview
Lumala 2017 [13]	two phases, retrospective	medical doctor	facility staff	PPH and severe pre-eclampsia, eclampsia	All in-patient cases in the study period, not referred and not receiving hydralazine or magnesium sulphate from the referring unit	238 (125 before, 133 after)	no
Mgaya 2017 [14]	two phases, retrospective	trained postnatal ward nurses, s (a consultant, a specialist and a midwife were also available for consultation)	facility staff (AN, L, MO, MW, P)	obstructed labour	All cases of obstructed labour with a single foestus in cephalic presentation, and no other severe medical conditions or PROM	510 (260 before, 250 after)	Yes
Kayiga 2016 [15]	two phases, prospective	NR	facility staff (MO, MW, M)	obstructed labour	all cases occurring in the study period	360 (180 before, 180 after)	yes
Mohd Azri 2015 [16]	first phase retrospective, second regular prospective	NR	facility staff (members of the obstetric department)	eclampsia	all cases occurring in the study period	51 (42 before, 9 after)	no
Gebrehiwot 2014 [17]	prospective	facility staff (MO, MW and other hospital staff + focal person)	facility staff	all NM + MD	all cases occurring in the study period	2568	no
Baltag 2012 [18]	prospective	facility staff involved in case management (MO, MD +	facility staff involved in case management (MO, MD +	NM	not pre-defined criteria, cases were chosen by director	30 approx (1 case per month in each hospital)	yes

		occasionally L, T, PHC)	occasionally L, T, PHC)				
Kidanto 2012 [19]	first phase retrospective, second prospective	1 senior doctor	facility staff	eclampsia and pre-eclampsia	all cases occurring in the study period	477 (389 before, 88 after)	no
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	prospective	facility staff	facility staff	PPH and severe pre-eclampsia	NR	not more than 10 in each hospital each year	yes
Van den Akker 2011 [22]	prospective every 2 to 3 weeks;	facility staff, occasionally external obs gyn	facility staff	infection, PPH, uterine rupture, preeclampsia, others) + MD	all cases occurring in the study period	45 (24 deaths; 21 SOC)	no
Bailey 2010 [23]	first phase retrospective, than regular prospective	facility staff (MO, N, M)	facility staff (MO, N, M)	severe preeclampsia, postpartum infection, prolonged/obstructed labour, PPH, organisation of emergency service	all cases occurring in the study period	558 (312 before, 246 after)	no
Van den Akker 2009 [24]	prospective every 2- 3 weeks for 3 months	facility staff (M,MA, MO, MW,N); 2 external obstetricians in the second phase	facility staff (MO, N, M)	uterine rupture	cases that appeared to be of particular educational value to the PI or any other hospital staff	35	no

Hunyinbo 2008 [25]	two phases, prospective	study investigator/s	facility staff (M,MA, MO, N,P, L)	PPH, uterine rupture, eclampsia, obstructed labour, sepsis	all cases occurring in the study period	130 (65 before, 65 after)	no
Kongnyuy 2008 [26]	two phases, prospective	facility staff (AN,M,MO,MW, L,T)	facility staff (quality improvement team)	PPH, obstructed labour, sepsis, preeclampsia/ eclampsia, neonatal care, CS , women-friendly care+ MD	NR	NR	no
Kongnyuy 2008 [27]	two phases, retrospective	district team (N, MW, CO,AN,T)	hospital staff (quality improvement team)	pre-eclampsia/ eclampsia, PPH, prolonged/ obstructed labour, retained placenta, sepsis, complications of abortion, ectopic pregnancy	all cases occurring in the study period	122 (60 before, 62 after)	no
Weeks 2005 [28]	first phase retrospective, second prospective	facility staff (including low grade staff)	facility staff	severe pre-eclampsia	all cases occurring in the study period	86 (43 before, 43 after)	no
Wagaarachchi 2001 [29]	first phase retrospective, second prospective	non-medical assistants (10% of cases validated by independent re-review)	facility staff (M,MO, M + all relevant staff)	PPH, eclampsia, infection, obstructed labor, uterine rupture	all cases occurring in the study period	889 (551 before, 338 after)	no

