Clean delivery practices during home deliveries in rural South Asia: effects on maternal and neonatal mortality and interventions aimed at improved use

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Thesis submitted for the degree of Doctor of Philosophy

October 2014

Declaration of Authorship

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background

Globally, puerperal and neonatal sepsis account for an estimated 8-12% and 23% of maternal and neonatal deaths respectively. Clean delivery practices are known to help prevent sepsis, but evidence is lacking on the extent to which they can improve survival following home deliveries in rural communities in low-resource countries. Evidence is also lacking on effective methods to increase the use of different clean delivery practices in these settings. To address these issues, I sought to: (1) determine the associations between clean delivery practices and neonatal and maternal mortality for home deliveries in rural South Asia; (2) review the literature on effective means to promote the use of clean delivery practices; and (3) to determine the effectiveness of community mobilisation through women's groups in promoting the use of clean delivery practices during home deliveries in rural South Asia.

Methods

I used data from four cluster-randomised controlled trials conducted in rural India, Bangladesh and Nepal. Each of these trials had the primary objective of evaluating the effect of a community mobilisation intervention through participatory women's groups on neonatal survival. Using pooled datasets from the control arms of these trials, I tested associations between clean delivery practices and neonatal and maternal survival. I also investigated the robustness of the estimates through sensitivity analyses. To assess the effectiveness of community mobilisation in improving the uptake of clean delivery practices, I conducted a meta-analysis using individual patient data from the control and intervention arms of the four previously mentioned trials.

Results

The use of all clean delivery practices, except wearing gloves, was associated with a reduction in neonatal mortality. Hand washing was the only clean delivery practice associated with a reduction in maternal mortality. Sensitivity analyses raised some doubt as to the extent to which clean delivery practices improved neonatal and maternal survival. Analyses of the effect of community mobilisation through women's groups on the use of

clean delivery practices suggested that this was an effective approach to improve their use, especially in the most disadvantaged populations.

Conclusions

The use of clean delivery practices for home births has the potential of saving thousands of unnecessary deaths due to unhygienic conditions during delivery. Given that a substantial proportion of all deliveries in low and middle-income settings are still likely to occur at home, the use of clean delivery practices should be promoted through community interventions in a context appropriate manner. Community mobilisation through women's groups may be an effective means of promoting the use of such practices, especially among the most vulnerable mothers.

Acknowledgements

Firstly, I would like to thank my primary supervisor, Audrey Prost; this thesis would not have been possible without her dedication and support. I would like to thank my secondary supervisors Mario Cortina Borja and Leah Li who offered invaluable statistical support. Importantly; I would like to thank Anthony Costello for hiring me to work at the Institute of Global Health in the first place, as well as his original contributions to the topic of clean delivery practices. I would also like to thank my work colleagues and friends at the Institute for Global health for their continued support throughout my PhD, particularly Tim Colbourn, Kelly Clarke, James Beard, and Carlos Grijalva-Eternod. I would also like to thank Andrew Copas for his statistical support and involvement in two of my papers to date. Finally, I would like to thank my dear friends and work colleagues, Melissa Neuman and Leila Younes, for their support and encouragement along the way.

Although my work was based on secondary data analysis data made available from cluster randomised trials, this thesis would not have been possible without the hard work of the field staff from our different partner sites, nor would it have been possible without the women who participated in the trials. In particular, I would like to thank the people who were responsible for the design and implementation of the studies including Anthony Costello, David Osrin, Audrey Prost, Sarah Barnett, Kishwar Azad, Dharma Manandhar, Prasanta Tripathy, and Nirmala Nair. I would also like to thank the field staff who lay the important ground work making these trials possible including Aman Sen, and Abdul Kuddus.

Lastly, I would like to thank my family for their dedication and support throughout this journey; in many ways this PhD is as much their accomplishment as it is mine. In particular, I would like to thank my husband, Brendon Caligari, not only for his emotional support but also for forgoing his holidays and weekends whilst I completed my thesis. My two children Emmanuelle and Raphael deserve particular gratitude as I became pregnant with them in the later stage of my thesis. Hopefully they will not bear the burden of my stress in their future health outcomes.

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Acronyms applied to the thesis

AHW	Auxiliary Health Worker
AIC	Akaike's Information Criterion
ANC	Antenatal Care
aOR	Adjusted Odds Ratio
aRR	Adjusted Rate Ratio
BIC	Bayesian Information Criterion
CBSV	Community-Based Survey Volunteers, based in Ghana for the Newhints trial[1]
CHREG	Child Health Epidemiology Reference Group
CHW	Community Health Worker
CI	95% Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRCT	Cluster Randomised Controlled Trial
DHS	Demographic and Health Survey
ENC	Essential Newborn Care
FCHV	Female Community Health Volunteer
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICC	Intra-Cluster Correlation
ICDS	Integrated Child Development Services
IPD	Individual Patient Data
IGH	Institute of Global Health
IRR	Incidence Rate Ratio
JSY	Janani Suraksha Yojana
LHWs	Lady Health Workers, local community health workers in Pakistan.
MAR	Missing at Random
MCAR	Missing Completely at Random
MDG	Millennium Development Goal

MI	Multiple Imputation
MICE	Multiple Imputation with Chained Equations
MMR	Maternal Mortality Ratio
MMRate	Maternal Mortality Rate
NFHS-2	National Family Health Survey 1998-1999
MNAR	Missing Not at Random
NFHS-3	National Family Health Survey 2005-2006
NGO	Non-Governmental Organisation
NMR	Neonatal mortality rate
NRHM	National Rural Health Mission
OR	Odds Ratio
pPROM	Preterm Premature Rupture of Membranes
PROM	Prolonged Rupture of Membranes
RCHP	Reproductive and Child Health Programme
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
TBA	Traditional Birth Attendant
UCL	University College London
UN	United Nations
VA	Verbal Autopsy
VIF	Variance Inflation Factor
WHO	World Health Organisation

Definitions

Abortion: pregnancy termination prior to 20 weeks gestation or a foetus born weighing less than 500g.[2]

Akaike's Information Criterion (AIC): The AIC is a penalized likelihood criterion used for comparing non-nested models. The AIC also includes a penalty that is an increasing function of the number of estimated parameters.[3]

Anganwadi workers: community-based workers responsible for delivering health and nutrition services to children younger than six years of age, as well as to pregnant and lactating women.[4]

Auxiliary Nurse Midwife: outreach workers trained to deliver infants, provide vaccinations and antenatal check-ups.[5]

Bayesian Information Criterion (BIC): The BIC similar to the AIC and is used to select the best model whereby the model with the lowest BIC is preferred. The BIC penalizes model complexity more severely than the AIC. [3]

Clean cord care: includes the following: (1) use of a clean blade to cut the cord (a blade that was part of a clean delivery kit, or supplied by a skilled birth attendant or by a trained birth attendant, or a blade that had been boiled); (2) use of a clean thread to tie the cord (a thread that was part of a clean delivery kit, or supplied by a skilled birth attendant or supplied by a trained birth attendant, or thread that had been boiled): and (3) use dry cord care or a disinfectant on the umbilical cord.

Clean delivery kit: a package that includes components related to World Health Organisation's "six cleans": hand washing of the birth attendant prior to delivery, use of a clean instrument to cut the umbilical cord, use of a clean cord tie, clean delivery surface, clean perineum, and a clean cloth for drying the infant.

Dais: local term to describe traditional birth attendants in South Asia.[6]

Direct causes of maternal deaths: deaths resulting from obstetric complications of the pregnancy state from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.[2]

High-income country/region: countries with a gross national income per capita of $12,746 or more.[7]

High neonatal mortality setting: a setting where neonatal mortality rates are greater than 30 per 1000 live births.[8]

Incidence rate ratio the ratio of two incidence rates. The incidence rate is the number of events divided by the person-time at risk.[9]

Indirect obstetric deaths: deaths resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the effects of pregnancy.[2]

Institutional delivery: a delivery that take place in a health care facility by a skilled birth attendant including a doctor, nurse, or a trained midwife.

Intra-cluster correlation coefficient: Is the ratio of variance between clusters to the total variance (both between clusters and within clusters).

Lady Health Worker: community-based workers introduced by the Government of Pakistan in 1994 to improve reproductive, maternal and child health in rural populations.[10]

Late maternal death: death of a woman from direct or indirect obstetric causes more than 42 days but less than one year after termination of pregnancy.[2]

Low-income country/region: countries with a gross national income per capita of $1,045 or less.[7]

Low neonatal mortality rates setting: a setting where neonatal mortality rates are less than 5 per 1000 live births.[8]

Low-resource setting: similar to low-income country.

High-resource setting: similar to high-income country.

Maternal death: defined by the World Health Organisation as death of a women while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.[2]

Maternal Mortality Rate: number of maternal deaths in a given period per 1000 women of reproductive age during the same time period.[11]

Maternal Mortality Ratio: number of maternal deaths during a given time period per 100 000 live births during the same time period.[11]

Millennium Development Goal 4: to reduce mortality in children under five by two-thirds between 1990 and 2015.[12]

Millennium Development Goal 5: to reduce the Maternal Mortality Ratio (MMR; the number of maternal deaths per 100 000 livebirths) by three quarters between 1990 and 2015.[13]

Neonatal death: death of a newborn infant up to 28 days after delivery.[2]

Neonatal sepsis: bacteria blood infection within the first 28 days of life.[2]

Odds Ratio: odds in the exposed group divided by the odds in the unexposed group.[9]

Other direct causes of maternal deaths: other causes of maternal death not relating to the following: pregnancies with an abortive outcome; hypertensive disorders during pregnancy, childbirth, and the puerperium; obstetric haemorrhage; and pregnancy-related infection. [2]

Puerperal sepsis: defined by the World Health Organisation as an infection of the genital tract that occurs any time between the rupture of membranes or labour and the 42nd day postpartum, in which fever and one or more of the following clinical symptoms are present:

pelvic pain, abnormal vaginal discharge, abnormal odour or discharge, and a delay in the rate of reduction of the size of the uterus.[2]

Receiver Operating Characteristic (ROC) curve: is a plot of the sensitivity verses one minus the specificity that quantifies the overall ability of a predictive model to discriminate between those with and without the outcome of interest based on a number of variables. If the model perfectly predicts those with the disease (i.e. 100% sensitivity and specificity) the area under the ROC curve has a value of 1. If the area under the curve has a value of 0.50, this indicates the model has no discriminatory ability.[14]

Rate Ratio: rate in the exposed group divided by the rate in the unexposed group.[9]

Relative Risk: rate in the exposed group divided by the rate in the unexposed group, also known as risk ratio.[9]

Risk Ratio: risk in the exposed group divided by the risk in the unexposed group, also known as relative risk.[9]

Skilled birth attendant: the definition of a skilled birth attendant is country specific and defined in relevant Demographic Health Surveys.[15-17]

Traditional birth attendant (TBA): a person who assists the mother during childbirth and initially acquired her skills by delivering infants herself or through an apprenticeship to other TBAs. [18]

95% uncertainty range: estimates of uncertainty **c**alculated by drawing 1,000 bootstrap samples and repeating the estimation steps for each sample in question. 95% uncertainty ranges are the 2.5th and 97.5th percentiles of the resulting distributions around the estimates.[19]

Chapter 1 Introduction

1.1 Overview

This introduction will provide an overview of the epidemiology of maternal and newborn health in rural South Asia, followed by a discussion of neonatal and puerperal sepsis and their influences on maternal and newborn health. I will provide a rationale for the thesis by contextualising home deliveries in South Asia in relation to clean delivery practices, puerperal and neonatal sepsis. This will be followed by an outline on the overall aim and objectives of this thesis. Finally, I will describe the structure of the thesis.

1.2 Epidemiology of maternal and neonatal health in rural South Asia

Globally, in 2012, there were approximately 2.9 million neonatal deaths and in 2013, an estimated 289 000 maternal deaths.[11, 20] South Asia has some of the world's highest absolute numbers of maternal and neonatal deaths: in 2012, there were approximately 1.1 million neonatal deaths across the region, and, in 2013 an estimated 69 000 maternal deaths.[11, 20] Improvements have occurred, including declines in neonatal mortality rates (NMRs) and maternal mortality ratios (MMR; the number of deaths per 100 000 live births), largely through better access to facility-based deliveries and improved education for women.[21] Nevertheless, this progress has not been uniform, with some countries such as Mali, Sierra Leone, and Guinea-Bissau, failing to make any improvements.[21]

The Millennium Development Goals (MDG) represent an international commitment to development and poverty eradication in low and middle-income countries.[13,22] Reducing child and maternal mortality is a major global health challenge addressed by the fourth and fifth MDGs.[13, 22] The fourth MDG aims to reduce mortality in children under five years of age by two-thirds between 1990 and 2015 (i.e. 4.4% per annum).[13, 22] The fifth MDG, aims to reduce the MMR by three quarters between 1990 and 2015.[13, 22]

1.2.1 Neonatal health

The World Health Organisation's (WHO) International Classification of Disease's tenth revision (ICD-10) defines a neonatal death as a death occurring up to 28 days after delivery.[2] Current estimates suggest that in 2012, 2.9 million neonatal deaths occurred worldwide, of which 2.8 million (98%) were in low and middle-income countries, and 1.1 million (40%) were in South Asia.[20]

In 2012, the major determinants of neonatal deaths were prematurity (36%), intrapartum-related events (23%) and infections including sepsis, meningitis, and pneumonia (23%).[23] In countries with both low and high NMRs (defined here as NMR<5 per 1000 live births and NMR>30 per 1000 live births respectively), preterm birth complications were the leading cause of death.[23] In countries with NMRs greater than 30 per 1000 live births, infections and intrapartum-related events shared a greater proportion of deaths.[23] In 2012, in Bangladesh, the three leading causes of neonatal deaths were preterm deliveries (28%), intrapartum-related events (27%), and sepsis (21%).[23] In India, the three leading causes of neonatal mortality were preterm deliveries (43%), intrapartum-related events (21%), and sepsis (16%).[23] In Nepal, the three leading causes of neonatal mortality were also preterm deliveries (29%), intrapartum-related events (27%), and sepsis (21%).[23]

Between 1990 and 2012, mortality rates in children aged between two months and five years of age were reduced by 47%, mainly due to reductions in deaths from pneumonia, diarrhoea, and measles.[20, 23, 24] However during the same time period, the global reduction in neonatal mortality occurred at a slower pace of 37%, and neonatal deaths now account for a greater proportion of all deaths in those under five years of age: in 2012, 44% of deaths to children under five years old occurred in the neonatal period, compared with 37% of deaths in 1990.[20] Globally, NMRs have declined at a rate of 1.7% per annum between 1990 and 2001 compared to 1.9% in South Asia.[19] Despite this, as of 2009 they remained high in many countries: 33.9 (95% uncertainty interval [UI]: 33.0 – 34.6) per 1000 live births in India, 29.5 (27.8–31.1) in Bangladesh and 26.5 (24.1–28.0) in Nepal.[19] The largest decreases in neonatal mortality were seen in deaths due to tetanus, which decreased by two thirds between 2000 and 2012, and in intrapartum-related complications, which decreased by one third during the same time period.

1.2.2 Maternal health

A maternal death is defined by the WHO as “the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes”.[2] 37% of all maternal deaths occur in South Asia.[25] There have been improvements: in 2013, there were 292 982 (95% UI: 261 017–327 792) maternal deaths compared to an estimated 376 034 (343 483–407 574) in 1990.[25] Between 1990 and 2003, the decline in MMR globally was 0.3% per annum, and this accelerated to a rate of 2.7% per annum from 2003 to 2013. In South Asia, the MMR declined at an annual rate of 1.4 % between 1990 and 2003 and 2.6% between 2003 and 2013. In 2013, the MMR was 281.8 (95% UI: 207.0–371.2) in India, 242.7 (171.2–326.9) in Bangladesh, and 272.3 (190.9–363.5) in Nepal.[25]

Reducing maternal deaths during pregnancy, childbirth and in the 42 days after delivery, is a major global health challenge.[13] Maternal mortality is notoriously difficult to measure for several reasons. It is common to misclassify maternal deaths as deaths due to other causes in countries with incomplete vital registration and medical certification.[25] Importantly, the reporting of maternal deaths does not occur in many countries, leading to a reliance on survey recall with high levels of sampling error. It is also difficult for mathematical and statistical models to derive accurate measurements for overall maternal mortality estimates when studies that report maternal deaths are uncommon.[25-28]

As with neonatal mortality, causes of maternal mortality differ between high and low-income countries, and also have changed over time.[25] In 2013, indirect and other causes of death were the most important causes of maternal deaths in high-income countries, while abortion-related deaths were most prevalent in 1990.[25] Globally, between 1990 and 2013, there has been a significant decrease in the number of maternal deaths due to haemorrhage, hypertension, and maternal sepsis.[25] However, the number of maternal deaths due to indirect and late maternal causes has increased during the same period.[25] In low-income countries, there has been no change between the most important causes of maternal death: other direct causes, abortion, and haemorrhage. In 2013, in Bangladesh, the three leading causes of death were late maternal death, haemorrhage, and hypertension. Estimates suggest that sepsis accounted for only 3.4% of maternal deaths (n=259, 95% UI: 141–400). In 2013, in India, the three leading causes of maternal deaths were late maternal deaths, followed by other direct causes, and haemorrhage. Sepsis accounted for 10% of maternal deaths in India (n=7326, 4761–10 511). In 2013, in Nepal, the three leading causes of maternal death were other direct causes, late maternal deaths, and haemorrhage. Sepsis accounted for 5% of all maternal deaths (n=77, 49–113).[25]

1.2.3 Country-specific situation for neonatal and maternal health

1.2.3.1 India

Although India has made substantial progress in neonatal and maternal survival, it is unlikely that it will meet targets for MDGs four and five in 2015.[4, 20, 29] As an example, there was a 36% reduction in the MMR from 398 per 100 000 live births in 1997–1998 to 254 per 100 000 live births in 2004–2006. It is therefore unlikely that India will meet the MDG five target of less than 100 maternal deaths per 100 000 live births. Reasons for this lack of progress are multifaceted and most likely include a combination of factors such as poor health care infrastructure, issues related to the management and finance of the health systems, large disparities between the wealthiest and poorest populations, and the inability of the infrastructure to meet the demand of the rapid increases in population of India's major cities.[4] Although facility-based deliveries have been promoted, the health care infrastructure has not been able to meet the increased demand for services, leading to reports of substandard conditions in intrapartum and neonatal care for facility-based deliveries.[4]

India, like other South Asian countries, has national programmes aimed at improving maternal and newborn health. The National Rural Health Mission (NRHM) initiated in 2005 was integrated in India's national Reproductive and Child Health Programme (RCHP). Evaluations have shown that the NRHM has had a positive impact on antenatal care, institutional deliveries, and immunisation rates.[4] Another national programme, the Integrated Child Development Services (ICDS), includes provisions such as health check-ups, supplementary nutrition, informal education, immunisation, and referral services.[4] The ICDS uses village-based Anganwadi workers who are responsible for delivering nutrition and health services to children younger than six years of age, as well as pregnant and lactating women.[4] Another major initiative is a conditional cash transfer program called *Janani Suraksha Yojana* (JSY), that aims to increase the uptake of antenatal care and institutional deliveries.[4]

The Annual Health Survey for 2012-2013, which included nine states in India, indicated that improvements in maternal and newborn health have occurred.[30] The proportion of facility births ranged from 40% in the state of Chhattisgarh to 83% in the state Madhya Pradesh.[30] This is an improvement on previous estimates, which suggested that 35% of births took place in facilities in Chhattisgarh and 76% in Madhya Pradesh.[30]

Results from the 2005–2006 National Family Health Survey (NFHS-3) indicated substantial inequities in health care provision and health outcomes. There were large differences between urban and rural areas: two thirds of deliveries in urban areas occurred in health facilities, compared with 29% of deliveries in rural areas. This was a slight improvement from the 1998–1999 survey (NFHS-2), where only a quarter of deliveries in rural areas took place in institutions. There were also substantial rural/urban differences in skilled birth attendance: NFHS-3 data indicated that 74% of deliveries in urban areas had a skilled birth attendant, compared with only 38% in rural areas.[16, 31] NMRs were approximately 50% higher in rural areas compared to urban areas.[16] The NMR in the highest wealth quintile was 24 per 1000 live births, compared to 49 per 1000 livebirths in the lowest wealth quintile.[16]

1.2.3.2 Bangladesh

Bangladesh has experienced a significant improvement in neonatal and maternal survival over the past 20 years.[32] The National Newborn Health Strategy, which included community-based interventions, has been described as key to this progress.[32] There were also increases in the coverage of key interventions, as indicated by the Demographic Health Survey (DHS) in 2000 and 2010, where the following was observed: increased coverage of facility-based deliveries from 8% to 29%, and an increased utilisation of skilled birth attendants from 12% to 28%.[15] Other important factors linked to these improvements include 55% of women receiving antenatal care from a skilled provider in 2010, compared to 51% in 2004.[15] Furthermore, in 2011, 26% of women received the WHO's recommended four antenatal care visits compared to only 16% in 2004.[15]