Abbreviations: AN= anesthetist of anesthetic technician, CO=clinical officer, CS= caesarian section, L= Laboratory, M= manager, MA=medical assistant, MD= maternal deaths, MO=medical officer, MW=midwife, N=nurse, ND= neonatal deaths, NM=Near miss, NR= not reported,P=Pharmacy, PHC= primary health care staff, PPH= post-partum hemorrhage, PROM= premature rupture of membranes, SOC= all severe obstetric cases, SEL= selected obstetric cases, T= technician

Table 3. Effectiveness of the NMCR cycle on morbidity and on process outcomes

Author	Morbidity and other health outcomes	Standards of care	Other process outcomes
Lumala 2017 [13]	_	Eclampsia and pre-eclampsia: 7/10 standards PPH: 3/4 standards	-
Mgaya 2017 [14]	SAMM (incidence: 9.0% vs. 8.8% (p = 0.98). Uterine rupture (incidence): 1/260 vs 0/250 (p=0.49) Perinatal severe morbidities and deaths and fresh stillbirths: 16% vs. 8.8% (p = 0.01)	Obstructed labour: 6/10 standards on diagnosis, 6/10 standards on case management	Significant reduction of time needed from decision to perform a caesarian section to delivery (mean difference:- 30 minutes, p< 0.001)
Kayiga 2016 [15]	Uterine rupture (Incidence): 8/180 vs 2/180 (p=0.04) Maternal sepsis (Incidence): 10/180 vs 2/180 (p=0.02) Post-spinal headache (incidence): 0/180 vs 13/180 (p<0.001) Baby admitted to intensive care: 27/180 vs 31/180 (p=0.61)	Obstructed labour: 2/6 standards, 4/13 measures of standards	-
Mohd Azri 2015 [16]	Eclampsia (incidence): 42/44818 vs 9/10784 (p> 0.05) Recurrent eclamptic fits: 8/42 vs 1/9 (p> 0.05) Newborn babies with Apgar score (< 7) at 5 minutes after birth: 8/42 vs 3/9 (p> 0.05) Birth weight less than 2500g 22/42 vs 5/9 (p> 0.05)	Improved adherence to 2/2 audit criteria that where substandard in the first phase (all other 10 criteria were already according to standards at baseline)	-
Gebrehiwot 2014 [17]	-	-	Reducing waiting time
Baltag 2012 [18]	-	-	Improved medical records Improved attitude towards patients
Kidanto 2012 [19]	-	Eclampsia and pre-eclampsia: 10/16 standards	Improved records keeping
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]	Improved patient satisfaction (NR)	-	Improved case management and monitoring (eg weighing of blood losses and documenting systematically)

Van den Akker 2011 [22]	SAMM (Incidence): 33/2295 vs 49/5291 (p=0.08) Major PPH (incidence): 17/2295 vs 15/5291 (p=0.006) Uterine rupture (Incidence): 14/2295 vs 4/5291 (p=0.03) Severe pre-eclampsia (Incidence): 6/2295 vs 16/5291 (p=0.3) Maternal infections (Incidence): 10/2295 vs 14/5291 (p=0.6)	-	Improved patients monitoring
Bailey 2010 [23]	-	Eclampsia: 12/18 standards Infections: 11/23 standards Obstructed labour: 1/1 standards PPH: 3/3 standards	-
Van den Akker 2009 [24]	Uterine rupture (incidence): 16/833 vs 19/3099 (OR 0.32; 95% CI, 0.16–0.63)	-	-
Hunyinbo 2008 [25]		SAMM: 8/31 standards	-
Kongnyuy 2008 [26]	-	-	Significant increase in the met need for EmOC (15.2% for 2005, 17.0% for 2006 and 18.8% for 2007, p for trend < 0.001).
Kongnyuy 2008 [27]	-	SAMM: 4 /7 standards (other criteria were already according to standards at baseline)	-
Weeks 2005 [28]	Eclampsia (incidence): 5/43 vs 5/43 (p> 0.05)	Severe pre-eclampsia: 5/9 standards	-
Wagaarachchi 2001 [29]	-	SA: 8/31 standards	-

Abbreviations: CFR= case fatality rate; MM= maternal mortality; MMO= maternal morbidity; NM= neonatal mortality; NR= not further specified; PM: perinatal mortality; PPH= post partum hemorrhage; SAMM: severe acute maternal morbidity

Table 4. Effectiveness of the NMCR cycle on the structure

Author	Physical structure	Staffing	Equipment and supplies	Training, monitoring and supervision	Local policies and organization of services
Lumala 2017 [13]					
Mgaya 2017 [14]				training on partograph, improved supervision	Improved dissemination and use of guidelines, Improved team work and internal communication among hospital staff
Kayiga 2016 [15]					Re-engineering hospital Red Alert System: list of responsible person to be contacted during Red Alert activation was put up in all obstetrics facilities; Information on the importance of activating the Red Alert in eclampsia cases was disseminated to all staff; hospital telephone operator was informed regarding existence of this system and how it functions.
Mohd Azri 2015 [16]		Better specification of roles and responsibilities		Training, improved awareness of standards, improved patient education	Reorganization of “red alert” system
Gebrehiwot 2014 [17]	Some hospitals expanded accommodate more cases	Staff organization: duties assignment; staff rotation every 12 h to avoid tiredness	Contribution of resources (stationery, transport)	Provision of training and feedback to health centers	Improved dissemination of protocols, increased use of partograph, Improved documentation and reporting improved coordination with health centers,
Baltag 2012 [18]			Improved equipment and supplies		Improved dissemination of protocols, organization of care and management
Kidanto 2012 [19]		Improved doctor availability 24/24h	Additional equipment purchased	Training	Improved dissemination of protocols, monitoring forms, reorganization of daily routine and setting of priorities, doctors assigned to manage cases of

					eclampsia
Sukhanberdiyev 2011 [20] **Hodorogea 2010** [21]		Rational use of staff by internal redistribution, optimization of human resources by reducing the working hours, increased role of mid-level staff (midwives and nurses)	Mobile devices for timely alert and warning, drugs and blood components, prostaglandins and uterotonics	Training on protocols and standards, periodic drills, improving time management skills	Developing, diffusing and use new evidenced-based protocols, developing emergency care algorithms and conditions for transportation from remote areas, identifying the responsible person for the readiness of the emergency kit, monitoring forms, weighing of blood losses and documenting systematically
Van den Akker 2011 [22]				Training, regular on job coaching, improved supervision, monitoring of ambulance use	Improved dissemination of protocols and use of partograph, doctors to visits critically ill patients at least once a day
Bailey 2010 [23]			Purchase of equipment (lab, car for oncall, telephone for emergency), wall flow charts	Training, supervision	Leadership on implementing changes, standardization of treatment with protocols and checklists, team work record keeping
Van den Akker 2009 [24]			More ambulances	Training, supervision, follow up visits in health centers	Improved dissemination of protocols, transport organization, organize session for theater staff with the intention to reduce delay in surgical care
Hunyinbo 2008 [25]			Pharmacy supply including oxytocins, MgSO4, blood and coagulation tests		Improved dissemination of protocols, clinical meetings, observational and fluid balance charts
Kongnyuy 2008 [26]	The number of comprehensive and basic EmOC facilities				

	did not change				
Kongnyuy 2008 [27]		Autonomy in decision making in MW-N	Better equipment and set up of service	Training	Reorganization of emergency care service, including use of ambulances,
Weeks 2005 [28]		Staff in the labour room reorganised giving each member a specific role in the management of emergencies; two extra midwives	Equipment (urine dipstick, BP machines)		Triage established, leadership (direct of labour appointed), protocol and chart, commitment to improve medical files, departmental meetings, fundraising (a fundraising committee was established to raise funds for the drugs and equipment in recommendations)
Wagaarachchi 2001 [29]			Record storage, blood cultures, structured patient records		Improved dissemination of protocols, reviewing supervisory responsibilities, organization of regular clinical meetings

Abbreviations: BP= Blood pressure; EmOC= Emergency Obstetric Care; N= Nurses; M=Midwives

LEGENDS

FIGURES

Figure 1. Study Flow Diagram

Figure 2. Pooled effect of the NMCR on maternal mortality

Figure 3. Pooled effect of the NMCR on perinatal or neonatal mortality

SUPPLEMENTARY TABLES

Table S1. Type of outcomes evaluated in the studies

Table S2. Risk of bias

Table S3. World bank classification of country income

SUPPLEMENTARY FIGURES

Figure S1. Sensitivity analysis: Pooled effect of the NMCR on maternal mortality in studies with at least 300 cases and 30 events

Figure S2. Sensitivity analysis: Pooled effect of the NMCR on perinatal mortality in studies with at least 300 cases and 30 events