There remain substantial inequalities in access to care between the poorest and the wealthiest women in Bangladesh. As an example, only 8% of women in the poorest wealth quintile delivered in a health facility, compared to 53% in the wealthiest quintile.[15] Only 20% of women in rural areas received the recommended four antenatal care visits compared to 45% in urban residences.[15] 77% of deliveries in rural settings occur in the home, compared to 50% in urban settings.[15] The NMR in urban settings was 32 per 1000 live births, compared to 33 per 1000 live births in rural settings.[15] However, whereas infants born to mothers in the lowest wealth quintile had an NMR of 34 per 1000 live births, the highest wealth quintile experienced rates of 23 per 1000 live births.[15]

1.2.3.3 Nepal

Between 2000 and 2010, Nepal has seen considerable improvements in newborn and maternal survival. This progress have been explained by a reduction in the total fertility rate, increased coverage of skilled birth attendants, community-based child health interventions, and improvements in female education.[33] Importantly, a Newborn Health Strategy that included the implementation of a community-based newborn care package through the use of female health volunteers has been successfully piloted in 10 districts, with plans to extend the project to a further 35 districts.[33] Skilled antenatal care was received by 58% of mothers in the five years prior to the 2011 DHS.[17] Furthermore, estimates from the 2011 survey indicate that 50% of women in Nepal received the WHO recommended four antenatal care visits, compared to 9% in 1996.[17] The 2011 DHS data also indicate that 63% of deliveries took place in the home and 35% occurred in health facilities. These indicators have improved considerably from 2006, when only 18% of deliveries occurred in health facilities.[17] The use of skilled birth attendants has also improved considerably: in 2006, 19% of deliveries were assisted by a skilled birth attendant, compared to 36% in 2011.[17]

In Nepal, data from the 2011 DHS indicate that the NMR in rural settings was 36 per 1000 live births, compared to 25 per 1000 live births in urban settings.[17] Mountainous regions had an NMR of 46 per 1000 live births compared to 25 per 1000 live births in southern, Terai areas.[17] In 2011, DHS data also indicated that infants born to mothers in the lowest quintile of wealth had an NMR of 37 per 1000 live births, compared to 19 per 1000 live births in the highest wealth quintile.[17]

1.2.4 Home deliveries and skilled birth attendants in South Asia

Skilled birth attendance has been identified as a key intervention to reduce the number of maternal deaths and meet the fifth millennium development goal.[34, 35] The previously mentioned inequities in health care provision and health outcomes between urban and rural regions, combined with recent estimates predicting that at least 90% of deliveries attended by an unskilled attendant will occur for home deliveries in rural areas, have important implications for the future of home deliveries in rural South Asia.[36] Indeed, these figures suggest that the issues surrounding unskilled birth attendance in home deliveries, such as unhygienic practices, are likely to be a concern for rural areas in low-resource settings for some time in the future.

1.3 Neonatal and Puerperal sepsis

1.3.1 Puerperal and neonatal sepsis in a historical context

During the perinatal period, the newborn infant and mother are vulnerable to an array of physical insults, in particular sepsis. The risks associated with puerperal sepsis have long been recognised: in the 19th century, puerperal and neonatal sepsis were two of the major determinants of mortality and morbidity in Europe and North America, mainly due to the lack of knowledge about the importance of appropriate hygiene during delivery.[37] Puerperal sepsis was the most common cause of maternal mortality in 19th century Britain, and was responsible for approximately 93 342 deaths between 1847 and 1903.[37] Additionally, between 1920 and 1929, an estimated 25 000 women in England and Wales, and a quarter of a million women in the United States died in delivery; it is thought that half of these women died as a result of puerperal sepsis that could have been averted through appropriate hygiene behaviours and antibiotic use.[37]

Ignaz Semmelweis was the first person to ascertain the cause of puerperal sepsis and demonstrate its infectious nature.[37] In the 1840's, he observed that women who were treated by clinicians who had just completed a dissection in the morgue were at increased risk of puerperal sepsis.[37] When Semmelweis attended the post-mortem exam of a work colleague who died of septicaemia, he noticed similar pathological lesions as those found on women who had died of puerperal sepsis. These observations led Semmelweis to conclude that the "cadaverous particles" could be causing the puerperal sepsis, which further led him to promote hand washing with chlorine solution.[37] Subsequently, rates of mortality due to puerperal sepsis declined from more than 900 per 1000 births to 300 per 1000 births between May 1847 and 1848, mostly as a result of hand washing promotion.[37, 38]. Unfortunately, Semmelweis' findings were largely ignored, despite the fact that after the implementation of hand washing, puerperal sepsis had been virtually eliminated from Vienna's Maternity Hospital, one of the world's most prestigious teaching hospitals in the nineteenth century.[39]

Besides Semmelweis, other scientists and clinicians made important contributions to the elimination of puerperal sepsis. Louis Pasteur was responsible for the identification of the bacterium *Streptococcus pyogenes* as the main causal agent of puerperal sepsis.[39] In 1932, Gerhard Domagk discovered sulphonamides, formally known as prontosil, resulting in the dramatic decline of puerperal sepsis due to *Streptococcus pyogenes* infection.[39] In 1935, Leonard Colebrook cured patients with life-threatening puerperal sepsis using sulphonamides at Queen Charlotte's hospital in England.[39, 40] After the introduction of penicillin during the second world war, most cases of puerperal sepsis were largely eliminated in England and Wales.[39]

Although maternal mortality did not decline significantly until the early 20th century in Europe, neonatal mortality began to fall in the late 19th century after the introduction of improved hygiene and improvements in the training of birth attendants.[37] Semmelweis was also responsible for major discoveries relating to neonatal sepsis. The observation that newborns born to mothers with puerperal sepsis who had had multiple vaginal examinations were themselves more likely to develop sepsis led Semmelweis to deduce that the two must have similar causal mechanisms. Semmelweis reasoned that contact with infectious particles in maternal blood led to the development of neonatal sepsis, and that hand washing could therefore potentially help prevent both puerperal and neonatal sepsis.[38]

1.3.2 Burden, epidemiology, and risk factors for puerperal and neonatal sepsis in the 21st century

Despite advances made in the understanding of the importance of hygiene in delivery during the 19th and early 20th centuries in Europe and North America, sepsis still remains a major determinant of neonatal and maternal mortality in many low and middle-income countries. The remainder of this chapter will review evidence on the burden and epidemiology of neonatal and puerperal sepsis today, including associated risk factors.

1.3.2.1 Neonatal sepsis

There is a paucity of data on the epidemiology of neonatal sepsis, defined as a bacterial blood infection that occurs within the first 28 days of life, in low-resource settings.[2] Estimates from direct causes of death data in 2012 suggested that sepsis led to up to 23% of the annual 2.9 million neonatal deaths that occur globally.[20, 23] One study estimated that between 30% and 40% of infections transmitted at the time of birth manifest as early-onset sepsis within the first 72 hours of life.[41] Recent estimates also suggested that interventions to improve hygiene at birth could avert between 20% and 30% of neonatal deaths due to sepsis and tetanus.[42]

In South Asia, where 56% of deliveries occur at home, most (51%) without skilled birth attendance, it is difficult to estimate the burden of neonatal sepsis because the technical expertise and equipment to identify positive blood cultures are often lacking.[43] Hence, diagnosis is usually determined by unskilled healthcare professionals using non-specific clinical symptoms that often overlap with other conditions such as those present in intrapartum-related events.[41] The lack of skilled birth attendance is therefore likely to result in the under-reporting of sepsis-related infections and deaths.[44]

1.3.2.2 Puerperal sepsis

The WHO defines puerperal sepsis as an "infection of the genital tract that occurs any time between the rupture of membranes or labour and the 42nd day postpartum, in which fever and one or more of the following clinical symptoms are present: pelvic pain, abnormal vaginal discharge, abnormal odour or discharge, and a delay in the rate of reduction of size of the uterus".[18] The ICD-10 has a different definition of puerperal sepsis, and defines the condition as a "temperature rise above 38.0 C maintained over 24 hours, or recurring during the period from the end of the first to the end of the 10th day after childbirth or abortion".[2] Puerperal infection is a more general term than puerperal sepsis and includes extra-genital sites (urinary tract and breast) as well as incidental infections (malaria, HIV, tuberculosis and pneumonia).[45] Differing definitions of puerperal sepsis make comparisons between studies difficult. Puerperal infections are also associated with early neonatal sepsis, in addition to being indirectly associated with other issues such as compromised mother-infant bonding and breastfeeding.[46]

As with neonatal mortality, obtaining cause-specific maternal mortality data for low and middle-income countries is difficult because many of the estimates come from hospital-based studies and are not representative of the majority of the births, which occur at home.[47] Adding to this uncertainty, a hospital-based study in Mozambique showed sensitivities of less than 50% for a clinical diagnosis of infection-related maternal death when compared to the gold standard of diagnosis through autopsy.[45] It is also suggested that morbidity due to puerperal sepsis affects between 5% and 10% of pregnant women.[48] Given the uncertainty surrounding diagnosis of cause-specific maternal mortality, it is possible that these findings underdiagnose sepsis-related maternal deaths and morbidity.

1.4 Risk factors for neonatal and maternal sepsis

1.4.1 Neonatal sepsis

Neonatal sepsis can be acquired through vertical transmission from the mother during delivery, or just after delivery from the horizontal transmission of pathogens present in the environment.[49] Sepsis acquired from the mother is transmitted prior to, or during delivery, as the neonate passes through the birth canal, and is mainly caused by bacterial organisms present in the placenta and genital tract.[50, 51] In low and middle-income countries, vertically transmitted infections acquired in hospital-based settings are caused predominately by Gram-negative organisms although Gram-positive and mixed infections can occur.[50, 51] Examples of such infections include *Klebsiella pneumonia, Escherichia coli, Pseudomonas* spp, *Acinetobacter* ssp, and *Staphylococcus aureus*.[49] Many of the above-mentioned pathogens may not be treatable in low-resource settings as they are not susceptible to low-cost antibiotics such as ampicillin and gentamicin.[49] Vertically transmitted infections acquired both in the community and the hospitals, are predominantly due to *Escherichia coli* and Group B *Streptococcus* organisms.[50] Horizontally transmitted sepsis occurs when the newborn infant acquires a bacterial infection from the environment such as the community or hospital.[50, 51] Responsible pathogens are varied and include *Escherichia coli*, *Staphylococcus aureus* and coagulase-negative *Staphylococcus*.[50]

Additional risk factors for vertical sepsis include preterm delivery, intrapartum hypoxia, and factors associated with maternal sepsis such as prolonged rupture of membranes (PROM), preterm premature rupture of membranes (pPROM), spontaneous preterm onset of labour, prolonged duration of labour, repeated vaginal examinations, chorioamnionitis, and maternal systemic infections.[52-56] Horizontally transmitted infections occurring in home deliveries in low-income countries, often occur in unhygienic conditions associated with poverty, exposing newborn infants to infections.[57] In addition, traditional postnatal practices such as discarding colostrum and bathing the infant immediately after birth leave them particularly vulnerable to infections.[58] Poor hygiene in the intrapartum and postpartum periods is also present in facility-based deliveries in low resource settings where infections three to twenty times higher than infection rates reported in high income countries.[49] Given the momentum in promoting facility-based deliveries, it is essential that hygiene is maintained so as not to deter from this process. Simple behavioural changes therefore have the potential to reduce neonatal sepsis.[49]

Umbilical cord infection (omphalitis) is an important cause of neonatal mortality in low-resource countries. Once the umbilical cord is cut, the open cord becomes susceptible to infection from bacteria present in the environment.[59] Omphalitis can quickly progress to systemic sepsis, which, if untreated, has a high case fatality rate.[59] As an example, omphalitis with redness extending to the abdominal wall was associated with a 46% increased risk of mortality in a nested case-control study in rural Nepal that used data from a cluster randomised controlled trial (cRCT).[60] Omphalitis occurs mainly due to unhygienic post-delivery practices such as applying traditionally used substances to the umbilical stump, for example turmeric or mud.[59] Omphalitis may also be caused by the use of non-sterile cord cutting instruments.[59]

1.4.2 Puerperal sepsis

Given the close relationship between mothers and newborns, it is unsurprising that they share similar risk factors and aetiologies for sepsis-related morbidity and mortality.[45] Some of the risk factors for puerperal sepsis cited in the literature include: low socioeconomic status, poor nutrition, primiparity, anaemia, prolonged labour, having a home birth in unhygienic conditions, PROM, more than five vaginal examinations, instrumental deliveries, postpartum haemorrhage, caesarean section, multiple pregnancy, and endogenous genital-tract bacterial infections.[61-64] The most important risk factor for postpartum infection is having a caesarean section.[61-64] It has also been suggested that differences in rates of maternal and newborn sepsis between developed and developing countries are partially due to more women being infected with urogenital organisms and having impaired immunity due to poor nutritional status.[65, 66] Community factors relating to puerperal sepsis include unhygienic delivery practices by birth attendants, delivery by an unskilled birth attendant, lack of knowledge about the symptoms of puerperal sepsis, cultural influences which may delay care-seeking and low status of women which contributes to their poor health.[46, 65, 66] Health system factors contributing to puerperal sepsis include the lack of transportation and distance from a woman's residence to the health facility, poor quality of care received in health facilities, and lack of availability of appropriate postnatal care.[46, 65, 66]

Multiple pelvic examinations leave women vulnerable to puerperal sepsis as endogenous bacteria present in the vagina can be transmitted to the uterus through hands or instruments.[67] Endogenous bacteria can also spread due to PROM.[67] It is possible to introduce exogenous bacteria into the vagina through the use of unhygienic practices such as poor hand hygiene, unsterile instruments, and droplet infection. These bacteria can also be introduced through external material such as herbs, oil or cloth, and through sexual intercourse.[67] Women can also be left vulnerable to puerperal sepsis in the postpartum period, due to trauma received during delivery. As an example, lacerations present in the genital tract leave a woman susceptible to infections, especially in an environment with compromised hygiene.[67] Sexually transmitted infections such as gonorrhoea and chlamydia can also result in uterine infections. Due to the uterus's close proximity to main arterial blood supplies, it is possible for local infections to quickly develop into septicaemia.[67]

1.5 Rationale for the thesis

The WHO advocates the use of 'six cleans' at the time of delivery: hand washing for the birth attendant prior to delivery, clean perineum, clean delivery surface, clean cord cutting implement, clean cord tie, and clean cloth for drying.[68] A clean delivery kit typically includes components that address the six cleans: soap for washing the birth attendant's hands and mother's perineum, a plastic sheet to provide a clean delivery surface, a clean string for tying the umbilical cord, a new razor blade for cutting the cord, and pictorial instructions to illustrate the sequence of events during a delivery.[44] A recent analysis suggested that locally made kits combined with programmes to improve clean delivery practices are highly cost effective, at an estimated US$215 per life saved.[69]

Despite the known benefits of a hygienic delivery using the previously mentioned 'six cleans', maintaining hygienic conditions during home births can still be challenging.[43] Although use of a boiled instrument to cut the cord is now common, other clean delivery behaviours could be improved.[15-17] As an example, data from the 2011 Bangladesh DHS indicate that dry cord care was applied in only 59% of births.[15] Data from the 2011 Nepal DHS indicate that only 5% of women bought a clean delivery kit.[17] The same DHS data also suggest that a new or sterilised blade was used to cut the umbilical cord in 68% of home deliveries, and that nothing was applied to the umbilical cord after 59% of home deliveries.[17] 2% of infants had chlorhexidine ointment placed on their stump after cutting the umbilical cord in home deliveries.[17] In India, data from the NFHS-3 suggested that a clean delivery kit was used in only 21% of home deliveries, but that a clean blade was used to cut the umbilical cord in 92% of home deliveries.[16]

Besides DHS surveys, other studies have described the use of clean delivery practices in South Asia. A study in a small urban centre in Nepal, published in 2006, revealed that the use of clean delivery practices was minimal: only 16% of women used a clean delivery kit and only 38% of birth attendants washed their hands prior to delivery.[70] A recent study from Uttar Pradesh, India, indicated that 36% of mothers surveyed practised clean cord care.[71] Another study from West Bengal indicated that a clean delivery kit was used in only 15% of home deliveries and 69% of home deliveries were conducted on the floor, without a clean delivery surface.[72] The same study also suggested that although the cord was cut with a clean instrument in 90% of home deliveries, a clean cord tie was used in only 25% of these cases. A study from Sylhet, Bangladesh, looking at new born umbilical cord and skin care, showed that dry cord care was practiced in only 48% of home deliveries and in instances where a substance was applied to the cord, turmeric was the most common application.[73] The same study found that clean delivery kits were used in 28% of deliveries and that the instrument used to cut the blade was boiled in 64% of cases.

In addition to the low uptake of clean delivery practices, there is also paucity of good quality evidence on the beneficial impact of these practices on newborn and maternal health. As an example, two recent systematic reviews suggested that there is a lack of good quality evidence that the use of clean delivery practices and clean delivery kits, improved neonatal and maternal survival in low-resource community-based settings.[68, 74] Furthermore, little work has been done to understand the effectiveness of various interventions in improving the use of clean delivery kits as well as each of the separate clean delivery practices at a population level.

Given the evidence on the burden of neonatal and puerperal sepsis, the risks associated with an unhygienic delivery, the low uptake of clean delivery practices, and the fact that behaviours associated with clean delivery practices can potentially be modified through low-cost interventions, it is important to generate reliable estimates for the effect of clean deliveries on neonatal and maternal survival. It is also essential to provide evidence on the effectiveness of potential interventions to improve hygiene during delivery, particularly for home births.

1.6 Thesis aims and objectives

1.6.1 Aim

This doctoral thesis aims to explore the associations between clean delivery practices, including the use of clean delivery kits, and maternal and neonatal mortality in rural South Asia, and to examine the effect of community-based interventions on the use of clean delivery practices.

1.6.2 Objectives

Specifically, the thesis will:

1. Describe the epidemiology of neonatal and puerperal sepsis globally and in low and middle-income countries

2. Provide a literature review of the evidence on hygiene practices during delivery and their association with maternal and newborn health outcomes

3. Examine the associations between clean delivery kit use, clean delivery practices and neonatal mortality among home births in three rural sites in India, Bangladesh, and Nepal

4. Evaluate the contribution of unhygienic delivery practices to maternal mortality among home births in the same three rural sites

5. Review the literature on community-based interventions to improve clean delivery practices and clean delivery kit use in low and middle-income countries

6. Assess the impact of one of these community-based interventions, community mobilisation through participatory women's groups, on clean delivery practices and clean delivery kit use

1.7 Thesis structure

This thesis is organised in eight chapters, with chapters two through seven relating to the objectives described in section 1.6.

Chapter one provides the background required to contextualise the information presented in the thesis. It includes information about key current issues in global maternal and neonatal health, with background information to neonatal and puerperal sepsis. Chapter one also provides an overview of the epidemiology of neonatal and puerperal sepsis, including known risk factors.

Chapter two provides a literature review that summarises studies examining the effect of interventions to improve hygiene during delivery, and their effects on maternal and newborn outcomes.

Chapter three provides background information on the trials from which the data used in this thesis arise, followed by an overview of statistical methods used to analyse them. In this chapter I discuss the challenges inherent to the different analyses conducted, and describe the statistical methods used to address these.

Chapters four and five involve two separate analyses examining the associations between clean delivery practices and newborn and maternal survival, using data collected from four separate cRCTs, details of which are provided in Chapter two. I initially explore associations between clean delivery practices and neonatal mortality, then the associations between clean delivery practices and maternal mortality. Both of these chapters include sensitivity analyses testing the robustness of the key findings.

Chapters six and seven involve a literature review of complex intervention packages that also include a component aimed at improving hygiene in delivery. This is followed by a meta-analysis of individual patient data to examine the effect of community-based intervention involving participatory women's groups on the use of appropriate clean delivery practices in home deliveries in rural South Asia.

The final chapter of the thesis, Chapter eight, discusses the main study findings in relation to the existing literature as well as the limitations of the analyses presented here. Future research priorities are also considered.

1.8 Contributions to analyses included in the thesis

1.8.1 Literature reviews

I conducted two literature reviews on the effect of clean delivery practices on neonatal and maternal survival, and a review of literature on complex interventions aimed at improving clean delivery practices.

1.8.2 Statistical analyses

All analyses use data from four separate cRCTs conducted in rural South Asia. Details of the individual trials are provided in Chapter three of the thesis. Briefly, each of the trials were designed in part by members of the Institute of Global Health including Anthony Costello, David Osrin (Makwanpur trial), Sarah Barnett (India trial and first Bangladesh trial), and Ed Fottrell (second Bangladesh trial).

While some of the components of the thesis were published as collaborative articles, I was the first author in all of them. The contributions of the different authors can be found in the published article on the effect of clean delivery practices on neonatal mortality and is located in Appendix 1. [75]

A second article on the associations of clean delivery practices with maternal mortality has been submitted to *PLOS One*, with reviewers returning their feedback asking for some revisions. A copy of the paper with the individual contributions from the different authors can be found in Appendix 3.

Chapter 2 Literature review on the effect of clean delivery practices on neonatal and maternal morbidity and mortality

2.1 Introduction

Despite the known importance of hygiene during delivery, sepsis still remains an important cause of neonatal and maternal deaths in low and middle-income countries. The previous chapter provided an overview on the burden of sepsis as well as risk factors for neonatal and puerperal sepsis which include poor hygiene during delivery. This chapter provides a literature review of the evidence relating to hygiene practices during delivery and their association with maternal and newborn health outcomes. This review summarises findings from two previous systematic reviews published in 2012, and provides updates where appropriate.[68, 74]

2.2 Methods

2.2.1 General

I reviewed published literature using the online medical databases Web of Science, PubMed, as well as Google Scholar and the Cochrane Libraries between January 1980 and January 2014. I have also drawn upon two recent systematic reviews on clean delivery kit use and clean delivery practices.[68, 74] The following terms were adapted from previous systematic reviews, and were used separately and in combination to identify relevant literature: "clean delivery kit", "birth kit", "clean delivery", "safe kit", "clean birth", "clean birth practices", "hygiene", "cord care", "hand washing", "umbilical cord", "birth canal", "chlorhexidine", "neonatal sepsis", "puerperal sepsis", "maternal sepsis", "tetanus", "meningitis", "infection", "neonatal mortality", "maternal mortality", "omphalitis/oomphalitis", "early neonatal sepsis", "late neonatal sepsis", "maternal death", "neonatal death", "newborn infection", "maternal infection", "Asia", "Africa", "South America", "low resource country", "low income country", "developing country". [68, 74]

2.2.2 Inclusion criteria

For this review, I included randomised and non-randomised trials as well as observational studies conducted in low-resource countries. Study participants included neonates and women aged between 15 and 49 years. I included studies with data on both home and health facility deliveries. I included observational studies if they attempted to adjust for confounding and reported the associations between clean delivery practices and maternal or neonatal mortality, or puerperal or neonatal sepsis. All studies were required to have a comparison group unexposed to the clean delivery practice of interest.

2.2.3 Exclusion criteria

I excluded experimental studies evaluating interventions aimed at reducing mortality and morbidity due to infections other than sepsis. I also excluded studies of complex community-based interventions that aimed to improve clean delivery practices or maternal and newborn health more broadly, if it was not possible to determine the specific contribution of the intervention on mortality or sepsis-related events.

2.2.4 Outcomes

The review included studies with the following outcomes: maternal or neonatal mortality; mortality due to neonatal sepsis or tetanus or maternal sepsis; morbidity due to neonatal sepsis or tetanus; omphalitis; or morbidity due to puerperal sepsis.

2.2.5 Exposures

Relevant exposures were preventive interventions for sepsis, including: the use of a clean delivery kit; the birth attendant washing their hands with soap prior to delivery; the use of gloves in delivery to improve hand hygiene; a clean perineum washed prior to delivery; a clean delivery surface using a new or clean plastic sheet or mat; a boiled or new blade to cut the cord; a new and clean string to tie the cord or cord clamp; a disinfectant using chlorhexidine to clean the birth canal; a disinfectant to clean the cord; or dry cord care.

2.2.6 Quality of evidence assessment

Studies included in this review that were also a part of the previous systematic reviews were assessed according to the Child Health Epidemiology Reference Group (CHERG) adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) technique.[76] I assessed the quality of the four additional studies, not included in previous reviews using the same criteria.[68]

2.3 Results

2.3.1 General

My searches retrieved a total of 65 studies, of which 61 were also identified in a previous systematic review. Of these 65 studies, 23 were excluded because they did not control for confounders (*n*=8), had no comparison group (*n*=10), were not original research studies (*n*=2), or were duplicates (*n*=2).[68] In total, 44 studies met inclusion criteria, of which four were cRCTs, two were systematic reviews, and 38 were observational studies.[68] Summaries of 38 of these studies identified in the previous systematic reviews can be found elsewhere.[68, 74]

2.3.2 Study countries and settings

Studies identified in the previous systematic review are summarised elsewhere. Briefly, these studies took place in low-resource settings, mainly South Asia and sub-Saharan Africa.[68, 74] The four additional studies not covered in the systematic review took place in rural Bangladesh, Pakistan, and India.[71, 77-79]

2.3.3 Study designs

The types of studies included in the two previous systematic reviews included cross-sectional, cohort, and case-control designs, as well as randomised controlled trials (RCT) and cRCTs.[68, 74] Of the trials not previously reviewed, two were cRCTs, one was a RCT, and one was a cross-sectional study.[71, 77-79]

2.3.4 Exposures

The exposures examined in these studies included: clean delivery kit use; chlorhexidine application to the umbilical cord and perineum; hand washing by the birth attendant prior to delivery; clean delivery surface; and clean cord cutting and tying.[68, 74] Three of the four studies that were not included in the previous systematic reviews had interventions involving the application of chlorhexidine to the umbilical cord.[77-79] The other study not included in the systematic reviews involved assessing the effect of clean cord care.[71]

2.3.5 Quality of evidence and associated bias

Authors of the two previous systematic reviews concluded that the overall quality of evidence was low. All studies assessing the effects of kit use were of low quality and part of larger antenatal care packages, making it difficult to dissociate their impact on neonatal mortality and maternal morbidity from that of other components in the intervention package.[68, 74] Other clean delivery practices were also of low quality or very low quality as determined by the CHERG adaptation of the GRADE technique.[68, 74, 76] Using similar methods, the three of the four additional studies not found in the systematic reviews were found to be of moderate or high quality, mainly due to their randomisation techniques.[77-79] The single observational study not present in the systematic reviews was graded as very low quality due to bias inherent in the study design and flaws in the analysis.[71] Details from the four additional studies not found in previous systematic reviews can be found in Table 2.1.

Table 2-1: Summary of single studies not included in previously published systematic reviews

Reference	Interven-tion	De-sign	Limit-ations	Country	Grade of evidence	Effect
Arifeen [77]	Cord cleansing with chlorhexidine	cRCT	Single study	Bangladesh	Moderate - randomised trial but with questionable results due to inconsistencies in the effect between single cleansing and multiple cleansing groups. More research is required on the timing of the application of chlorhexidine that may have influenced these results.	Neonatal mortality in single cleansing group: relative risk=0.80, 95% CI: 0.65–0.98 Neonatal mortality in multiple cleansing group: relative risk=0.94, 0.78–1.14 Omphalitis in single cleansing group: relative risk=0.77, 0.40–1.48 Omphalitis in multiple cleansing group: relative risk=0.35, 0.15 0.81
Soofi[78]	Cord cleansing with chlorhexidine	cRCT, factorial design	Single study	Pakistan	High quality-cRCT, with no serious flaws.	Neonatal mortality: risk ratio=0.62, 0.45–85 Omphalitis: risk ratio=0.58, 0.41–0.82
Agrawal[71]	Clean cord care[a]	Observational, cross-sectional survey	Single study	India	Very low - observational study adjusting for cofounders but no adjustment for clustering, and included intervention arm of study from which the data were drawn.	Neonatal mortality: adjusted odds ratio=0.63, 0.46–0.87[b]
Saleem[79]	Chlorhexidine vaginal and infant wipe	RCT in three different hospitals	Single study	Pakistan	Moderate- bias was possible. Did not account for the fact that study participants were from three separate trials	Neonatal mortality: Relative risk=0.91, 0.67–1.24 Neonatal sepsis: Relative risk=0.96, 0.73–1.27

a. Clean cord care defined as use of clean instrument to cut the cord (new blade from a kit or blade used by skilled or trained birth attendants, or sterilised blade), use of clean thread to tie the cord (thread from a kit, or brought by a skilled or trained birth attendant, or a sterilised thread) and application of antiseptic or nothing to the cord

b. Odds ratio adjusted for maternal age, education, caste/tribe, religion, household wealth, newborn thermal care practice and care seeking during the first week after birth and study arms.

2.3.6 Study results

2.3.6.1 Clean delivery kit use

A systematic review published in 2012 assessed the effects of clean delivery kits and clean delivery practices on neonatal health outcomes.[68] Authors of the review concluded that there is no evidence on the independent effect of birth kits, since most studies where reductions in neonatal mortality were observed included kits as part of broader intervention packages.[68] Another systematic review published around the same time came to a similar conclusion after reviewing studies exploring the impact of kit use on neonatal and maternal outcomes.[74] In both reviews, only nine studies were identified reporting the effects of birth kits (all as part of broader intervention); only one of the studies was a cRCT.[68, 74] Of these nine studies, the reviews identified four studies showing a reduced rate of omphalitis, three studies showing improved neonatal survival (two of which demonstrated reductions in neonatal mortality due to tetanus), and three studies identifying reduced puerperal sepsis.[68, 74] The review also identified a cRCT from rural Pakistan evaluated the effect of kit use on maternal mortality but the sample size was not large enough to detect an effect with sufficient precision.[74, 80]

2.3.6.2 Kit use and neonatal mortality

The three studies included in the systematic review examining the association between kit use and improved neonatal survival were of varying quality.[68] The cRCT from Pakistan examined the effect of training traditional birth attendants (TBAs) and supplying them with clean delivery kits on neonatal mortality.[80] TBAs in the intervention clusters were trained in the following: antepartum, intrapartum, and postpartum care; how to conduct a clean delivery; use of a disposable delivery kit; when to refer women for emergency obstetric care; and essential newborn care. Additionally, two teams of obstetricians offering outreach clinics in obstetrical consultation were in place in two centres within the intervention clusters. The clean delivery kit included sterilised gloves, soap, gauze, cotton balls, antiseptic solution, umbilical cord clamp, and a surgical blade. At the end of the study, neonatal mortality was 35 per 1000 live births in the intervention clusters and 49 per 1000 live births in control clusters (OR 0.71, 95% CI: 0.62–0.82). Again, the specific contribution of kit use to the mortality reduction could not be estimated because the trial evaluated the impact of a broad package of antenatal and delivery care. However, kits were used in 35% of deliveries in intervention clusters compared with only 3% in control clusters. Neither of the other two trials looking at the association of kit use with overall neonatal mortality and neonatal mortality due to sepsis could separate the effect of kits from that of broader intervention packages.[81, 82] Other studies showed that, while kits modified practices directly linked to their physical components, for example use of a clean, sterilised blade, they often did not affect more distal caring practices depicted in accompanying instructions and educational leaflets, for example early breastfeeding and wrapping the newborn infant.[83]

2.3.6.3 Kit use and omphalitis

Four studies examining the effect of complex interventions on omphalitis, including the use of clean delivery kits, showed positive effects.[59, 83-85] However the studies were of low quality and did not adjust for confounding appropriately.[68, 74] Additionally, studies used different definitions of cord infection, making comparisons difficult.[68, 74]

Examples of study findings include results from a cross-sectional survey from Egypt that demonstrated an independent association between kit use and reduced cord infection (OR 0.42, 95% CI: 0.18–0.97) and results from a stepped-wedge cross-sectional study taking place in Tanzania that found cord infection was 13.1 times more likely ($p<0.001$) among neonates whose mothers did not use a kit.[84, 85] A study from Nepal revealed that newborns for whom kits were used had a reduced risk of infection compared to those for whom did not use a kit and who did not use a new or sterilised blade or a clean cutting surface (risk ratio 0.45, 95% C.I 0.25–0.81).[83] However, the same study demonstrated there was no difference in omphalitis when comparing kit users to women who used a clean blade to cut the cord on a hygienic cutting surface.[83] Results from the final study, also taking place in Nepal, found that newborns for whom the birth attendant had washed their hands with soap had a reduced risk of infection compared to those for whom no kit was used (adjusted rate ratio [aRR] 0.49, 95% CI: 0.43–0.56).[59] Research examining the effectiveness of birth kits need to take into account the effects of other interventions (e.g. concurrent kit promotion activities), as well as important potential confounders that could influence their impact on neonatal mortality.

2.3.6.4 Kit use and maternal health outcomes

The previously mentioned systematic review of studies examining the effect of clean delivery kits that were part of a broader intervention package on maternal health outcomes identified three studies.[80, 84, 85] Results from these studies indicate that clean delivery practices, especially the use of clean kits, improve maternal outcomes, in particular puerperal sepsis. Only one of these studies was considered of sufficient quality because it used a cRCT design. Results from this study showed a significant reduction in puerperal sepsis in the intervention clusters compared to control clusters (OR 0.18, 95% CI: 0.14–0.22).[80] The same study attempted to evaluate the effect of kits use on maternal mortality; there was a non-significant reduction in maternal deaths, perhaps due to lack of statistical power.[74] It was not possible to determine the effect of kit use alone on maternal health outcomes because, in all studies, kits were a part of a larger intervention package.

2.3.6.5 Cord care

The WHO currently recommends dry cord care; however these recommendations are based on results from a 2004 Cochrane review largely including studies from high-income countries, which differ substantially from low and middle-income countries in hygiene practices and exposure to infectious agents.[86, 87] This review was unable to address the effect of topical care on systemic infections or mortality.[88] The WHO acknowledged that antiseptics may be of some benefit in low-resource countries with higher rates of infection, and encouraged the use of an appropriate antimicrobial in these circumstances.[86] Until recently, there was lack of evidence supporting topical application of disinfectant to the umbilical cord stump.

The most up-to-date, robust evidence available on cord care comes from three cRCTs supporting the application of disinfectant to the umbilical cord in rural, low-resource settings. A cRCT in Sarlahi district, Nepal, compared topical applications of chlorhexidine to the umbilical cord to dry cord care in reducing cord infections and neonatal mortality. Using the omphalitis definition of severe redness with purulence, risk was reduced by 75% (incidence rate ratio [IRR] 0.25, 95% CI 0.12– 0.53).[89] Mortality was also reduced by 34%, from 21.6 to 14.4 per 1000, (relative risk [RR] 0.66, 95% CI: 0.46–0.95) for newborn infants enrolled and treated within 24 hours.[89] However, infants who were not treated within 24 hours did not experience a significant reduction in mortality (RR 0.76, 95% CI: 0.55–1.04).[89] Two recently published cRCTs testing the effect of cord cleansing with chlorhexidine on neonatal mortality and omphalitis in rural Bangladesh and Pakistan also found beneficial effects on omphalitis and neonatal survival with cord cleansing using chlorhexidine.[77, 78] The Bangladesh study was a parallel cRCT where participants were randomised to one of three arms: single cleansing of the cord with chlorhexidine as soon as possible after birth, daily cleansing with chlorhexidine for seven days after birth, or promotion of dry cord care.[77]

Neonatal morality was lower in the single cleansing group compared to the dry cord care group (relative risk [RR] 0.80, 95% CI: 0.65–0.98) but not in the multiple cleansing group (RR 0.94, 95% CI: 0.78–1.14). [77] There was however, a significant reduction in the occurrence of severe cord infection in the multiple cleansing cord group compared to the dry cord care group (RR 0.35, 95% CI: 0.15–0.81) but not in the single cleansing group (RR 0.77, 95% CI: 0.40–1.48).[77] The occurrence of a significant reduction in neonatal mortality in the single cleansing group but not the multiple cleansing group is surprising. It could mean that the lack of a significant reduction in neonatal mortality in the multiple cleansing group occurred by chance. The authors concluded that cleaning a newborn infant's umbilical cord with chlorhexidine will improve survival, but that further studies are required to determine the optimal frequency of antiseptic application.[77] The Pakistan study was a two by two factorial design cRCT, with the following interventions included in each arm: birth kits containing 4% chlorhexidine solution with soap and educational messages promoting hand washing (group a); hand washing only (group b), chlorhexidine solution only (group c); standard dry cord care in the control group (group d). Results indicated a relative reduction in omphalitis and neonatal mortality with chlorhexidine application compared to no chlorhexidine application (risk ratio 0.58, 95% CI: 0.41–0.82) and (risk ratio 0.62, 95% CI: 0.45–0.85) respectively (i.e. comparing group a to c and group b to d).[78] All three South Asian trials suggest that applying chlorhexidine to the umbilical cord reduces cord infection and neonatal mortality.

One observational study examined the effect of clean cord care on neonatal mortality, but it was impossible to tease out the effect of disinfectant on mortality as clean cord care included either the application of an antiseptic or dry cord care.[71] This study showed that the use of all three cord care practices including using a clean blade to cut the cord, a clean thread to tie the cord, and either dry cord care or application of disinfectant, resulted in a significant reduced odds in neonatal mortality (adjusted odds ratio [aOR]=0.63; 95% CI 0.46–0.87). The aOR was adjusted for maternal age, education, caste/tribe, religion, household wealth, newborn thermal care practice and care seeking during the first week after birth and study arms. The individual clean cord care practices also had significant effects on neonatal mortality: use of a clean blade resulted in a significant reduction in neonatal mortality (aOR 0.20, 95% CI: 0.11–0.38), as did the use of clean thread to tie the cord (aOR 0.70, 95% CI: 0.54–0.91), and the application of nothing or antiseptic to the cord (aOR 0.70, 95% CI: 0.53–0.91).

2.3.6.6 Chlorhexidine for the birth canal

As many cases of neonatal sepsis are acquired through transmission of bacteria in the birth canal, it is possible that cleansing the canal with an antimicrobial agent prior to delivery could lead to reductions not only in neonatal sepsis, but also puerperal sepsis.[90] Although some research has shown that application of chlorhexidine to the vagina or the newborn infant's umbilical cord had no effect in low-risk settings, there is potential for improvement in both newborn and maternal outcomes in higher-risk settings.[79, 91-97] A hospital-based study in Egypt showed a significantly greater number of maternal admissions to hospital during the time period where no intervention (i.e. antiseptic) was received ($p<0.001$) as well as a significantly higher rate of neonatal admissions due to sepsis ($p<0.001$) and sepsis-related neonatal mortality ($p=0.004$).[91] However the choice of study design was poor, with no distinct control and intervention arms and no attempt to control for confounding factors. A study in Malawi examining cleansing of the birth canal found significant reductions in neonatal admissions due to sepsis (OR 0.43, 95% CI: 0.28–0.67) as well as in neonatal deaths due to sepsis (OR 0.33, 95% CI: 0.15–0.70).[92] Maternal admissions due to sepsis were also significantly reduced (OR 0.37, 95% CI: 0.13–0.82).[92] This study had the limitation of having a relatively poor design, with no attempt to control for confounding. A hospital-based RCT from Pakistan examining the effects of chlorhexidine on maternal vaginal wipes and neonatal wipes on maternal mortality, perinatal mortality and neonatal sepsis reported no beneficial effects.[79] It is possible that infections acquired in the hospital-based Pakistan study were different to those seen in rural community-based populations in other South Asian countries.

2.3.6.7 Hand hygiene and puerperal sepsis

Trials evaluating the effectiveness of hand washing in delivery are unethical due to the overwhelming evidence that hand hygiene is the most important clean delivery practice in infection control, and can easily be achieved with soap and water.[98] For this reason, trials testing the effect of hand washing on puerperal sepsis are unavailable, and the best evidence remains that provided by Semmelweis in the 19th century.[37] After he introduced chlorine solution with lime, rates of maternal mortality declined from 900 per 10,000 birth to 300 per 10,000 births.[37] Gloves have also been proven effective in preventing the spread of infection, however they may also reduce compliance with standard hand hygiene recommendations.[98] Despite the known beneficial effects of hand washing, this basic clean delivery practice is not always applied in low-resource settings.[99-101] Basic antiseptic practices can even be difficult to maintain in high-income countries.[102]

2.3.6.8 Other clean delivery practices

A recent systematic review found 15 studies examining the associations between clean delivery practices and outcomes including neonatal tetanus, omphalitis, and neonatal mortality.[68] Eight published studies on hand washing prior to delivery reported associations with reduced tetanus-specific neonatal mortality, or general reductions in neonatal mortality.[59, 68, 83, 103-108] Three studies examined the relationship between having a clean delivery surface and neonatal tetanus or omphalitis, and showed both positive and negative associations.[68, 107, 109, 110] Studies examining clean cord cutting and cord tying practices and the association with neonatal tetanus and/or sepsis also had conflicting conclusions.[68, 84, 103, 109-113]

2.4 Discussion

The review conducted for this thesis echoes findings from two systematic reviews published in 2012.[68, 74] Findings from these reviews suggested that there is little evidence on the effect of clean delivery practices on maternal and neonatal morbidity and mortality, and that the existing evidence is of low quality. Since the publication of these reviews however, better quality evidence has been published on the effectiveness of chlorhexidine in reducing neonatal mortality and sepsis.[77, 78]

Although historical evidence shows that clean delivery practices have an important role in improving maternal and neonatal survival, further quantification of their effects in low-resource settings can help to estimate their potential benefit both alone and as part of intervention packages. It is unethical to conduct RCTs of clean delivery practices given that the biological mechanisms leading to reduced morbidity and mortality have been known for some time.[68] Instead, in order to quantify the potential effects of clean delivery practices on survival, good quality observational studies are required that minimize bias. In every article identified in the two 2012 systematic reviews, authors failed to adequately control for confounding and address other forms of bias. Subsequent chapters of this thesis seek to examine the effects of clean delivery practices on neonatal and maternal mortality in three South Asian low-resource settings, whilst accounting for potential biases.