Figure S3. Subgroup analysis Pooled effect of the NMCR audit on maternal mortality by country income

Figure S4. Subgroup analysis: Pooled effect of the NMCR on perinatal mortality by country income

Figure S5. Funnel plot: effect of the NMCR on maternal mortality

Figure S6. Funnel plot: effect of the NMCR on perinatal mortality

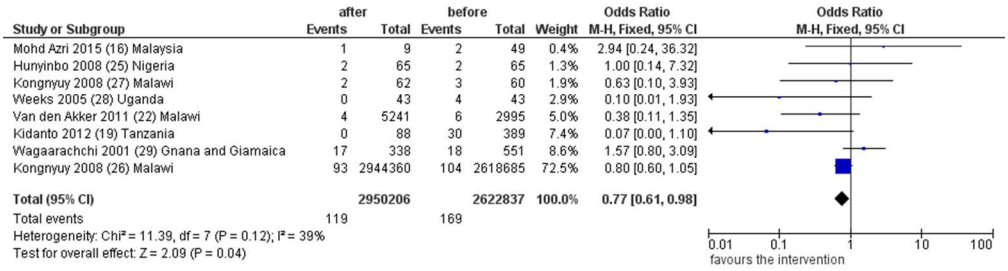

Figure 1. Study Flow Diagram

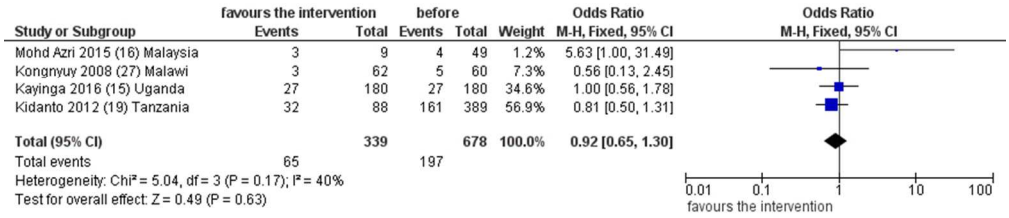

Figure 2. Pooled effect of the NMCR on maternal mortality

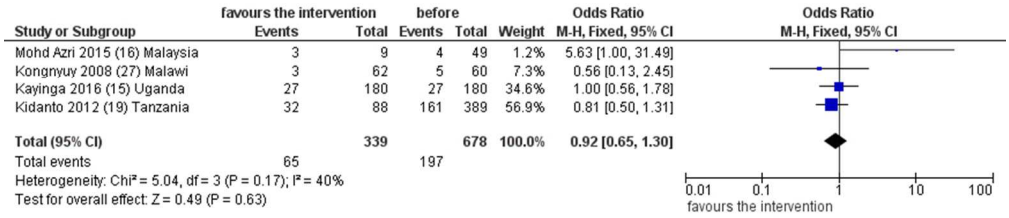

Figure 3. Pooled effect of the NMCR on perinatal or neonatal mortality

Figure S1. Sensitivity analysis : Pooled effect of the NMCR on maternal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Studies with at least 300 cases and 30 events						
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.5%	1.57 [0.80, 3.09]
Kidanto 2012 (19) Tanzania	0	88	30	88	19.8%	0.01 [0.00, 0.18]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	71.8%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**2944786**		**2619324**	**100.0%**	**0.71 [0.55, 0.90]**
Total events	110		152			
Heterogeneity: Chi² = 14.50, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Test for subgroup differences: Not applicable						

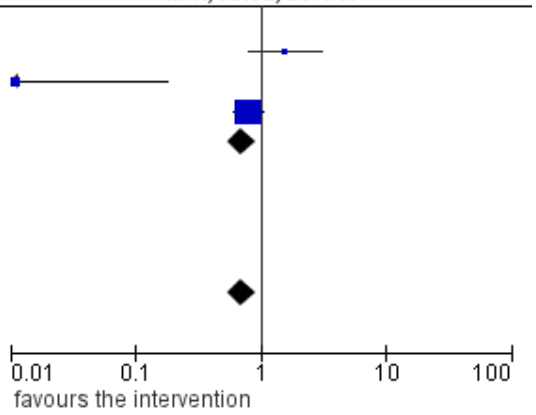

Figure S2. Sensitivity analysis : Pooled effect of the NMCR on perinatal mortality in studies with at least 300 cases and 30 events