Chapter 3 Methods

3.1 Introduction

This chapter will provide details on the cRCTs from which the data used in this thesis were drawn, including information on the study locations, populations, designs, data collection systems, and ethical approval. For each objective of the thesis, I provide details of outcome ascertainment, exposure verification, confounder selection, and statistical methods. Lastly, I describe the limitations of the analyses using traditional methods, and describe more advanced approaches applied to overcome these.

3.2 Background of cRCTs

3.2.1 General

Over the past twelve years, University College London's Institute for Global Health (IGH) has conducted seven cRCTs to evaluate the impact of community-based participatory interventions with women's groups on maternal and newborn health outcomes.[99-101, 114-117] For this thesis, data were drawn from the four rural South Asian cRCTs. Details of the individual trials can be found in Table 3.1. The studies were chosen because they were the only trials that collected data on relevant clean delivery practices. All four studies took place in rural areas with high neonatal mortality rates: one was conducted in three districts in Jharkhand and Orissa states in eastern India, two trials took place in identical locations within the three districts of Bogra, Moulavibazar and Faridpur in Bangladesh, and one trial took place in Makwanpur district, Nepal. Additionally, after the successful completion of the cRCT in Nepal, the intervention was applied to previous control clusters and similar surveillance and data collection methods continued, adding to the previous evidence base. In India, data were available from a baseline surveillance system implemented prior to the intervention. After an initial unsuccessful cRCT in Bangladesh, the trial was repeated for four additional years whilst increasing the intervention coverage rates, also adding data to the existing evidence base.

Objectives three and four of this thesis are to explore the associations between clean delivery practices and neonatal and maternal mortality. To address these objectives, I used data from the trials' control clusters only, as it was possible that the intervention may have influenced the use of clean delivery practices. The fifth objective of this thesis is to evaluate the impact of a community-based participatory intervention with women's groups on the use of clean delivery practices. For this reason, data from both intervention and control arms were used.

3.2.2 Intervention and study designs

Each of the cRCTs from which data were drawn used an intervention consisting of a community action cycle involving participatory women's groups adapted from an earlier study in Bolivia.[118-120] The Bolivian intervention encouraged community members, and particularly women, to come together in groups to identify, prioritise and address common maternal and newborn health problems. After three years of intervention, perinatal mortality rates fell from 117 per 1000 births to 44 per 1000 births. However, this study used a non-randomised before and after design, so that confounding and other forms of bias had not been accounted for.

The interventions tested in the cRCTs from which data for this thesis were taken consisted of monthly women's group meetings.[99-101, 114] The intervention was divided into four separate phases: in phase one, the women's groups identified and prioritised maternal and newborn health problems; in phase two, they discussed and prioritised locally feasible strategies to address these problems; in phase three, they put the strategies into practice; finally, in phase four, they assessed the effects of their actions. Participatory games and storytelling followed by discussions were used to discuss ideas on how to improve maternal and newborn health. Women's groups also organised large village-level meetings at least twice during the cycle in order to share their prioritised problems and chosen strategies with the wider community and enlist their support. Women's group facilitators were local women selected from the community and trained in participatory communication techniques. Supervisory meetings were held, usually on a bimonthly basis, to train and support group facilitators.[99-101, 114]

A cRCT design was used for each study, with some important differences between each of the four study sites. The Nepal study used a closed cohort design where women were recruited in pregnancy and followed up throughout the trial, whereas all other studies used an open cohort design where women 'joined' if they gave birth in the study areas during the trial period. The Nepal study also used a matched study design: 12 pairs of clusters were matched based on population densities. The first study in Bangladesh used a factorial design that included both a women's group intervention and a resuscitation intervention aimed at reducing the incidence of intrapartum hypoxia. As the resuscitation intervention had no impact on any study outcomes and no differences were noted between this study arm and the other three study arms for any mortality outcomes or care practices including clean delivery practices, this intervention was ignored and this treatment arm was treated as a control arm.[100] The Ekjut study and second Bangladesh study each had one intervention and one control arm.

Figure 3.1: Map showing the locations of the four cRCTs in India, Bangladesh, and Nepal

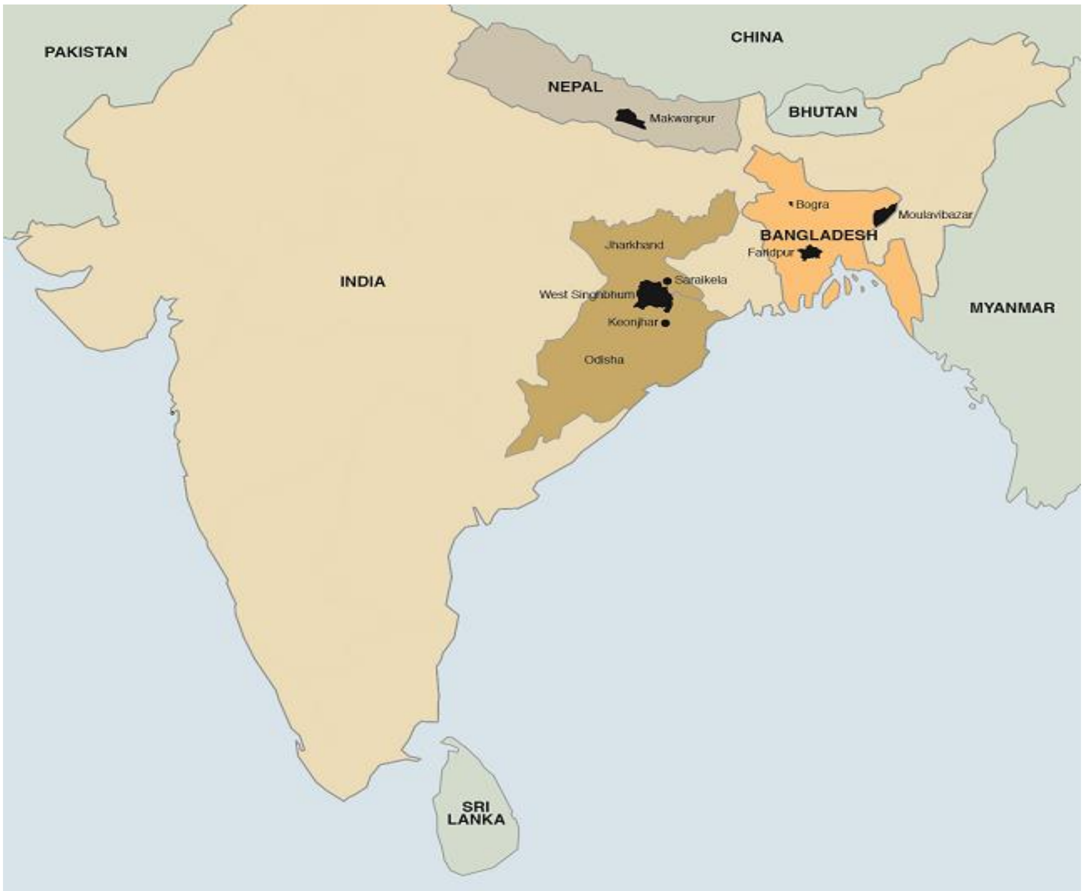


Table 3-1: Details of individual cRCTs

	India	Bangladesh	Nepal
Location	Three districts of Jharkhand and Orissa (eastern India): Keonjhar, West Singhbhum and Saraikela	Three rural districts: Bogra, Maulvibazaar and Faridpur	Makwanpur district
Study period	Baseline surveillance: Nov 2004 - July 2005 cRCT: July 2005 to July 2008	1st cRCT: Feb 2005 to Dec 2007 2nd cRCT: Jan 2009 to June 2011	cRCT: Nov 2001 to Oct 2003 Surveillance data: Nov 1, 2003 - March 2005
Design	Baseline surveillance: control and intervention arms from upcoming cRCT cRCT: open cohort	1st cRCT: factorial design, cRCT, open cohort 2nd cRCT: cRCT, open cohort.	cRCT: matched design and closed cohort Post cRCT: roll-out of intervention into control clusters
Cluster characteristics	8-10 villages with residents classified as tribal or OBC	Villages making up a union	Village Development Committees
Clusters included in study, n	36	18	24
Participants	Women aged between 15 and 49 who had given birth in study period, and their infants.	Women aged between 15 and 49 who had given birth in study period, and their infants.	Women aged between 15 and 49, married and with potential to become pregnant in study period, and their infants.
MMR prior to initial intervention	510 [99]	380 [121]	539 [122]
NMR prior to initial intervention	58 [99]	41 [123]	60[124]
Contents of clean delivery kits	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Plastic coin to use as surface to cut the cord. Instructions available in government kits only.
Individual clean delivery practices on which data were collected, aside from kit use	Hand washing, use of sterilised blade to cut cord, type of cord application (dry or other), use of sterilised thread to tie the cord, use of plastic sheet and use of gloves.	Hand washing, use of sterilised blade to cut cord, type of cord application (dry or other), use of sterilised thread to tie the cord, use of plastic sheet and use of gloves.	Hand washing, use of sterilised blade to cut cord, type of cord application (dry or other).
Concurrent activities to promote clean delivery practices and kit use	In both intervention and control areas, strengthening the activities of village health and sanitation committees.	Training was provided to nurses, doctors and paramedical staff in essential newborn care, including the six cleans.	Health service strengthening across intervention and control areas included training of all health workers on the six cleans.

3.2.3 Surveillance systems

Each of the studies used similar data collections systems, referred to here as 'surveillance systems'. These surveillance systems relied upon the use of key informants to monitor vital events (births and deaths). Key informants were usually village members, sometimes TBAs. Their responsibility was to report any births, maternal or newborn deaths, as well as deaths to women of reproductive age (i.e. between the age of 15 and 49).[99-101, 114] Once a month, the key informant met with an interviewer who verified all births and deaths, and collected details on the mother, the antenatal delivery and postnatal period through a structured questionnaire. Examples of information collected included details of maternal education and age, parity, complications in the antenatal and delivery periods, care providers, and essential newborn care practices. This questionnaire was administered approximately six weeks after delivery and also included questions about clean delivery practices.[99-101, 114]

In each data collection area, a monitoring manager, an interviewer supervisor and approximately 12 interviewers were responsible for data collection. An overall monitoring manager supervised field-based activities.[99-101, 114] In the event of a neonatal death or stillbirth, a verbal autopsy was administered with either the mother or other individuals present at the time of the birth. If a woman of reproductive age had died, information was gathered from family members to ascertain whether the woman was pregnant or had recently given birth. If a maternal death had occurred, the monitoring supervisors carried out verbal autopsies with a relative. Information from this verbal autopsy was analysed by physicians to determine cause of death.

3.2.4 Study population

Study participants included women between the ages of 15 and 49 who had given birth to a live born or stillborn infant. In order to explore the associations between clean delivery practices and neonatal and maternal mortality (objectives 3 and 4), I used data from the control arms of the cRCTs. In order to examine the effects of the women's group intervention on the use of clean delivery practices (objective 6), I used data from intervention and control arms.

3.2.5 Ethics

Research ethics approval for the cRCTs came from in-country Ethical Review Committees (ERCs): the ERC of the Diabetic Association of Bangladesh (BADAS); an independent ERC in Jamshedpur, India (Ekjut trial); and the Nepal Health Research Council. Approval was also obtained from the Institute of Child Health and Great Ormond Street Hospital for Children (UK) Research Ethics Committee. All trials were conducted in disadvantaged areas with low levels of female literacy, and all participants gave consent in writing or by thumbprint.

3.3 Study outcomes and exposures

Three main outcomes were used for the different study objectives. Their definitions can be found in Table 3.2. For each neonatal or maternal death, the date of death was recorded. For the third study objective, the outcome of interest was a neonatal death, defined by ICD-10 as a death occurring up to 28 days after delivery.[2] For the fourth study objective, the outcome was postpartum maternal deaths, or a death that occurred up to 42 days after delivery.[2] For reasons specified later, maternal deaths that occurred during pregnancy and delivery were not included in this analysis. For the sixth study objective, the main outcomes were the previously listed clean delivery practices, including clean delivery kit use.

Table 3-2: Definitions of outcomes used

Outcome	Thesis objectives	Definition
Neonatal mortality	3[a]	Death of a newborn within 28 days of delivery.[2]
Postpartum maternal death	4[b]	This is an adaptation of ICD-10 definition and includes death t of a women just after and up to 42 after delivery.[2]
Clean delivery practices	6[c]	See Table 3.3 below

a. Examining associations between clean delivery practices and neonatal mortality.
b. Examining associations between clean delivery practices and postnatal maternal mortality.
c. Evaluating the effectiveness of a women's group intervention on the use of clean delivery practices.

In all study areas, kits were promoted and distributed through the health system as part of government initiatives to improve birth outcomes. They included the following as a minimum: soap, clean string, a razor blade, and a plastic sheet. Sterilisation of string and blade was also recommended. In India, mothers received kits from health facilities, made some themselves, and also purchased some from each other as well as from TBAs. In Nepal, kits included a plastic disc against which the cord could be cut. Instructions on kit use were included in Nepal and Bangladesh, and in government manufactured kits in India. Questions administered to study participants on kit use were delivered differently in Nepal, compared to Bangladesh and India. In Bangladesh and India, women were asked whether or not a kit was used. In Nepal, women were shown a kit and asked if they knew what a kit was. If women knew what a kit was, they were then asked whether or not a kit was used during the delivery.

Besides kit use, information was also collected on other clean delivery practices for each study site. Interviewers asked about appropriate hand hygiene, including whether the birth attendant washed her hands with soap prior to delivery (in all study sites) and whether gloves were used during delivery (in Bangladesh and India only). Information was collected on appropriate cord care included the following: use of a sterilised blade to cut the cord (all study sites); use of a sterilised thread to tie the cord (Bangladesh and India only); what substance was applied to the cord after it was cut (all study sites). Additionally, information was collected about whether a plastic sheet was used as a clean delivery surface (India and Bangladesh only). Table 3.1 details the information on the different clean delivery practices collected at each study site.

In each of the study sites, mothers were asked whether any substance was placed on their newborn's umbilical cord, and their response was coded as “dry cord care” if no substance had been applied. Table 3.3 provides definitions for the exposures relevant to each of the study objectives and sites.

Table 3-3: Definitions of exposures

Exposure	Thesis objectives	Definition	Relevant study site
Clean delivery kit	3[a] 4[b]	Package containing the following items: soap, razor blade to cut the cord, thread to tie the cord, plastic sheet for a clean delivery surface, and a piece of gauze.	All sites
Hand washing by birth attendant	3[a], 4[b]	Birth attendant washing hands with soap prior to delivery	All sites
Clean cord cutting instrument	3[a]	Sterilised blade	All sites
Clean cord tying instrument	3[a]	Sterilised thread	Bangladesh, India
Disinfectant applied to cord compared to dry cord care	3[a]	Chlorhexidine or other disinfectant applied to cord after cutting, compared to dry cord care, defined as the practice of putting nothing on the newly cut umbilical cord, or cleaning soiled skin in the periumbilical area with soap and water, wiping it with a dry cotton swab or cloth, and allowing the area to air dry.[86]	All sites
Gloves	3[a]	Use of gloves to deliver the baby	Bangladesh, India
Clean birth surface	3[a]	Use of new/clean plastic sheet	Bangladesh, India
Women's group intervention	6[c]	Giving birth in a geographical cluster where women's groups meetings have been occurring.	All sites

a. Examining associations between clean delivery practices and neonatal mortality.
b. Examining associations between clean delivery practices and postnatal maternal mortality.
c. Evaluating the effectiveness of a women's group intervention on the use of clean delivery practices.

3.4 Analytical challenges

While data from these multiple trials provided us with a unique opportunity to explore the associations between clean delivery practices and maternal/neonatal mortality in South Asia, they also presented methodological challenges. The first challenge was that the cRCTs sometimes collected data on exposures in different ways. The second challenge related to the use of these as observational data. Below I describe these challenges in further detail and outline the steps taken to address them.

3.4.1 Heterogeneity between study sites

The four cRCTs from which data were drawn for this thesis were quite similar, due to the use of comparable surveillance systems and survey questionnaires. However, differences did exist between sites and these may have created issues for the different analyses. For instance, as the survey questionnaires for the different studies were not validated, questions may have been administered differently to study respondents, evoking different responses to similar questions. In other instances, similar questions were worded slightly differently across different questionnaires, resulting in substantial differences in the type of data collected. For example, in Nepal, respondents were asked whether or not they knew what a clean delivery kit was and presented with a kit. If respondents knew what a kit was, they were then asked whether or not it had been used during their last delivery. As a result, women who did not know what a kit was did not answer the second question about kit use. Although it is reasonable to assume that women who did not know what a kit was did not use a kit, technically we cannot guarantee this, and there is a possibility that women who indicated that they did not know what a kit was had a birth attendant who used the kit without their knowledge. Hence, from this point onward, in instances where respondents indicated that they did not know what a kit was, were treated as missing. Respondents for the cRCTs in India and Bangladesh were asked one question on kit use which also gave them the opportunity to indicate if they did not know whether a kit had been used or not.

To check for important differences in data between the different study sites, I compared the prevalence of exposures of interests and confounders between sites. I then explored any substantial differences by discussing them with the data collection teams in each study sites. I applied sensitivity analyses to address some of these issues (e.g. differences in some measures and missing data on kit use due to maternal deaths). Details of statistical approaches are given in Sections 3.5.2 and 3.5.3.

3.4.2 Use of observational data

A conventional analysis of observational data typically relies on random error to quantify the uncertainty of study estimates. However, this approach is questionable where there has been no random sampling or randomisation, and recent advances in epidemiology have shown that this often leaves reported estimates open to bias.[125] An RCT is the gold standard to measure causal effects; however its implementation is not always possible due to feasibility, logistical, and ethical constraints. For these reasons, the use of observational data is commonplace in medical research, and new ways to addresses biases must be utilised. Due to ethical constraints, randomised trials are not always possible for research in maternal and newborn health. It would be unethical to test the effects of clean delivery practices on maternal and newborn survival using a RCT design for example, given the biological plausibility of the known benefits of such clean practices.

The use of observational data in any analysis is based on a set of assumptions, including the following: a study participant has equal probability of being classified as exposed or unexposed; there is no measurement error in the classification of an exposure; assignment of potential confounders occurs randomly in the exposed and unexposed groups (i.e. no unmeasured confounding); and selection, participation and missing data occur randomly for the exposure and confounders.[125] In instances where these assumptions are not met, estimates are likely to be biased and do not adequately express the uncertainty about the estimated effect.[125] The very nature of observational data used in these analyses implies that the above-mentioned assumptions must be met and that if they are not, these limitations must be appropriately addressed or described.

The Bradford Hill criteria are widely accepted as important benchmarks to assess causation, especially when using observational data.[126] Over the past two decades however, new techniques have emerged indicating that these criteria alone are insufficient to prove causation. The counterfactual approach on the other hand, assumes that a treatment/exposure is causal only if, had the treatment not been administered, the outcome would have differed.[127] Rothman coined the term a "sufficient-component causal model" to describe a set of factors which, acting together, are sufficient to induce a binary response so that, if at least one of the factors were removed, the outcome would change.[128] Modern causal inference techniques that have moved beyond the Bradford Hill criteria have been shown to reduce biases associated with observational data by aiding the analyst in selecting appropriate confounders and applying robust sensitivity analyses. By ensuring the effect of a treatment or exposure is causal for outcome, we can be more certain that the effects seen are not just associations, but instead are the results of cause-effect mechanisms. The remainder of this chapter will discuss the causal inference methods which, when applied to the different analyses in this study, will help to reduce the bias in effect estimates and thus increase our confidence in the study findings.

3.5 Causal inference techniques used to reduce the bias in effect estimates associated with observational data

3.5.1 Confounding bias

3.5.1.1 Background on confounding bias

Traditionally, a confounder has been defined as a variable associated with the exposure and the outcome and is not on the causal pathway between these two.[129] However new epidemiological techniques have shown that traditional methods used to select and adjust for confounding factors may be inadequate.[129] Causal inference methodologists define confounding as a bias that occurs when the treatment and outcome share a common cause, resulting in the lack of comparability or exchangeability between exposure groups.[130] In the event of randomisation of a treatment, the exposed and unexposed are exchangeable. This is known as marginal exchangeability and is similar to having no confounding present.[127] However, in observational data, we cannot ensure this exchangeability and the treatment and exposure are said to be conditionally associated. This association must be accounted for by adjusting for confounders.[127]

Many researchers feel they are being rigorous by adjusting for all potential confounders thought to be associated with both the outcome and exposure. However in doing so, they may potentially create new biases including collider bias.[131] When the exposure and outcome share no common causes but a common consequence, there is no confounding through causation, and this variable should not be adjusted for as this creates collider bias.[131] Figures 3.2 and 3.3 depict confounding bias and collider bias, respectively. In Figure 3.2, C is a common cause of both E and D, and is therefore considered to be a confounder. As an example, if we are measuring the effect of clean delivery kit use on neonatal mortality, we would expect to see a decrease in neonatal mortality with kit use. However, because maternal age is a 'risk' for both kit use and neonatal mortality, failure to condition on this variable would result in a confounding bias through the backdoor path, resulting in a stronger association than expected. Figure 3.3 depicts a relationship where neonatal sepsis is associated with unhygienic deliveries as well as puerperal sepsis. In this relationship, neonatal sepsis is a consequence of the unhygienic delivery as well as the puerperal sepsis. Bias introduced by a common consequence is similar to the bias created by confounding, and as with confounding bias, collider bias can introduce an under or over-estimation of the true effect. The difference between the traditional definition of a confounder based on associations and the structural definition of a confounder is that the latter requires a priori causal assumptions or decisions based on expert opinion, while the former relies on statistical associations detected in the data.[127]

Figure 3.2: Example of a confounder where exposure and disease are its consequences

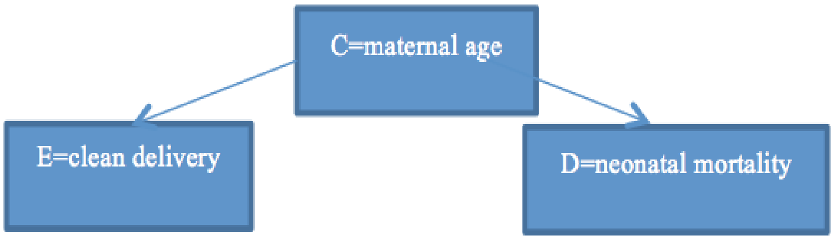
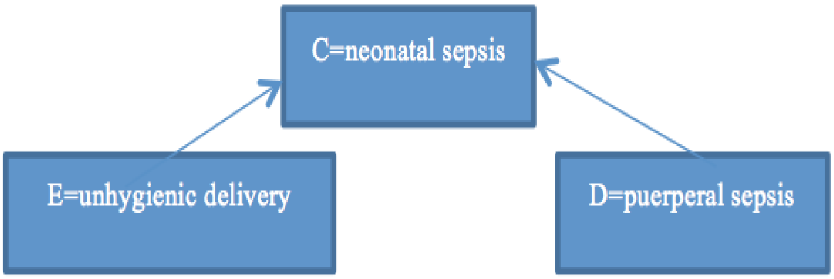


Figure 3.3: Example of collider bias, introduced when a covariate that is a common consequence of the exposure and disease is conditioned on.



3.5.1.2 Methods to control for confounding bias

For the purpose of this thesis, I consider confounding to be a bias that occurs when a treatment and outcome share a common cause, resulting in the lack of comparability or exchangeability between exposure groups.[132] The confounders selected for these analyses will be mapped in relation to each other, together with exposures and with the outcome of interest using DAGitty®, a tool for creating and analysing causal models using directed acyclic graphs (DAGs).[132] A DAG can help to better understand whether potential bias is present by allowing for a graphical representation of the causal relationships between all variables being considered for a model.[129] A DAG uses an arrow, connecting two variables to represent causation, whereas variables that are not considered confounders and do not have a direct causal association, do not have a connecting arrow.[129] Specifically, a graphical representation of a confounder using a DAG shows arrows directed from the confounder to both the exposure and the outcome (Figure 3.2). For study objectives three and four, DAGs will be used to help inform the statistical modelling of the relationships between each of the separate clean delivery practices and neonatal and maternal mortality, taking confounders into account.[132] Using this methodology, all potential confounders will be included in the DAG, and arrows drawn to indicate whether the variable in question is causal for both the exposure and the outcome (i.e. a confounder). If a variable is introducing bias into the model, this will be made obvious by the direction of the arrows.[129]

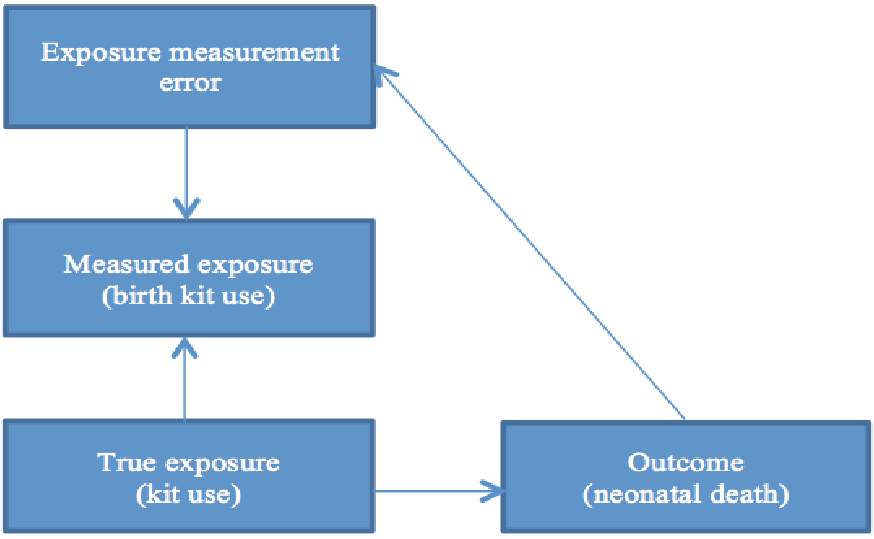
3.5.2 Misclassification (measurement) bias

3.5.2.1 Background

When the exposure or outcome has been misclassified, the strength of the association between the two could be strengthened or weakened.[127] In many observational analyses, the exposure variable is a measured exposure and not the true exposure. In this thesis, I will assume that the outcome measurement of neonatal and maternal mortality has 100% sensitivity and specificity and therefore no misclassification bias, due to the detailed way in which the verbal autopsies were performed and analysed for each of the studies.

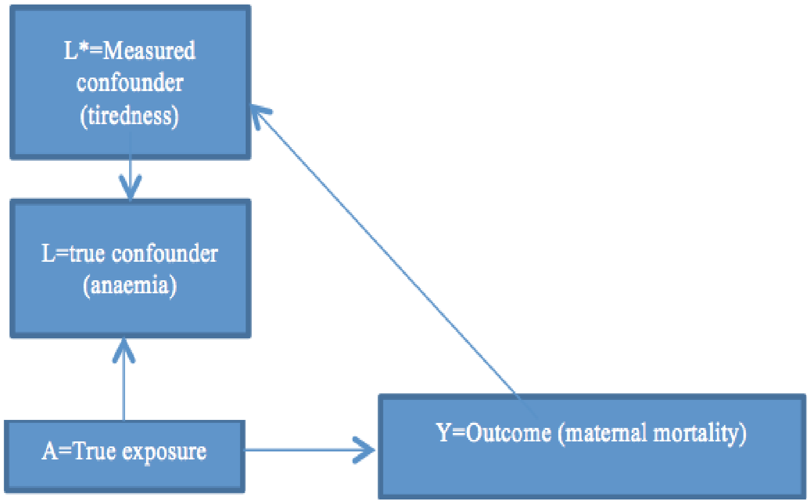
Figure 3.4 is a DAG depicting the causal nature of misclassification bias.[127] The true exposure is causal for not only the outcome, but also the measured exposure. The exposure measurement error is all other factors affecting the error present in measured exposure besides the true exposure. The causal arrow from treatment outcome to exposure measurement error indicates that the treatment outcome is causal for exposure measurement error (i.e. differential measurement error). As an example, the death of a newborn may increase or decrease the exposure measurement error, which in turn will influence whether or not observed data refer to actual birth kit use. This form of measurement error is commonly referred to as recall bias.

Figure 3.4: DAG depicting the causal nature of misclassification bias



Misclassification error can occur not only in the treatment and outcome measures, but also in the measurement of confounders. Including confounders in any observational study assumes that these confounders were adequately measured.[125] In order to ensure that confounders are measured as accurately as possible, it is important to ensure that the questions being asked have been externally validated as without this validation, we cannot assure that we are measuring what we are intending to measure. There is a possibility that confounders included in these analyses were not measured with complete accuracy. One would expect that a mother would be better at recalling certain events than others, depending on her circumstances. For instance, mothers may be more prone to recalling problems in the antenatal, delivery and postnatal period if their newborn has died. Or, as an example, in some of the cRCTs the interviewer asked respondents whether or not the mother was tired around the time of delivery: this is ambiguous and could indicate any number of conditions, including the intended measurement of anaemia. Figure 3.5 shows how misclassification bias occurs when confounders are not measured accurately.[127] When the miss-measured confounder, L*, is the variable being conditioned on, the true backdoor path cannot be blocked by conditioning on the confounder that was not measured accurately.[127] As will be discussed in sections 4.2.3 and 5.2.4, which relate to each of the separate analyses, potential confounders included variables such as maternal age and parity, and not variables that are subject to bias such as how a mother feels in pregnancy. For this reason, in this thesis, I assume that all potential confounders were measured adequately.

Figure 3.5: An example of how conditioning on a miss-measured confounder will not block the backdoor pathway between the true confounder, the true exposure and the true outcome.



3.5.2.2 Sensitivity analysis to test for potential measurement error

Although the best way to reduce measurement error is to ensure that it is not introduced in the data in the first place, this is not always possible. In this thesis, I explore the effect of potential misclassification in the reporting of clean delivery practices on the strength of the association with neonatal and maternal survival in chapters four and five, respectively. For these analyses, independent differential misclassification was assumed, whereby the accuracy in reporting on the use of the clean delivery practices was different depending on whether the newborn or mother survived. Death was used as a proxy to gage the accuracy in the reporting of clean delivery practices. It was assumed that, in the event of a death, there would be reduced sensitivity in the ability to accurately report clean delivery practices. As an example, in the event of a death, the person reporting clean delivery practices may have been searching for explanations as to why the death occurred, and may partially seek to explain why the death occurred by under-reporting behaviours that improved survival, decreasing sensitivity. Using the same reasoning, if a mother and newborn infant survived, specificity may have been reduced as a mother might have reported using clean practices in order to describe socially desirable behaviours. Both instances (reduced sensitivity in the case of death, or reduced specificity in the case of survival) would lead to an over-estimation of the effect of the clean delivery practice on survival.

In order to address misclassification bias, I used methods based on a weighted logistic regression model developed by Lyles and Lin that allowed adjusted odds ratios to be estimated whilst accounting for differential misclassification rates of the main exposure.[133] I calculated the required weights used to adjust the odds ratios using positive and negative predictive values computed using pre-specified sensitivities and specificities, the outcome of interest, the observed exposure of interest and other important covariates.[133] The dataset was expanded, whereby the records were duplicated to account for the potential misclassification of the exposure variable (i.e. if a record in the original dataset reported the birth attendant washing her hands, the expanded dataset would contain the original record, and a duplicated record reporting the birth attendant as not washing her hands).[133] Records in the original observed dataset that reported hand washing were assigned a weight based on the positive predictive value and records in the expanded dataset weighted the misclassified record based on one minus the positive predictive value. Using the same reasoning, records in the original observed dataset that reported no hand washing were assigned a weight based on one minus the negative predictive value, and records in the expanded dataset weighted the misclassified record based on the negative predictive value. The jackknife standard error was used to account for the uncertainty associated with the observational nature of the data.[133] The jackknife procedure systematically calculates a new estimate, by leaving out one observation at a time, and in doing so accounting for the bias and variance associated with the use of observational data.[134]

The final logistic regression model included: clean delivery practices of interest (exposures), maternal or neonatal death (main outcomes), study site and maternal age (both potential confounders). Due to complexities in assigning different weights to each level of the model parameters (i.e. creating an expanded dataset for all possible combinations of the misclassified variable), only those confounders with the greatest effects on effect estimates were included.

Differential misclassification assumed that sensitivities and specificities differed depending on whether the mother or newborn lived or died. With this in mind, the weight assigned to a record was determined by whether a mother or newborn lived or died. Based on this assumption, several combinations of sensitivities and specificities were used to test the robustness of the study findings. The main limitation of this approach is that the following restrictions must be imposed on the choice of different sensitivities and specificities as a necessary condition for adequate model fitting:

Sensitivity (hand washing)> probability (hand washing)

Specificity (hand washing)>1- probability (hand washing)

These restrictions meant that only a small range of sensitivities and specificities could be considered to explore potential misclassification bias. As differential misclassification was assumed, restrictions were imposed depending on whether there was a death or not. Table 3.4 shows the ranges of the sensitivities and specificities these restrictions imposed on this analysis. As an example, in the event of a neonatal death, it was only possible to explore the effects of potential misclassification bias for sensitivities greater than 0.19. Likewise, in the event of a maternal death, it was only possible to explore the effects of potential misclassification bias for sensitivities greater than 0.72. Appendix 1 provides an example of the SAS code used for this sensitivity analysis.

Table 3-4: Minimum sensitivities and specificities that could be used to determine the extent of misclassification bias on estimates in the instance of neonatal or maternal survival and death

Outcome measure	Sensitivity	Specificity	Sensitivity	Specificity
	Death		Survival	
Neonatal	0.19	0.94	0.29	0.91
Maternal	0.72	0.89	0.86	0.85

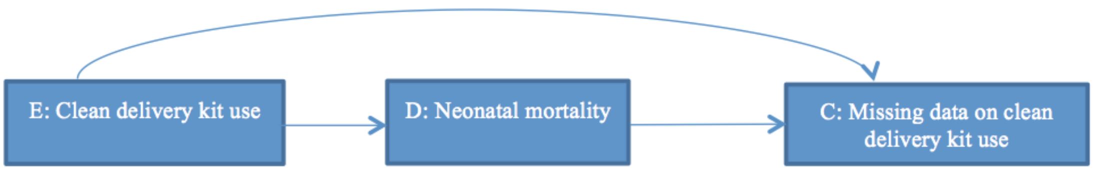
3.5.2.3 Missing data bias

3.5.2.4 Background

Missing data is a common issue in many studies, and when data is not missing completely at random, is often dealt with using inappropriate methods, and is considered a form of selection bias.[135] A recent review of published RCTs in major medical journals has described the ways in which missingness is handled.[135] Of the 71 trials reviewed, only 21% reported sensitivity analyses and, of 37 trials with repeated outcome measures, 46% performed complete case analysis.[135] Despite the fact that Consolidated Standard of Reporting Trials (CONSORT) guidelines recommend that the number of patients with missing data are reported by treatment arm, an estimated 65% of studies in PubMed journals do not report how missing data were handled.[136, 137] Traditional methods in dealing with missing data include complete case analysis, imputation of a mean, creating an extra category, last observation carried forward and assuming unknown data is missing. All of the aforementioned methods are prone to serious biases.[137]

Missing data bias is depicted graphically in Figure 3.6. If clean delivery kit use is causal for a reduction in neonatal mortality, conditioned on C, (i.e. using complete case analysis), the result will be an association between kit use and neonatal mortality, regardless of whether or not there is a true causal relationship. If the analysis had not been conditioned on the effect or consequence of kit use and neonatal mortality (collider) C, then the only open path between treatment and outcome would be that between kit use and neonatal mortality.

Figure 3.6: DAG depicting an example of missing data bias



3.5.2.5 Sensitivity analysis used to test for missing data bias

As described in section 3.2.3, surveillance systems used to collect data for all cRCTs included in this thesis had a key informant system for collecting data on births and deaths, as well as interviewers who collected information about the antenatal, delivery and postnatal periods approximately six weeks after delivery. The survey questionnaire allowed questions to have an unknown or missing response. If large amounts of data on clean delivery practices were found to be missing (i.e. >10%), this could bias the study findings due to reasons previously discussed. To investigate the likelihood that missing data substantially biased subsequent analyses, I compared basic demographic, antenatal and delivery characteristics and maternal and neonatal outcomes, for respondents with complete data on the clean delivery practice of interest and those with missing data, using chi-squared or Fisher's exact tests where appropriate. After this analysis, I explored patterns of missing data to help determine the reasons for missingness.

There are three possible missing data mechanisms: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).[138] MCAR implies that data are missing for reasons unrelated to all study variables and this type of missingness does not bias the study findings. MAR implies that the missing data mechanisms do not depend on unseen data, or in other words, whether or not data are missing depends on the values of observed study variables. MNAR implies that the missingness mechanism depends on unobserved data. Multiple imputation (MI) methods rely on the parameter estimates from a number of imputed datasets generated accounting for the distributions of the model's variables (e.g. Gaussian, binomial, multinomial), and assuming a particular missingness mechanism. Conditional distributions (regression models) are specified for each variable with missing values, conditional on all variables in the imputation models. Parameter estimates from the imputed datasets are then combined to obtain overall estimates and standard errors usually computed with Rubin's rules.[139]

Where there were more than 10% of missing data in any model, I used the MI with chained equations (MICE) using the *mi* command in Stata 12, under the assumption that data were missing at random (MAR) to minimise bias and loss of information due to missing data.[140] Due to differences in the way data were collected, differences in predictors of missing data, and differences in the amount of missing data between the three study sites (i.e. Nepal had substantially more missing data on kit use and hand washing), I assumed that the missing data mechanism was different for the individual study sites. I therefore imputed data separately for India, Bangladesh, and Nepal. In the observational datasets used in these analyses, missing values were present for binary, categorical and continuous variables. These different types of variables have different distributions that need to be accounted for MI models. I used MICE methods that accounted for these distributions and the different imputation requirements for these variables (i.e. continuous, categorical and binary) using a fully conditional specification. Variables used in the MI models included the outcomes of interest (i.e. maternal/neonatal deaths), previously mentioned confounders as well as covariates found to be significant in the multivariable analysis assessing predictors of missingness such as obstetric haemorrhage. The later covariates are discussed in the relevant analyses. Rubin's rules were used to summarize estimates and their standard errors from analysis of 15 imputed datasets.[139]

Some datasets used in the analysis had a hierarchical data structure, with clustering in the outcomes of interest. Ignoring this clustering in the imputation models would have resulted in biased estimates of the parameters of interest. In Chapter four for example, there was significant clustering present for the outcome of neonatal mortality. To handle this clustering, REALCOM-impute software was used to impute data.[141] I then uploaded the imputed data from REALCOM to Stata, where I used the *mi estimate* command to generate estimates based on Rubin's rules.[139]

REALCOM impute software was originally developed to handle missing data with a hierarchical data structure. Imputation of missing data is made possible by fitting a multivariate response models to a two-level data structure. REALCOM-impute software models continuous variables using the multivariate normal distribution whereby a mean, level two random intercept and level one residual are fit for each level one response, and level two variables are fit with a level two residual. Residuals at level one and level two are assumed to be independent with a mean of zero, and separate covariance matrices. If all variables are normally distributed, covariance matrices are assumed to be unstructured. For distributions, other than the Gaussian, appropriate covariance structures are required that use the latent normal model for discrete data.[142]

While we assumed the missingness mechanism is MAR, given all the variables included in the MI model, we cannot be certain whether data are MAR or MNAR.[143] When performing MI under the assumption that the data is MAR, estimates for the association between clean delivery practices and neonatal mortality or maternal mortality (i.e. Chapters four and five respectively) as well as the association between the women's group intervention and clean delivery practices (i.e. Chapter seven) would be subject to bias if data is MNAR (i.e. missingness mechanism is dependent on the unobserved outcome).[144]

To assess the sensitivity of the findings against modest departures from the MAR assumption, a weighted sensitivity analysis using the Selection Model Approach was applied.[145-147] Briefly, data were first imputed under MAR, parameter estimates from each imputed dataset were reweighted to allow for the data to be missing not at random (MNAR). An example of why data may be MNAR is in the instance of a maternal or neonatal death, where this may have affected a respondent's ability to complete the questions on clean delivery practices. The chosen weights, used to reweight the data to account for MNAR, were dependent on the assumed degree of departure from MAR. The parameter used to re-weight the data, denoted by δ, was the log odds ratio of the probability of the variable of interest being observed when the exposures occurred compared to when the variable did not occur.[145-147] If $\delta=0$, the variable of interest was considered to be MAR. Positive values of δ, indicated that the odds of observing the variable of interest when the exposure occurred was greater than when it did not, and negative δ's indicated that the odds of observing the variable of interest when it occurred was less. In this thesis, the variables of interest were clean delivery practices with at least 10% of the data missing in any study site. Due to the potential social desirability bias in reporting clean delivery practices, I assumed that it was more likely that clean practices were missing in instances where they were not used, compared to when they were used (i.e. $\delta>0$).