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Studies with at least 300 cases and 30 events						
Kayinga 2016 (15) Uganda	27	180	27	180	37.8%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	62.2%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**268**		**569**	**100.0%**	**0.88 [0.61, 1.27]**
Total events	59		188			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						

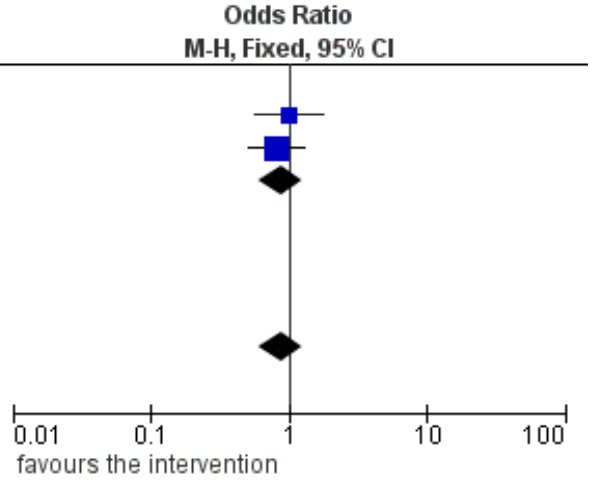

Figure S3. Subgroup analysis : Pooled effect of the NMCR audit on maternal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Studies in low income countries						
Hunyinbo 2008 (25) Nigeria	2	65	2	65	1.3%	1.00 [0.14, 7.32]
Kongnyuy 2008 (27) Malawi	2	62	3	60	1.9%	0.63 [0.10, 3.93]
Weeks 2005 (28) Uganda	0	43	4	43	2.9%	0.10 [0.01, 1.93]
Van den Akker 2011 (22) Malawi	4	5241	6	2995	5.0%	0.38 [0.11, 1.35]
Kidanto 2012 (19) Tanzania	0	88	30	389	7.4%	0.07 [0.00, 1.10]
Wagaarachchi 2001 (29) Gnana and Giamaica	17	338	18	551	8.6%	1.57 [0.80, 3.09]
Kongnyuy 2008 (26) Malawi	93	2944360	104	2618685	72.5%	0.80 [0.60, 1.05]
Subtotal (95% CI)		**2950197**		**2622788**	**99.6%**	**0.77 [0.60, 0.98]**
Total events	118		167			
Heterogeneity: Chi² = 10.38, df = 6 (P = 0.11); I² = 42%						
Test for overall effect: Z = 2.16 (P = 0.03)						
1.3.2 Studies in upper middle income countries						
Mohd Azri 2015 (16) Malaysia	1	9	2	49	0.4%	2.94 [0.24, 36.32]
Subtotal (95% CI)		**9**		**49**	**0.4%**	**2.94 [0.24, 36.32]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**2950206**		**2622837**	**100.0%**	**0.77 [0.61, 0.98]**
Total events	119		169			
Heterogeneity: Chi² = 11.39, df = 7 (P = 0.12); I² = 39%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.1%						

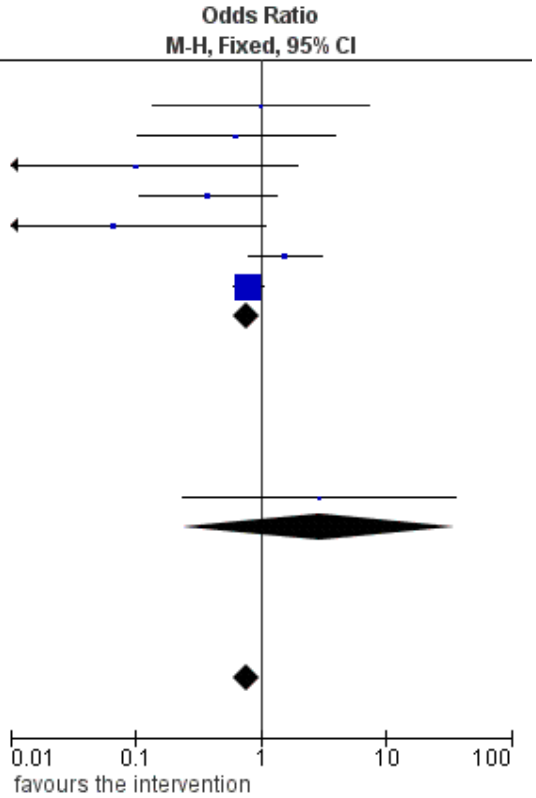

Figure S4. Subgroup analysis : Pooled effect of the NMCR on perinatal mortality by country income

Study or Subgroup	after Events	after Total	before Events	before Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Studies in low income countries						
Kongnyuy 2008 (27) Malawi	3	62	5	60	7.3%	0.56 [0.13, 2.45]
Kayinga 2016 (15) Uganda	27	180	27	180	34.6%	1.00 [0.56, 1.78]
Kidanto 2012 (19) Tanzania	32	88	161	389	56.9%	0.81 [0.50, 1.31]
Subtotal (95% CI)		**330**		**629**	**98.8%**	**0.86 [0.60, 1.23]**
Total events	62		193			
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.4.2 Studies in upper middle income countries						
Mohd Azri 2015 (16) Malaysia	3	9	4	49	1.2%	5.63 [1.00, 31.49]
Subtotal (95% CI)		**9**		**49**	**1.2%**	**5.63 [1.00, 31.49]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**339**		**678**	**100.0%**	**0.92 [0.65, 1.30]**
Total events	65		197			
Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.49 (P = 0.63)						
Test for subgroup differences: Chi² = 4.39, df = 1 (P = 0.04), I² = 77.2%						

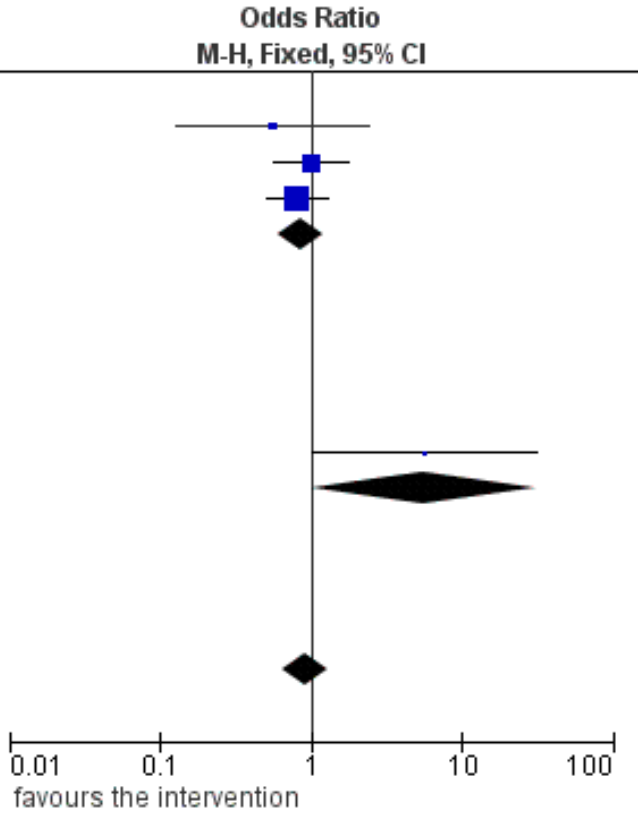

Figure S5. Funnel plot: effect of the NMCR on maternal mortality

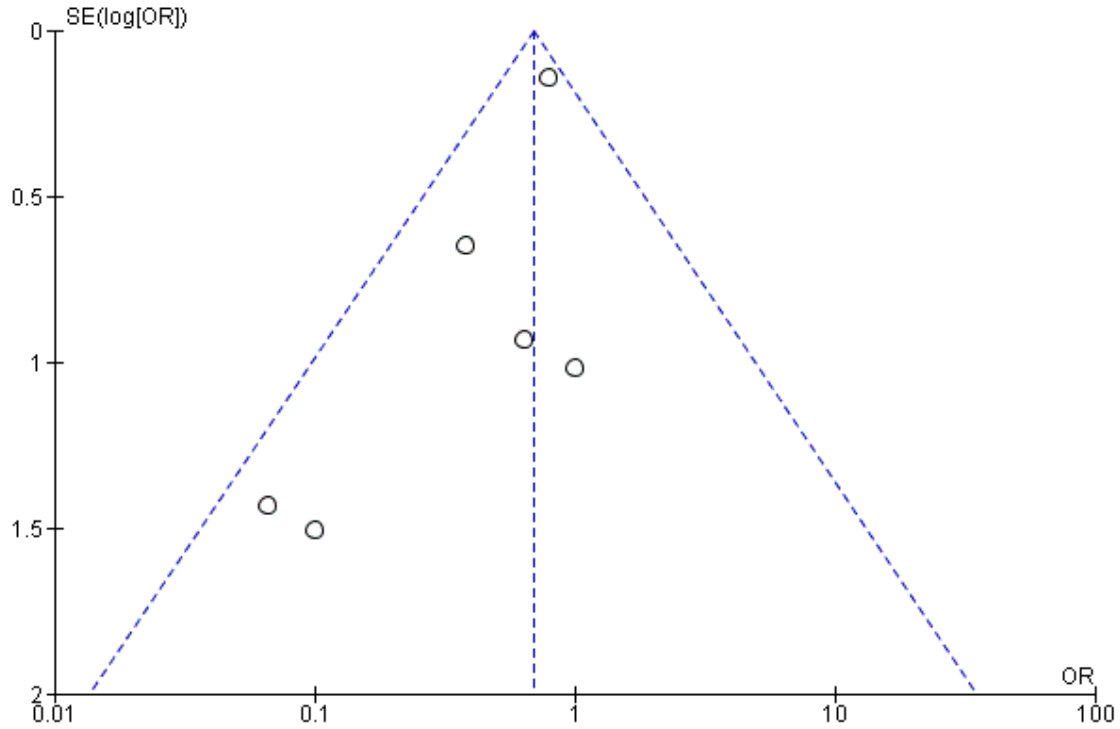

Figure S6. Funnel plot: effect of the NMCR on perinatal mortality

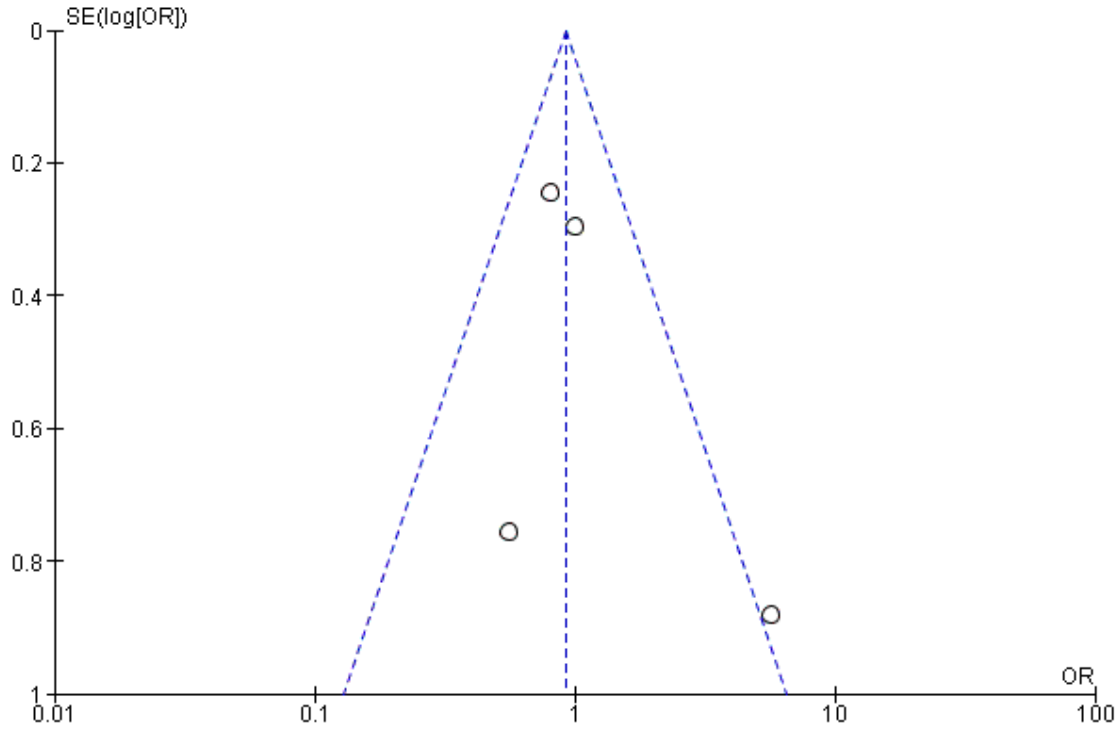

Table S1. Type of outcomes evaluated in the studies

Author	Patient centrality and acceptability	Accessibility Timely care	Efficiency and equity	Safety	Effectiveness
Lumala 2017 [13]	—	yes	—	—	yes
Mgaya 2017 [14]	—	yes	—	—	yes
Kayiga 2016 [15]	—	—	—	—	yes
Mohd Azri 2015 [16]	—	—	—	—	yes
Gebrehiwot 2014 [17]	—	yes	—	—	yes
Baltag 2012 [18]	yes	—	—	—	yes