To gain insight into the missing data mechanism, I fitted logistic regression models to the outcome of missing clean delivery practices on the imputed values of its potential predictors of missingness, including neonatal and maternal mortality as well as the separate clean delivery practices.[147]

To test the stability of the models, I considered different degrees of departure from the MAR assumption by taking into account plausible values of δ ranging from 0.10 to 0.40. This range corresponds to odds ratios for the data being observed when the clean delivery practice occurred compared to when it did not, ranging from 1.11 to 1.50 (i.e. exponential of 0.10 and 0.40). Appendix 2 provides an example of the code used for the sensitivity analysis involving the Selection Model Approach.

3.5.3 Unmeasured and residual confounding

3.5.3.1 Background

Unmeasured and residual confounding are major sources of bias in any observational study.[148] Residual confounding occurs when there is measurement error in any confounder. Unmeasured confounding occurs due to omission or unavailability of a confounder from the analysis.[148] The inability to capture all sources of confounding will result in unmeasured or residual confounding and a biased estimate for the effect of the exposure in question.[148]

Several observational studies have shown significant associations between an exposure and an outcome, but when these were put to the test with a well-designed RCT, they didn't show any significant effect. As an example, despite the fact that several observational studies have shown a positive effect of antioxidants on cancer survival, cardiovascular disease and mortality, properly designed RCTs showed no effect.[149-153] It has been suggested that the associations seen in these observational studies were due to social and behavioural confounders that occur throughout the life course.[154] Accounting for these using single or even multiple covariates to model the complexities of factors that occur throughout the life time is extremely difficult and most likely does not encompass all confounding, leaving the results open to bias through residual and unknown confounding.[155] One can speculate that the evaluation of the effects of clean delivery practices on neonatal and maternal mortality will be susceptible to similar biases. Additionally, due to the fact that the cRCTs from which the data for this thesis arise were not specifically designed to answer the questions posed in this thesis, it is possible that key confounding variables were missing, leading to unmeasured confounding bias.

3.5.3.2 Methods to test for potential unmeasured or residual confounding

In some instances it is possible to speculate that an important confounder was missing and that this is potentially biasing estimates. In such cases an external adjustment can be made for the unmeasured confounder. To test for sensitivity of unknown confounding in this thesis, the possibility of unmeasured confounders as well as residual confounding was discussed with the different partners in India, Bangladesh, and Nepal sites. Although sensitivity models were not applied to test for unmeasured or residual confounding, the potential effects of residual confounding on the study findings are discussed in each chapter.

3.6 Summary

This chapter has described the methodological challenges posed by analyses contained in this thesis, and methods used to overcome them. The following chapters will elaborate on statistical methods when required. In particular, the final analysis testing the effects of women's group intervention on the use of clean delivery practices involved methods that were substantially different to those in the other two main analyses, and details are provided in the relevant chapter.

Chapter 4 Clean delivery kit use, clean delivery practices and neonatal mortality

4.1 Introduction

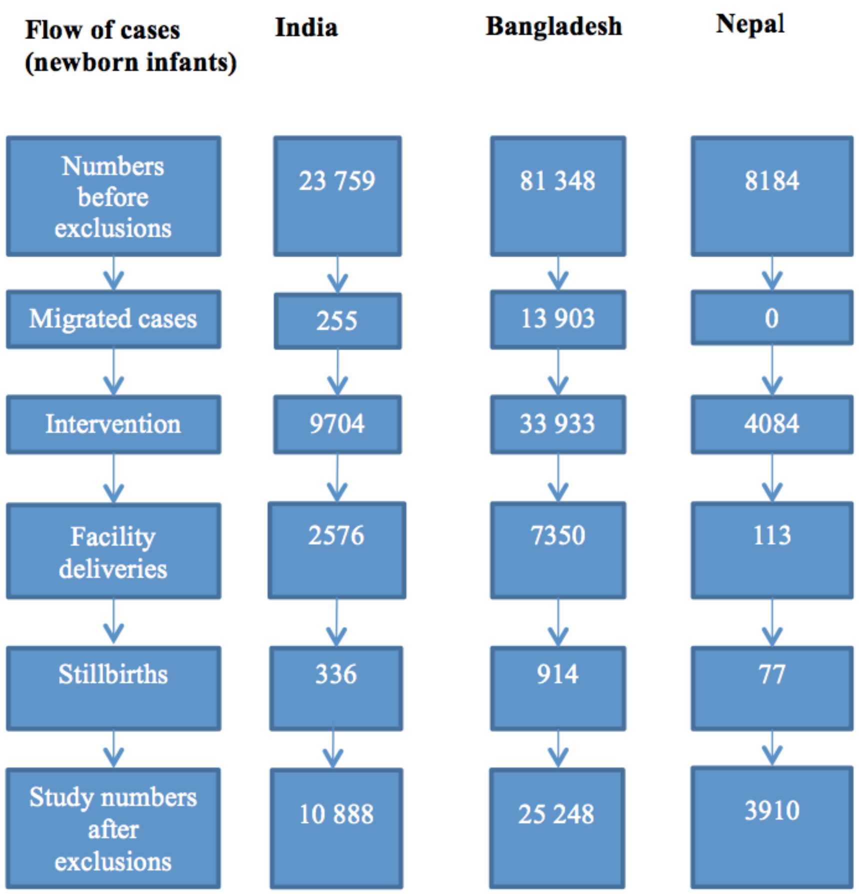
This chapter investigates the association of clean delivery kit use and clean delivery practices with neonatal mortality. It uses data from the control arms of four cRCTs that took place among rural, underserved populations in South Asia[99-101, 114] The chapter has four specific objectives: first, to examine the association of kit use with neonatal mortality; second, to examine the association of individual clean delivery practices (hand washing, using a plastic sheet, use of gloves, sterilising the blade, sterilising the string, and applying antiseptic to the umbilical stump compared to dry cord care) with neonatal mortality; third, to determine the cumulative effect on neonatal mortality of using four clean delivery practices, irrespective of kit use; lastly, to apply sensitivity analyses to account for potential biases in the analyses. Results from similar analyses have been published in *PLoS Medicine*, attached here as Appendix 3 (A3).[75]

4.2 Methods

4.2.1 Study populations and interventions

Data were used from 40 046 home births available from the control arms of four community-based cRCTs carried out between 2000 and 2011 in India (*n*=10 888), Bangladesh (*n*=25 248), and Nepal (*n*=3910).[99-101, 114] In India, baseline data collected prior to the cRCT using the same data collection methods were also included. In Nepal, data collection continued after the completion of the cRCT and before the intervention was implemented in control clusters, allowing for the use of additional data from control clusters. Figure 3.1 shows the different locations and Table 3.1 describes the characteristics of each study population, the timeline of studies, the contents of clean delivery kits available in each site, and baseline neonatal mortality rates. Figure 4.1 demonstrates how the number of cases was arrived at for each study site, after removing facility deliveries, stillbirths, and migrated cases.

Figure 4.1: Flow of cases (newborn infants) from original datasets to numbers used for current analysis



4.2.2 Exposures and outcome ascertainment

Table 3.1 describes the data collected by vital events surveillance systems that were similar in all three sites. In this chapter, the main outcome of interest was a neonatal death, defined using the ICD-10 definition as death to a newborn infant within the first 28 days of life.[2] The main exposures of interest in this analysis were clean delivery kit use, hand washing with soap by the birth attendant before delivery, use of a sterilised blade to cut the cord, use of sterilised thread to tie the cord, use of plastic sheet as a clean delivery surface, use of gloves to ensure hand hygiene, and application of antiseptic to the cord compared to dry cord care. Although data were available on many different substances that were applied to the cord, I was only interested in whether there were differences in neonatal survival between those infants who had dry cord care and those who had an antiseptic applied to the umbilical cord. Details of the exposures included in this analysis can be found in Table 3.4. This analysis was limited to home deliveries of live born infants in the control arms of the cRCTs only.

4.2.3 Confounder selection

Confounders were selected based on evidence from existing literature on risk factors for neonatal sepsis, and included the following:

- Maternal age (15 – 49 years)
- Maternal education (none, primary, secondary and higher)
- Number of antenatal care visits (0 – 4+)
- Delivery assisted by a skilled birth attendant (country-specific definitions were aligned with those of Demographic Health Surveys, i.e. in India and Nepal, a skilled birth attendant was a doctor, nurse or trained midwife; in Bangladesh, a doctor, nurse, trained midwife, family welfare visitor, community skilled birth attendant) [15-17]
- A household asset was a categorical variable with three categories created from household items common to all three study sites. The category of 'all assets' included households with any of the following items; television, fridge, electricity. Some assets referred to households having any one of the following; a bicycle, radio, fan or phone. No assets referred to a household not having any of the above mentioned assets.
- Parity (0 – 4+ children)
- Study site

I initially performed univariable analyses to assess whether potential confounders, clean delivery practices, and neonatal mortality differed between deliveries with and without kit use, using a pooled analysis as well as separately for each site. Following the univariable analyses, DAGs were used to map the relationships between the above-mentioned confounders, the individual clean delivery practices (exposures) and neonatal death. These relationships are depicted using DAGs in Figure 4.2 below. Figure 4.3 depicts similar relationships for other individual clean delivery practices besides clean delivery kit use. The DAGs were used to design the statistical modelling of the relationships between each of the separate clean delivery practices and neonatal mortality, taking potential confounders into account. These diagrams demonstrate that the main difference in assessing the association between clean delivery practices and neonatal mortality and the association between kit use and neonatal mortality, was that examining the first association required conditioning for clean delivery kit use.

Figure 4.2: DAG depicting the relationships between clean delivery kit use, neonatal mortality, and potential confounders

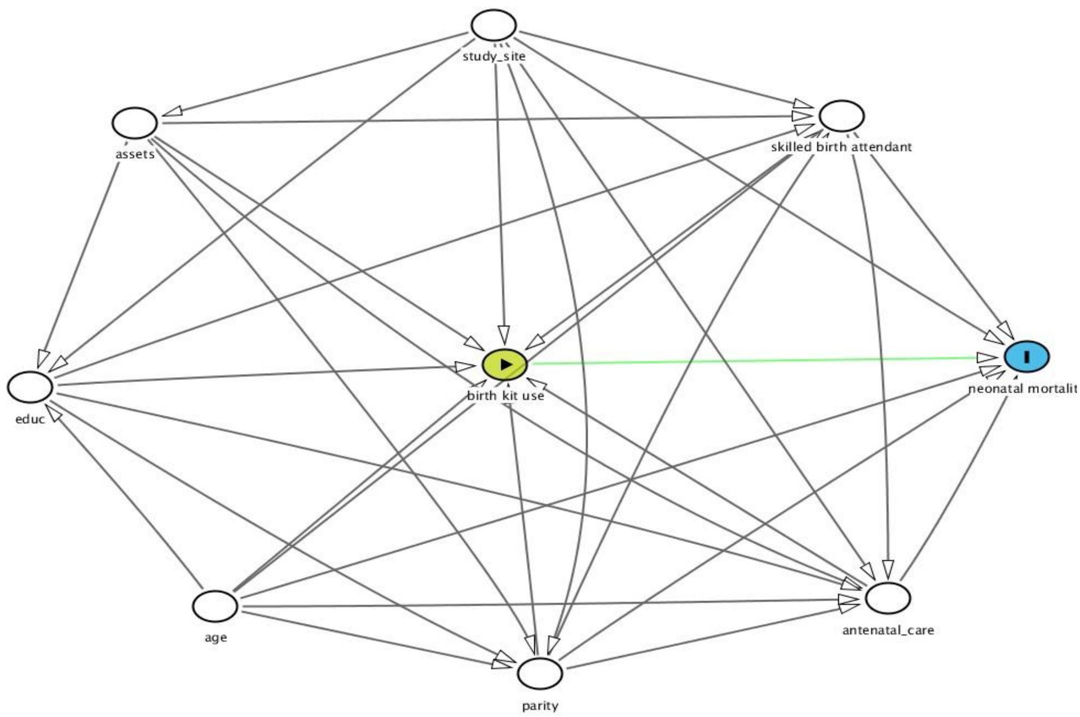
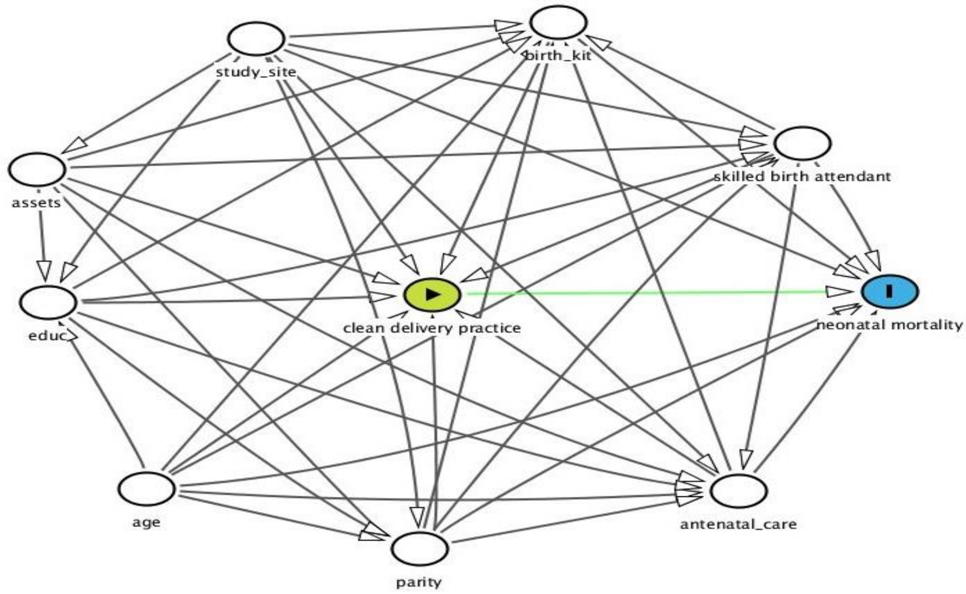


Figure 4.3: DAG depicting the relationships between clean delivery practices, neonatal mortality, and potential confounders



4.2.4 Statistical methods

Statistical methods for these analyses were described in Chapter three. Briefly, I carried out univariable analyses comparing deliveries with kit use to deliveries without kit use. Kit use, a proxy for all other clean delivery practices, was used as the main comparator. Given the number of multiple significance tests that were performed in this univariable analysis, it is more likely than not, that a significant findings would occur.[156] However, this is a univariable analysis, and results are used to help gain insight as to the relationships between those deliveries where a clean delivery practice was used, and those deliveries where a clean delivery practice was not used, and findings were not used to validate the main study findings. For this reason, no correction factor was applied to account for multiple significance testing. After the univariable analysis, I then applied mixed-effects logistic regression models to examine the association between individual clean delivery practices and neonatal mortality controlling for kit use and all other confounders. To assess the relationship between kit use and neonatal mortality, it was not necessary to control for other clean delivery practices, as illustrated in Figure 4.1. I conducted analyses using the pooled dataset, and then separately for the different study sites. The Nepal dataset did not contain information on use of a sterilised thread, use of a plastic sheet, or use of gloves, so these practices were examined using the pooled data from Bangladesh and India only, as well as separately for each of the two sites.

To determine if the clean delivery practices documented in India and Bangladesh (Nepal did not have information on all the clean practices) had an augmented collective benefit, a covariate representing the number of practices followed was added to the model, along with kit use and potential confounders. The covariate representing the number of clean practices included only those variables found to be significant in the analysis on individual clean delivery practices that were also contained in a clean delivery kit (i.e. hand washing, use of a sterilised blade, use of sterilised thread, and a plastic sheet). A test of linear trend for number of clean delivery practices was applied to the model, and a likelihood ratio statistic with $p<0.05$ considered significant. For all models, I tested for possible modifying effects of the confounders on the association between clean delivery practices and neonatal mortality by including a two-way interaction term, where it was decided a priori that there was a plausible explanation for this effect.

It was possible that data on neonatal mortality were correlated as they were collected from geographical clusters. The estimated intra-cluster correlation coefficient (ICC) for neonatal mortality was 0.005 in the pooled dataset, indicating that such correlation was present, but minimal. I therefore fitted mixed-effects logistic regression models, with random effects on the geographical clusters. Mixed-effects models assume that the distribution of the residuals at each level is a multivariate normal. To test this assumption, level two residuals were graphed using a normal scores plot. The appearance of the level two residuals occurring in a straight line indicated the normality assumption had been fulfilled.[157] Variance inflation factors (VIF) showed no evidence of multicollinearity in any model.

4.2.5 Sensitivity analysis

4.2.5.1 Cause of death analysis

To check the robustness of the main study findings, an additional cause of death analysis was carried out using verbal autopsy data. This is different from the original cause of death analysis that was performed by physicians, using data collected from the verbal autopsies that were a part of the original surveillance questionnaires. A mathematical modelling tool, InterVA version 4.02 (www.interva.net) was used to create cause-specific classifications of neonatal deaths. InterVA uses a probabilistic method that estimates the probability of specific causes of death based on reported signs, symptoms and circumstances derived through verbal autopsy.[158] Using the Bangladesh and India data only (verbal autopsy data were not available from Nepal); InterVA assigned a cause of death for each neonatal death. A combination of sepsis and pneumonia was used for an infectious related neonatal death due to the difficulty in distinguishing between the two events as a cause for neonatal death.[158] I then modelled the associations between each of the clean delivery practices and cause-specific neonatal mortality using the pooled dataset and by site, whilst adjusting for confounders, using similar methods as in the main analysis.

4.2.5.2 Missing data analysis

Chapter three described the methods used to handle missing data as well as the sensitivity analyses testing the MNAR assumption. Here I discuss some the assumptions made regarding missing data for this analysis. Initial exploratory analyses revealed that the extent of missing data differed across sites. Data on kit use were missing for 0.9% (n=95) of births in India, 1.4% (n=346) in Bangladesh, and 82.7% in Nepal (n=3233). Data on hand washing were missing for 14.6 % (n=5841) of births in the pooled analysis, 5.9 % (n=644) of births in India, 14.1% (n=3571) of births in Bangladesh and 41.6% (n=1626) of births in Nepal. No other clean delivery practices had greater than 10% of missing values. Given the fact kit use and hand washing by the birth attendant had at least 10% of missing values either in the pooled analysis, or the individual study sites, comparisons were made for differences in demographic, antenatal and delivery characteristics between those with missing data for these variables and those with complete data. Results for comparisons on missing kit use and hand washing are shown in Tables A3b and A3c respectively.

Multiple logistic regression models were used to gain insight into the missingness mechanisms by exploring the relationship between missing data on kit use and hand washing, and potential predictors for missingness. Results for missing kit use indicated that maternal age, number of antenatal care visits, study site, skilled birth attendants, postpartum haemorrhage, hand washing, maternal death, and household assets were predictors of missingness. The Receiver Operator Characteristic (ROC) curve indicated that a model including these variables was a very good fit (ROC=0.97). Results for missing data on hand washing by the birth attendant indicated that study site, maternal age, number of antenatal care visits, skilled birth attendant, postpartum haemorrhage, kit use, and parity were significant predictors of missingness. The ROC curve indicated that this model was a moderate to poor fit (ROC=0.69). There was no evidence that neonatal death was associated with missing hand washing or kit data. To gain further insight into missing data mechanisms for kit use and hand washing, I explored patterns of missing using the Stata command *mi misstable pattern*. Results of the missing data patterns indicate the combination of variables most commonly found to be missing and this helps to determine reasons behind the missingness.