Kidanto 2012 [19]	—	yes	—	—	yes
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	yes	yes	—	—	yes
Van den Akker 2011 [22]	—	yes	—	—	yes
Bailey 2010 [23]	—	yes	—	—	yes
Van den Akker 2009 [24]	—	yes	—	—	yes
Hunyinbo 2008 [25]	—	yes	—	—	yes
Kongnyuy 2008 [26]	—	yes	—	—	yes

Kongnyuy 2008 [27]	—	yes	—	—	yes
Weeks 2005 [28]	—	yes	—	—	yes
Wagaarachchi 2001 [29]	—	yes	—	—	yes

Table S2. Risk of bias

Author	Study design	Risk of bias criteria for RCTs, CCTs, CBAs, UCBAs					Additive risk of bias criteria for ITS		
		Random sequence generation	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective reporting*	*Intervention independent of other changes?*	*Shape of the intervention effect prespecified?*	*Intervention unlikely to affect data collection?*
Lumala 2017 [13]	ITS	high	high	high	low	unclear	high	low	high
Mgaya 2017 [14]	NCBA	high	high	high	low	unclear	-	-	-
Kayiga 2016 [15]	NCBA	high	high	high	low	unclear	-	-	-
Mohd Azri 2015 [16]	NCBA	high	high	high	low	unclear	-	-	-
Gebrehiwot 2014 [17]	NCBA	high	high	high	low	unclear	-	-	-
Baltag 2012 [18]	NCBA	high	high	high	low	unclear	-	-	-
Kidanto 2012 [19]	NCBA	high	high	high	low	unclear	-	-	-
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	NCBA	high	high	high	low	unclear	-	-	-
Van den Akker 2011 [22]	ITS	high	high	high	low	unclear	high	low	high
Bailey 2010 [23]	NCBA	high	high	high	low	unclear	-	-	-
Van den Akker 2009 [24]	NCBA	high	high	high	low	unclear	-	-	-

Hunyinbo 2008 [25]	NCBA	high	high	high	low	unclear	-	-	-
Kongnyuy 2008 [26]	NCBA	high	high	high	low	unclear	-	-	-
Kongnyuy 2008 [27]	NCBA	high	high	high	low	unclear	-	-	-
Weeks 2005 [28]	NCBA	high	high	high	low	unclear	-	-	-
Wagaarachchi 2001 [29]	NCBA	high	high	high	low	unclear	-	-	-

Table S3. World bank classification of country income

Author	Country	WB classification *
Lumala 2017 [13]	Uganda	L
Mgaya 2017 [14]	Tanzania	L
Kayiga 2016 [15]	Uganda	L
Mohd Azri 2015 [16]	Malaysia	UM
Gebrehiwot 2014 [17]	Ethiopia	L
Baltag 2012 [18]	Moldova	LM
Kidanto 2012 [19]	Tanzania	L
Sukhanberdiyev 2011 [20] Hodorogea 2010 [21]	Kazakhstan	UM
Van den Akker 2011 [22]	Malawi	L
Bailey 2010 [23]	Vietnam	L §§
Van den Akker 2009 [24]	Malawi	L
Hunyinbo 2008 [25]	Nigeria	L §§
Kongnyuy 2008 [26]	Malawi	L
Kongnyuy 2008 [27]	Malawi	L
Weeks 2005 [28]	Uganda	L
Wagaarachchi 2001 [29]	Ghana and Jamaica	L §§

§ L=Low income; LM=Lower middle income; UM=Upper middle income

§§ Ghana, Jamaica, Nigeria and Vietnam were classified as low income countries during the time of the study, while they were upgraded to lower middle income in 2010, 2007 2008, and 2009 respectively.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	42 (box 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-4 Figure 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 Figure 1-2 e S1-S4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 Table S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 Figure S1-S6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-13

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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

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