To reduce bias due to missing data and to improve the efficiency of model estimates, MI was used under the assumption that data was missing at random (MAR). As data showed evidence of clustering, REALCOM impute software was used to impute missing data, as Stata cannot currently impute data with multilevel data structures.[141] Variables included in the models included the outcome of a neonatal death, previously mentioned confounders, and key variables that were found to be predictors of missingness including obstetric haemorrhage, and maternal death.[104] For the imputation models testing exposure of kit use, hand washing was also included as a predictor of missingness. For the imputation model testing the exposure of hand washing, kit use was used as a predictor of missingness. Once data for each of the study sites had been imputed separately in REALCOM, the data were uploaded into Stata for analysis using the *mi estimate* command and the mixed-effects command of *xtmelogit.*

Although kit use and hand washing were the only clean practices with more than 10% of missing data, MI was performed for models to explore the associations between all clean delivery practices and neonatal mortality (kit use, hand washing, use of a sterilised blade, use of a sterilised thread, gloves, plastic, and use of antiseptic to the cord compared to dry cord care). The reasoning for this was that models assessing the effects of other clean delivery practices included kit use as a potential confounder; by not performing MI analysis, a considerable amount of data would be lost, making bias due to missing data a potential issue.

To test the sensitivity of the study findings against modest departures from the MAR assumption, a weighted sensitivity analysis using the Selection Model Approach was applied to the study findings.[145-147] Once data had been imputed under MAR, parameter estimates from each imputed dataset were re-weighted to allow for the data to be missing not at random (MNAR). The chosen weights used to reweight the data to account for MNAR were dependent on the assumed degree of departure from MAR. The parameter used to re-weight the data, denoted by δ and described in section 3.6.3, is the log odds ratio of the probability of kit use/hand washing data being observed when kit use/hand washing occurred, compared to when kit use/hand washing did not occur.[145-147] If δ=0, the clean delivery practices could be considered to be MAR. Positive values of δ indicate that the odds of observing clean practices when they occurred were greater than when it did not. Negative δs indicates that the odds of observing clean practices when clean practices occurred were lower. As δ decreases from zero, the odds of kit use/hand washing data being observed when they occurred was less than the odds of the data being observed when hand washing did not occur (i.e. greater probability of missing clean variables when they occurred). I hypothesised that, due to social desirability bias in reporting clean delivery practices, it was more likely that the clean variables were missing in instances where they were not used, compared to when they were used (i.e. δ>0).

4.2.5.3 Exposure misclassification bias

Misclassification bias was discussed in detail in the methods section. Briefly, the accuracy of recall of the main exposures of clean delivery practices may depend on whether there was a neonatal death or not. Based on this assumption, a neonatal death was used as a proxy measure to assess differential sensitivities and specificities for the ability of respondents to accurately indicate whether kit use occurred. I hypothesised that all clean delivery practices would be subject to similar misclassification as kit use and, for this reason, kit use served as a proxy to assess the extent to which all clean delivery practices were potentially misclassified. I followed the methods developed by Lyles and Lin, in which estimated odds ratios accounting for misclassification rates of the main exposure, kit use, were obtained fitting logistic regression models with appropriate weights based on assumed sensitivities and specificities.[133] Standard errors for these estimates were calculated using a jackknife procedure.[133] Due to complexities in assigning different weights to each level of the model parameters, the only confounders used were those with greatest effect on estimates assessing the association between kit use and neonatal mortality as determined by the Akaike's information criterion (AIC): these were maternal age and study site.

4.3 Results

4.3.1 Study population

I analysed data from a total of 40 046 mothers who gave birth at home between 2005 and 2011 in India (*n*=10 888), Bangladesh (*n*=25 248), and Nepal (*n*=3910). Univariable analyses revealed that kits were used for 15.2% (*n*=1653) of home births in India, 15.3% (*n*=3872), in Bangladesh, and 4.1% (*n*=159) in Nepal. The mean maternal age was 25.7, 24.8, and 27.7 years in India, Bangladesh, and Nepal, respectively. There was substantial variation in female education: in India, 74.6% (*n*=8128) of mothers had no education, in Bangladesh 28.2% (*n*=7111), and in Nepal 86.8% (*n*=3394). In India, 5.3% (*n*=570) of home-delivered infants had a skilled birth attendant, compared with 2.4% (*n*=617) in Bangladesh, and 0.2% (*n*=7) in Nepal.

Table A3a presents a comparison of births with and without clean delivery kit use. Using a clean delivery kit was significantly associated with neonatal survival in India and Bangladesh, but not in Nepal ($p<0.001$, $p=0.004$, and $p=0.475$ respectively). Kits did not necessarily guarantee clean delivery practices: in India, for example, hand washing with soap prior to delivery occurred in only 43.7% (723/1653) of births for which a kit was used. However, kit use was strongly associated with birth attendants washing their hands with soap prior to delivery ($p<0.001$ in all countries). The same was true for other clean delivery practices, in that deliveries assisted by kits were also more likely to have been assisted by other clean delivery practices, except for dry cord care.

Maternal secondary education was significantly associated with kit use compared to non-use ($p<0.001$ in all sites). Household assets were also associated with kit use in Bangladesh and Nepal ($p<0.001$ in Bangladesh, and $p=0.029$ in Nepal). Parity was also associated with kit use compared to non-use in India, and Bangladesh ($p=0.005$ in India, and $p<0.001$ in Bangladesh). Delivery by a skilled birth attendant was also associated with kit use in all countries ($p<0.001$ in India and Bangladesh, and $p=0.013$ in Nepal).

4.3.2 Clean delivery kits, clean delivery practices, and risk of neonatal mortality

Table 4.1 presents results of the unadjusted analyses, examining the association between kit use, clean delivery practices, and neonatal mortality, within and across study sites. Table 4.2 presents results from adjusted analyses for the same associations, both with and without MI. After adjustment for confounders common to all study sites, kit use was associated with a 36% relative reduction in neonatal mortality in the pooled dataset (aOR 0.64, 95% CI 0.53–0.76), and the association did not differ significantly between sites. Use of a kit was associated with a 52% relative reduction in neonatal mortality in India (0.48, 0.35–0.66) and a 22% relative reduction in Bangladesh (0.77, 0.61–0.97). Due to the large number of missing data in Nepal, it was not possible to obtain country-specific estimates for any of the clean delivery practices or clean delivery kit use.

Tables 4.1 and 4.2 describe the association of seven individual clean delivery practices with neonatal mortality for all sites combined and separately. The use of a sterilised blade to cut the cord, antiseptic to clean the cord, a sterilised thread to tie the cord, and a plastic sheet for a clean delivery surface were all associated with significant relative reductions in mortality when controlling for kit use and confounders common to all sites in the pooled dataset. Use of antiseptic on the cord compared to dry cord care was also associated with significantly decreased odds of death in the pooled dataset (aOR 0.18, 95% CI 0.12–0.28), as well as in India (0.42, 0.18–0.96) and Bangladesh (0.14, 0.09–0.24). Finally, Table 4.2 shows results for a pooled analysis combining data from India and Bangladesh to explore the effect of each additional individual clean delivery practices on neonatal mortality. The clean practices represented in this variable include the following; hand washing, use of a plastic sheet, sterilised thread to tie the cord and sterilised instrument to cut the cord. With each additional clean delivery practice, we found a 15% relative reduction in mortality (0.85, 0.80–0.90).

Table 4-1: Unadjusted odds ratios (OR), 95% CI for the association between clean delivery practices with neonatal mortality

Clean delivery practices	Pooled data		India		Bangladesh		Nepal	
	OR[a] (95% CI)	***p*-value[b]**	**OR (95% CI)**	***p*-value[b]**	**OR (95% CI)**	***p* value[b]**	**OR (95% CI)**	***p*-value[b]**
Use of clean delivery kit	0.65 (0.55–0.77)	<0.001	0.56 (0.43–0.74)	<0.001	0.72 (0.58–0.9)	0.004	0.54 (0.18–1.66)	0.284
Washing hands prior to delivery	0.68 (0.60–0.78)	<0.001	0.79 (0.64–0.96)	<0.001	0.60 (0.60–0.72)	<0.001	0.73 (0.49–1.10)	0.137
Use of sterilised blade to cut the cord	0.75 (0.66–0.85)	<0.001	0.66 (0.51–0.86)	0.002	0.79 (0.68–0.92)	0.002	0.71 (0.45–1.11)	0.134
Use of sterilised thread to tie the cord	0.80 (0.70–0.91)	0.001	0.71 (0.53–0.94)	0.017	0.82 (0.71–0.96)	0.011	c	
Use of antiseptic to clean the cord compared to dry cord care	0.23 (0.16–0.34)	<0.001	0.66 (0.37–1.19)	0.171	0.16 (0.10–0.26)	<0.001	d	
Use of plastic sheet	0.60 (0.52–0.69)	<0.001	0.43 (0.29–0.65)	<0.001	0.63 (0.54–0.74)	<0.001	c	
Use of gloves	0.97 (0.79–1.20)	<0.001	0.54 (0.31–0.94)	<0.001	1.11 (0.89–1.40)	0.355	c	

Clean delivery practices	**Pooled data**		**India**		**Bangladesh**		**Nepal**	
	OR[a] (95% CI)	***p*-value[b]**	**OR (95% CI)**	***p*-value[b]**	**OR (95% CI)**	***p* value[b]**	**OR (95% CI)**	***p*-value[b]**
Use of each additional clean delivery practice	0.85 (0.80–0.90)	<0.001	0.84 (0.74–0.95)	<0.001	0.84 (0.74–0.95)	<0.001	c	

a. Pooled analysis adjusted for study site and clustering

b. *p*-value obtained through the use of a Wald test

c. India and Bangladesh data only

d. Model would not converge

Table 4-2: Results from mixed-effect logistic regression models with and without MI, showing aOR for the association between clean delivery kit use, clean delivery practices, and neonatal mortality

Clean delivery practice	Model type	Pooled data aOR (95% CI)	Pooled data *p*-value[a]	India aOR (95% CI)	India *p*-value[a]	Bangladesh aOR (95% CI)	Bangladesh *p*-value[a]	Nepal aOR (95% CI)	Nepal *p*-value[a]
Use of clean delivery kit	mixed-effects models[b,f]	0.64 (0.53–0.76)	<0.001	0.48 (0.35–0.66)	<0.001	0.77 (0.61–0.97)	0.024	[e]	
	MI[d,f,]	0.66 (0.56–0.80)	<0.001	0.55 (0.41–0.73)	<0.001	0.77 (0.61–0.97)	0.024	[e]	
Washing hands prior to delivery	mixed-effects models[b]	0.74 (0.64– 0.85)	<0.001	0.89 (0.71–1.11)	0.301	0.65 (0.55–0.78)	<0.001	[e]	
	MI[d]	0.73 (0.64–0.83)	<0.001	0.81 (0.65–1.01)	0.063	0.70 (0.59–0.83)	<0.001	[e]	
Use of a sterilised blade to clean the cord	mixed-effects models[b]	0.79 (0.69–0.85)	<0.001	0.71 (0.54–0.95)	0.022	0.80 (0.69–0.94)	0.005	[e]	
	MI[d]	0.78 (0.69–0.89)	<0.001	0.67 (0.52–0.87)	0.003	0.81 (0.69–0.94)	0.006	[e]	

Clean delivery practice	Model type	Pooled data aOR (95% CI)	*p*-value[a]	India aOR (95% CI)	*p*-value[a]	Bangladesh aOR (95% CI)	*p*-value[a]	Nepal aOR (95% CI)	*p*-value[a]
Use of sterilised thread to tie the cord	mixed effects models[b]	0.83 (0.73–0.96)	0.006	0.74 (0.54–1.01)	0.061	0.85 (0.73–0.99)	0.031	[c]	
	MI[d]	0.82 (0.72–0.84)	0.004	0.71 (0.53–0.76)	0.018	0.84 (0.72–0.99)	0.038	[c]	
Use of antiseptic to clean the cord compared to dry cord care	mixed-effects models[b]	0.18 (0.12–0.28)	<0.001	0.42 (0.18–0.96)	0.039	0.14 (0.09–0.24)	<0.001	[e]	
	MI[d]	0.16 (0.14–0.26)	<0.001	0.38 (0.25–0.89)	0.037	0.10 (0.08–0.19)	<0.001	[e]	
Use of plastic sheet	mixed-effects models[b]	0.69 (0.59–0.81)	<0.001	0.54 (0.31–0.94)	0.030	0.70 (0.59–0.92)	<0.001	[c]	
	MI[d]	0.68 (0.59–0.79)	<0.001	0.54 (0.33–0.88)	0.013	0.69 (0.59–0.81)	<0.001	[c]	
Use of gloves	mixed effect models [b]	1.09 (0.85–1.39)	0.506	0.51 (0.25–1.05)	0.067	1.23 (0.94–1.60)	0.131	[c]	
	MI[d]	1.08 (0.85–1.36)	0.531	0.58 (0.31–1.07)	0.067	1.21 (0.93–1.57)	0.145	[c]	

Clean delivery practice	Model type	Pooled data aOR (95% CI)	Pooled data *p*-value[a]	India aOR (95% CI)	India *p*-value[a]	Bangladesh aOR (95% CI)	Bangladesh *p*-value[a]	Nepal aOR (95% CI)	Nepal *p*-value[a]
Use of each additional clean delivery practice	mixed-effects models[b]	0.85 (0.80–0.90)	<0.001	0.84 (0.74–0.95)	0.006	0.85 (0.79–0.90)	<0.001	[c]	
	MI[d]	0.83 (0.79–0.87)	<0.001	0.83 (0.73–0.92)	0.001	0.84 (0.79–0.90)	<0.001	[c]	

a. *p*-value obtained through the use of a Wald test

b. Adjusted for maternal age, maternal education, parity, number of ante natal care visits, skilled birth attendant, clean delivery kit use, household assets, and for the pooled analysis, study site

c. India and Bangladesh data only

d. MI models taking into account variables described in b, and the predictor of missingness, obstetric haemorrhage, maternal death, hand washing (kit use model only)

e. It was not possible to obtain estimates as models would not converge

f. Controlling for other clean delivery practices was not appropriate here according to results from DAGs

Table 4-3: aOR for the association between clean delivery kit use and clean delivery practices with cause-specific neonatal mortality, using data from Bangladesh and India

Clean delivery practices	**Infection-related death**			**Prematurity**			**Intrapartum event**		
	Pooled analysis	**India**	**Bangladesh**	**Pooled analysis**	**India**	**Bangladesh**	**Pooled analysis**	**India**	**Bangladesh**
	aOR [a] (95% CI)			**aOR [a](95% CI)**			**aOR [a](95% CI)**		
Use of clean delivery kit[a,c]	0.64 (0.46–0.88)	0.42 (0.23-0.78)	0.73 (0.52–1.11)	0.44 (0.26–0.73)	0.27 (0.13–0.59)	b	0.79 (0.56–1.13)	0.72 (0.38–1.35)	0.79 (0.56–1.13)
Washing hands prior to delivery[a]	0.62 (0.48–0.80)	0.52 (0.30-0.90)	0.66 (0.49–0.88)	0.60 (0.42–0.86)	0.68 (0.41–1.14)	0.55 (0.34–0.90)	0.62 (0.45–0.85)	0.61 (0.32–1.15)	0.62 (0.45–0.85)
Use of sterilised blade to cut the cord[a]	0.89 (0.71–1.11)	0.46 (0.23-0.91)	1.00 (0.78–1.28)	0.94 (0.66–1.35)	0.98 (0.57–1.68)	0.92 (0.58–1.47)	0.81 (0.61–1.08)	0.58 (0.27–1.24)	0.81 (0.61–1.08)
Use of sterilised thread to tie the cord[a]	0.93 (0.74–1.16)	0.59 (0.31-1.15)	1.01 (0.79–1.28)	0.90 (0.63–1.29)	0.70 (0.26–1.35)	1.04 (0.66–1.64)	0.78 (0.59–1.04)	0.50 (0.21–1.18)	0.78 (0.59–1.04)
Use of gloves[a]	0.70 (0.44–1.10)	b	0.93 (0.59–1.47)	0.37 (0.13–1.04)	0.24 (0.03–1.82)	0.50 (0.16–1.60)	1.51 (1.00–2.27)	0.59 (0.18 –1.96)	1.51 (1.00–2.27)

Clean delivery practices	Infection-related death			Prematurity			Intrapartum event		
	Pooled analysis	India	Bangladesh	Pooled analysis	India	Bangladesh	Pooled analysis	India	Bangladesh
	aOR [a] (95% CI)			aOR [a](95% CI)			aOR [a](95% CI)		
Use of plastic sheet[a]	0.61 (0.48–0.78)	0.44 (0.17-1.09)	0.63 (0.49–0.81)	0.46 (0.30–0.71)	0.20 (0.05–0.81)	0.56 (0.35–0.90)	0.63 (0.47–0.84)	0.38 (0.12–1.26)	0.63 (0.47–0.84)
Use of antiseptic to clean the cord compared to dry cord care[a]	0.27 (0.13–0.52)	b	0.27 (0.14–0.53)	0.16 (0.04–0.64)	b	0.16 (0.04–0.64)	0.13 (0.05–0.31)	0.61 (0.08–4.67)	0.13 (0.05–0.31)

a. Models were adjusted for maternal age, maternal education, parity, number of antenatal care visits, skilled birth attendant, clean delivery kit use, household assets, and for the pooled analysis, study site.

b. It was not possible to obtain estimates as models would not converge

c. Controlling for other clean delivery practices was not appropriate here according to results from DAGs

4.3.3 Sensitivity analyses

4.3.3.1 Findings from Cause-of-Death Data

To check the plausibility of the effect sizes, I used cause-specific mortality data available from the control arms of the Indian and Bangladesh cRCT to examine the association of kits and other clean delivery practices with infection-related neonatal death, and with death due to the other two primary causes of newborn mortality (consequences of preterm birth and intrapartum-related deaths, or intrapartum event). Using the pooled dataset, kit use was associated with relative reductions in infection-related mortality (aOR 0.64, 95% CI 0.46–0.88). Other clean delivery practices associated with reductions in infection-related neonatal mortality includes hand washing by the birth attendant prior to delivery (0.62–0.48–0.80), use of a plastic sheet (0.61, 0.48–0.78), and use of antiseptic to clean the cord compared to dry cord care (0.27, 0.13–0.52). Results are shown in Table 4.3.

Using the same pooled dataset, kit use was also associated with relative reductions in mortality ascribed to prematurity (aOR 0.44, 95% CI 0.26–0.73). Reassuringly, kit use was not associated with reductions in mortality due to an intrapartum event (0.79, 0.56–1.13). Hand washing by the birth attendant was also associated with reductions in neonatal mortality due to prematurity (0.60, 0.42–0.86) as well as an intrapartum event (0.62, 0.45–0.85). Use of a plastic sheet as a delivery surface was associated with reductions in neonatal mortality due to a preterm delivery (0.46, 0.30 – 0.71), as well as an intrapartum event (0.63, 0.47–0.84). The use of antiseptic to clean the cord, compared to dry cord care was also associated with relative reduction in neonatal mortality due preterm delivery (0.16, 0.04–0.64), and an intrapartum event (0.13, 0.05–0.31).

There were differences in the association between clean delivery practices and cause-specific neonatal mortality between the different study sites. Importantly, hand washing, use of a plastic sheet and application of antiseptic to the cord were all associated with reductions in neonatal mortality due to an intrapartum event in Bangladesh, but not in India. Additionally, the use of a kit was associated with a reduction in infection-related neonatal deaths in India (aOR 0.42, 95% CI: 0.23–0.78) but not in Bangladesh (0.73, 0.52–1.11). The same finding was also true for the use of a sterilised blade to cut the cord: this practice was associated with a reduction in infection-related deaths in India (0.46, 0.23–0.91) but not in Bangladesh (1.00, 0.78–1.28). Although the use of a plastic sheet was associated with a reduction in infection-related deaths in Bangladesh (0.63, 0.49–0.81), this was not the case in India (0.44, 0.17–1.09).

4.3.3.2 Missing data

Table A3b presents a comparison between deliveries with and without missing data on kit use. Neonatal deaths were more likely to have missing data on kit use in India, but not in Bangladesh and Nepal (p=0.052, p=0.305 and p=0.676). In most cases, newborns with missing information on kit use were also more likely to have missing information on other clean delivery practices, except for in the instance of dry cord care in Bangladesh. Women with a secondary education or higher were more likely to have missing information on kit use in Bangladesh only (p=0.005). Deliveries assisted by a skilled birth attendant were more likely to have missing data than deliveries not assisted by a skilled attendant in India and Bangladesh (p<0.001).

Table A3c presents data for those with complete data on hand washing and those deliveries without data on hand washing. There was evidence that having missing data on hand washing was associated with neonatal mortality in India (p=0.062), Bangladesh (p=0.002), and Nepal (p=0.062). As with clean delivery kit use, those deliveries where there were missing data on hand washing were also more likely to have missing data on the other clean delivery practices (p<0.001), except dry cord care in India (p=0.830). Women with a secondary education or higher were more likely to have missing data on hand washing in India (p=0.005), Bangladesh (p<0.001), and Nepal (p=0.005). Women who had more than four antenatal care visits were more likely to have missing hand washing data in India (p=0.001) and Nepal (p=0.001). Deliveries that were assisted by a skilled birth attendant were more likely to have missing data on hand washing in all three study sites (p<0.001).

Table A3d shows that the missing data patterns for the models exploring the association between kit use or hand washing and neonatal mortality were identical with 76% of the data being present. The most common patterns of missing data were missing hand washing only (10% of cases), kit use only (5%), missing both kit use and hand washing (4%), and missing maternal age only (4%). The remaining patterns of missingness were random and included a combination of various missing variables.

Results from the MI models indicated that missing data did not affect the estimates in the pooled analysis. The estimate quantifying the association between kit use and neonatal mortality without accounting for missing data (aOR 0.64, 95% CI 0.53–0.76) was similar to the estimate accounting for missing data (0.66, 95% CI 0.56–0.80).

In India, missing data was more of an issue due to 40% (n=4338) of data being missing for maternal age. Without accounting for the missing data, the adjusted odds ratio for the association between kit use and neonatal mortality was 0.48, 95% CI 0.35–0.66. Once the missing values had been accounted for, the adjusted odds ratio moved towards the null at 0.55, 95% CI 0.42–0.73. In Nepal, it was not possible to estimate the association between kit use and neonatal mortality, due to 82% of data being 'missing' for kit use.

The sensitivity analysis testing whether or not the MI results on kit use were compatible with the MNAR assumption indicated that estimates were robust to MNAR mechanisms. When assuming that the probability of kit use being reported when it occurred was greater than the probability of kit use being reported when it did not, the strength of the association between kit use and neonatal mortality remained similar to the analysis assuming data were MAR. The aOR ranged from 0.66 (0.56–0.78) to 0.67 (0.56–0.79). Details of the estimates under different values of δ, using the MNAR assumption can be found in Table 4.4. Table 4.5 shows results from a similar analysis testing a similar assumption, but with hand washing as the main exposure. It shows that estimates were also robust to the MNAR mechanism where the aOR ranged from 0.73 (0.64–0.84) to 0.73 (0.64–0.82).

Table 4-4: aOR (95% CI) for different departures from the missing at random assumption (□) for kit use, assuming greater probability of kit data being missing when kit did not occur

	aOR (95% CI)
0.40	0.663 (0.561 – 0.784)
0.30	0.663 (0.561 – 0.784)
0.20	0.664 (0.562 – 0.786)
0.15	0.665 (0.563 – 0.786)
0.10	0.665 (0.563 – 0.786)

Table 4-5: aOR (95% CI) for different departures from the missing at random assumption (□), for hand washing, assuming greater probability of hand washing data being missing when hand washing did not occur

δ	aOR (95% CI)
0.400	0.728 (0.644–0.824)
0.300	0.730 (0.642–0.829)
0.200	0.732 (0.644–0.831)
0.150	0.732 (0.643–0.834)
0.100	0.732 (0.640–0.836)

4.3.3.3 Exposure misclassification bias

The sensitivity analysis to assess whether estimates from the complete case analysis were subject to differential misclassification bias revealed that the strength of the association between kit use and neonatal mortality was not affected, as previously hypothesised: estimates did not move towards the null with decreasing sensitivities and specificities in the instance of death and survival respectively. Table 4.6 provides a range of estimates for different combinations of proposed sensitivities and specificities for the ability to accurately recall kit use. aORs did not appear to be affected by decreasing sensitivities. As an example, assuming differential misclassification with specificities of 0.94 and 0.91 in the instance of neonatal death and neonatal survival, a range of different combinations of sensitivities from 0.62 to 0.94, yielded adjusted odds ratios between 0.64 and 0.63 respectively. If the hypothesis had been correct, the adjusted odds ratios would have moved towards the null with decreasing sensitivities, and not remain the same. On the other hand, as the specificities decreased, the adjusted odds ratio moved away from the null rather than towards it, as previously hypothesised. As an example, assuming differential misclassification with sensitivities of 0.62 and 0.67, in the instance of neonatal death and survival respectively, a range of different combinations of specificities between 0.91 and 0.98 yielded aORs varying between 0.641 and 0.846. Another finding from this sensitivity analysis was that although the adjusted estimates did not change with different sensitivities, they were sensitive to a range of different specificities.

Table 4-6: aOR (95% CI) for different combinations sensitivity and specificity values, assuming differential misclassification in the instance of neonatal death and neonatal survival of the exposure variable of kit use

Assumed sensitivity (neonatal death, neonatal survival	**aOR (95% CI) Assumed specificity (neonatal death, neonatal survival**		
	94, 91	0.96, 0.91	0.98 , 0.94
0.62, 0.67	0.641 (0.428–0.950)	0.923 (0.688–1.240)	0.846 (0.671–1.067)
0.72, 0.77	0.642 (0.431–0.955)	0.925 (0.692–1.234)	0.849 (0.678–1.062)
0.82, 0.87	0.642 (0.433–0.952)	0.925 (0.696–1.231)	0.848 (0.679–1.059)
0.90, 0.94	0.634 (0.428–0.938)	0.914 (0.689–1.213)	0.837 (0.672–1.043)

a. 95% CI calculated using jackknife standard error

b. Complete case analysis adjusted for maternal age and country only

4.4 Discussion

Results from the pooled analysis across study sites indicated a significant relative reduction in neonatal mortality following kit use in home births among rural South Asian communities. The non-significant results found in Nepal may be due to the small number of kit users in this sample, resulting in lack of power. The results also indicated the importance of individual clean delivery practices: a combination of hand washing, use of sterilised blade, use of sterilised thread, and plastic sheet was linearly associated with a relative reduction in the odds of neonatal mortality with each additional clean delivery practice used.

Many governments and non-governmental organisations encourage the use of clean delivery kits, both with and without accompanying promotion programmes. This analysis demonstrated that distributing kits, even with instructions, did not guarantee that essential clean delivery practices were used. These findings concur with those of a qualitative study from Nepal in which 51 mothers and TBAs were interviewed about their perceptions of clean delivery kits.[159] Few users took out the instructions for the kit, and when they did, they had difficulties understanding them. For example, delivery and postnatal practices including cord care and immediate breastfeeding are culturally patterned, and understanding the context in which kits are used is key to developing and evaluating culturally appropriate promotion activities.[58]

Given the potential of kits to improve neonatal survival following home births, it is important to find effective methods in ensuring appropriate use and distribution. Programmes have employed several approaches, including dissemination through health facilities, community health workers, and private providers such as pharmacists, but few of these initiatives have been evaluated. In the study sites relevant to this analysis, an intervention involving community mobilisation through participatory women's groups was used to improve birth outcomes. Women's groups discussed clean delivery and care-seeking behaviour through stories and games that facilitated discussions about prevention and care for typical problems in mothers and newborn infants. As a result of these discussions, some groups made and promoted clean delivery kits, resulting in significant increases in kit use within intervention clusters in Nepal and India.[99-101, 114] In a recent Pakistani trial, Lady Health Workers (LHWs) conducted participatory group sessions with mothers to promote beneficial practices in the antenatal, delivery, and postnatal period. Clean delivery kits were available from LHWs in both intervention and control clusters, but kit use for home deliveries was more common in the intervention clusters (35% versus 3%; $p<0.0001$).[80] Findings from these trials suggest that group-based community interventions can significantly increase the use of clean delivery kits for home births.

The content and cost of kits also need consideration. Most kits do not currently contain antiseptic to clean the umbilical cord. In this analysis, application of antiseptic to the cord, compared to dry cord care was associated with reduced odds of neonatal death in the pooled analysis as well as in India and Bangladesh separately. Due to small numbers, it was not possible to assess for the relationship between antiseptic application to the cord and neonatal mortality in Nepal. A cRCT in Sarlahi district, Nepal, compared topical applications of chlorhexidine to the umbilical cord to dry cord care in reducing cord infections and neonatal mortality. Mortality was reduced by 34%, from 21.6 to 14.4 per 1,000, (OR 0.66, 95% CI 0.46 – 0.95) for those infants enrolled and treated within 24 hours.[89] Similarly, two recently published cRCTs in Bangladesh and Pakistan also showed significant reductions in omphalitis and neonatal mortality when the umbilical cord was cleansed with chlorhexidine.[77, 78] For the Bangladesh study, neonatal morality was lower in the single cleansing group compared to the dry cord care group (relative risk [RR], 0.80, 95% CI, 0.65 – 0.98) but not in the multiple cleansing group. There was also a significant reduction in the occurrence of severe cord infection in the multiple cleansing cord group compared to the dry cord care group (RR 0.35, 95% CI 0.15 – 0.81).[77] Results from the Pakistan study indicated a relative reduction in omphalitis and neonatal mortality with chlorhexidine application (risk ratio, 0.58, 95% CI: 0.41 – 0.82) and (risk ratio, 0.62, 95% CI: 0.45 – 0.85) respectively.[78] The WHO has considered this evidence and now formally recommends using chlorhexidine on the umbilical cord in settings where neonatal mortality rates are greater than 30 per 1000 live births.[160]

When the trials included in this study took place, the cost of a clean delivery kit was US$0.44 in India (20 Indian rupees), US$0.40 in Nepal (30 Nepalese rupees), and US$0.27 in Bangladesh (20 Bangladesh taka). While the kit can be considered a low-cost intervention, there have been no studies on willingness to pay for kits, and these costs may still be prohibitive for the poorest women.

This analysis was limited to home births. Initiatives to promote access to skilled care at birth in South Asia have already resulted in substantial increases in institutional deliveries.[161, 162] Since this trend is likely to continue in the future, further research is needed to understand the possible population-level impact on neonatal mortality of promoting kits through different channels, for example through women's groups, for community-based skilled birth attendants and in health facilities. In particular, we need to understand whether the promotion of clean delivery kits and clean delivery practices for home births dis-incentivises institutional deliveries, whether promoting kits for home births in the context of increasing institutional deliveries is cost-effective, and the potential of kits to prevent infections during institutional deliveries.[68]

The very nature of observational data used in this analysis means that the study findings must be interpreted with caution. However, the different sensitivity analyses testing the robustness of the estimates suggest that little bias has been introduced into the analysis. Sensitivity analyses testing the MNAR assumption obtained similar estimates to those assuming data was MAR. This is unsurprising given that a neonatal death was not a significant predictor of either missing kit use or missing hand washing.[147] Although it is likely that data was to some degree MNAR, this does not appear to have affected the estimates from the MI analysis assuming data was MAR. The sensitivity analysis testing for misclassification bias indicated that differential misclassification in the event of a neonatal death was unlikely. Although estimates moved towards the null with increased specificities, the possibility of this actually occurring in the field is unlikely and results are most likely a chance finding. Findings from these sensitivity analyses will be discussed in greater detail in the final chapter of this thesis.

The associations found between kit use, other clean delivery practices, and neonatal mortality were greater than expected based on previous estimates of cause-specific neonatal mortality due to sepsis. There is a possibility of residual or uncontrolled confounding, which could have biased the study findings, as was described in Chapter three. For example uncontrolled confounding could be present as kit users could have had other personal attributes that were not measured in this study and could have reduced the risk of neonatal death. It is possible that women who used kits and whose birth attendants adopted clean delivery practices were different from women who did not. When the different study partners were asked to provide information on uncontrolled confounders, the general consensus was that use of clean delivery practices is possibly a measure of the social support system present at the time of delivery. This social support system may provide better overall care such as transport to a facility in obstructed labour, appropriate use of clean delivery practices as well as encouragement of essential newborn care practices. A confounder such as this social support system is difficult, if not impossible to measure. Residual confounding may have been present due to miss-measured confounders. I assumed that confounders such as maternal age, whether a skilled birth attendant was present, and maternal education were subject to minimal reporting inaccuracies.

Results from the analysis of cause-specific mortality data from India and Bangladesh confirm the associations between kit use, hand washing by the birth attendant, use of plastic sheet as a clean delivery surface, use of antiseptic to clean the cord, and reduced odds of neonatal death due to infections (sepsis and pneumonia). However, the findings also raise some doubts as they suggest that hand washing, use of a plastic sheet and antiseptic to clean the cord, were associated with a reduction in neonatal deaths from an intrapartum event. There are a few possible explanations for these findings, including a chance association. Interestingly, only the Bangladesh site had these unexpected findings, and not the India site. It could be that, in Bangladesh, women who reported using clean delivery practices were inherently different to women who did not use clean delivery practices, and that these differences were impossible to measure, resulting in unmeasured confounding. If this were the case, then we would expect the estimates for the effect of clean delivery practices on all cause neonatal mortality to be more a reflection of a 'healthy lifestyle' that led not only to the use of clean delivery practices, but also other behaviours essential for newborn and maternal health. There is also the possibility of additional residual confounding: confounders may not have been measured with complete accuracy allowing for some measurement bias. It is also possible that this unexpected finding could be a reflection of the InterVA tool, where cause-specific diagnoses are dependent on the quality of the data fed into the VA tool.[158] Another potential explanation is linked to the fact that the InterVA tool is a probabilistic model where assigning more than one cause of death to an individual is possible.[158] As an example, in this analysis there were a few instances where InterVA assigned a cause of death as infection-related, and also had a high probably of death being linked to an intrapartum event or prematurity. Despite these limitations, overall the analysis of the effect of clean delivery practices on cause-specific neonatal mortality is supportive of the main study findings.

4.5 Conclusions

Findings from this chapter suggest that the use of clean delivery kits and clean delivery practices are associated with an increased likelihood of neonatal survival for home births in rural settings in South Asia where access to skilled birth attendants and institutional deliveries are limited. The use of kits may not always be accompanied by clean delivery practices, and the latter should be emphasised when promoting them. Further research should explore the context of kit use in order to develop and test locally appropriate promotion strategies, as well as examine the potential of kits to improve neonatal survival in the context of increasing institutional delivery rates.

Chapter 5 Associations between clean delivery practices and postpartum maternal mortality

5.1 Introduction

The previous chapter highlighted positive associations between clean delivery practices and neonatal survival, and these findings were supported by results of sensitivity analyses. Given the close relationship between puerperal and neonatal sepsis, it is hypothesised that clean delivery practices will also positively impact on rates of maternal morbidity and mortality.

As a maternal death is a rare event, exploring associations with clean delivery practices will be challenging. A large sample size will be required to detect even small associations that will be particularly vulnerable to biases such as measurement error due to recall and reporting bias. Reasons for these biases may in part be due to the fact that in the event of a maternal death, the cRCT interviewers administered the questionnaire to a close relative of the deceased, whereas in the case of a neonatal death, if the mother was alive, she was invited to answer the interview questions. Obtaining estimates for these associations using observational data requires adjustment for potential sources of bias such as confounding, missing data, and misclassification as was done in the previous chapter. To date, there has been a lack of high quality studies with sufficient power to examine the effects of clean delivery practices on maternal mortality whilst accounting for such biases using appropriate methods.

In this chapter, the same observational dataset from the control arms of four previously conducted cRCTs was used to examine the associations between the use of a clean delivery kit and hand washing with soap by the birth attendant with maternal mortality in rural South Asian communities.[99-101, 114] This chapter has the following objectives: to examine the association between kit use and hand washing by the birth attendant and maternal mortality and to apply sensitivity analyses to determine whether different forms of bias could have influenced the findings. A manuscript detailing results of this analysis has been submitted to PLOS One and can be found in A4.

5.2 Methods

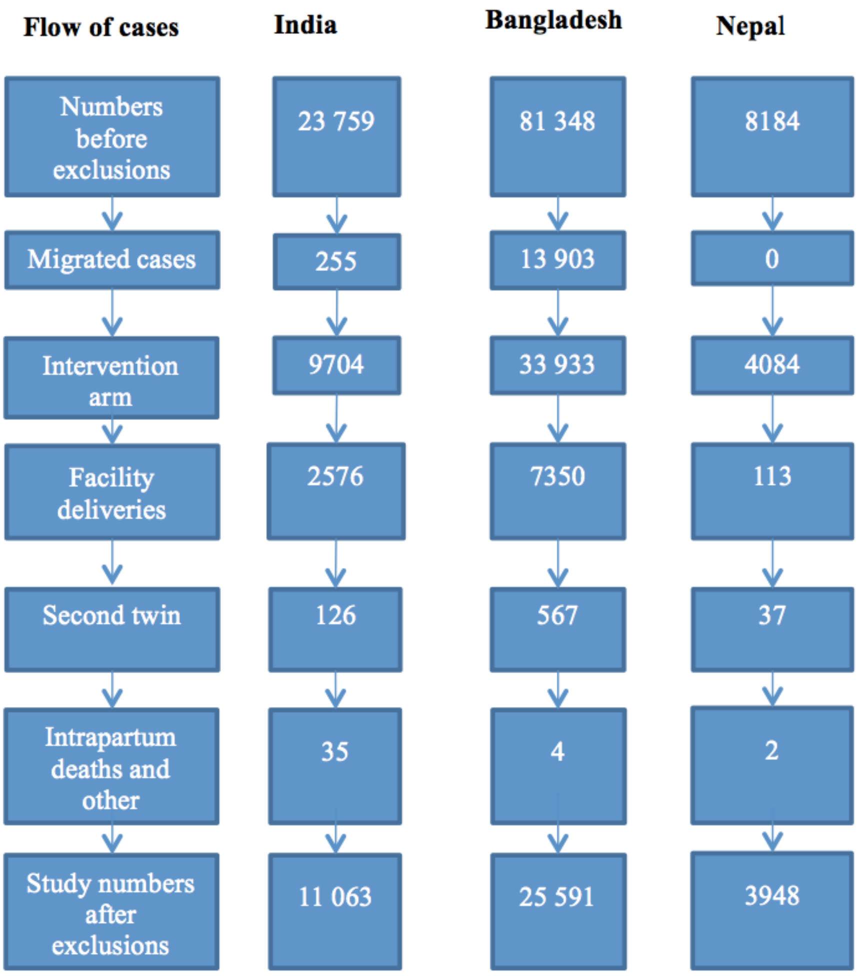
5.2.1 Study populations

I analysed data from 40 602 home deliveries in the control arms of four community-based cRCTs carried out between 2000 and 2011 in India, Bangladesh and Nepal.[99-101, 114, 163] In India, baseline data collected prior to the cRCT using the same data collection methods were also included. In Nepal, data collection continued after the completion of the cRCT and before the intervention was implemented in control clusters, allowing for the use of additional data from control clusters. Figure 5.1 demonstrates how the numbers for these analyses were arrived at through the elimination of migrated cases, cases from the intervention arm, facility-based deliveries, second twins or second and third triplets in multiple births to ensure women were only counted once, as well as intrapartum deaths.

5.2.2 Surveillance systems: data collection and management

Chapter three gave details of the individual surveillance systems used in each trial, and Table 3.1 summarised their characteristics. Further details on surveillance systems can be found elsewhere.[99-101, 114, 163]

Figure 5.1: Flow of cases from original datasets to the number of cases used in these analyses



5.2.3 Exposures and outcome

Table 3.1 described the data on clean delivery practices collected by vital events surveillance systems in the three sites. Maternal death has been defined by ICD-10 as death of a woman during pregnancy or up to 42 days after delivery or termination of pregnancy.[2] As the study objective was to determine the effect of hygiene during delivery on maternal deaths, I used postpartum maternal death (maternal death after delivery and within 42 days) as the main outcome for these analyses. The exposures of interest were two intrapartum practices that could potentially reduce puerperal sepsis: use of clean delivery kit and hand washing with soap by the birth attendant.

5.2.4 Confounders

Confounders used in the analyses on clean delivery practices and neonatal mortality (Chapter four) were also found to be applicable in these analyses.[45, 164] The use of a clean delivery kit was considered a potential confounder in analyses exploring the effects of hand washing on postpartum maternal death. Initially, univariable analyses were performed to assess whether potential confounders, clean delivery practices and maternal mortality differed between deliveries with and without hand washing by birth attendant, for each study site (Table A5a).

Directed acyclic graphs (DAGs) were used to model the associations between selected confounders with individual clean delivery practices (exposures), and with the outcome of postpartum maternal death. These DAGs then informed the statistical modelling of the relationship between each of the separate clean delivery practices and maternal mortality.[132] In order to better map potential causal relationships, the DAGs were designed using a timeline encompassing the pre-conception phase to the postpartum period. Figure 5.2 shows the relationship between hand washing and postpartum maternal death, and the appropriateness of selected confounders. Figure 5.3 shows the relationship between using a clean delivery kit and postpartum maternal death and illustrates the inappropriateness of including individual clean delivery practices as potential confounders.

Figure 5.2: DAG showing possible causal relationships between hand washing, maternal mortality, and potential confounders

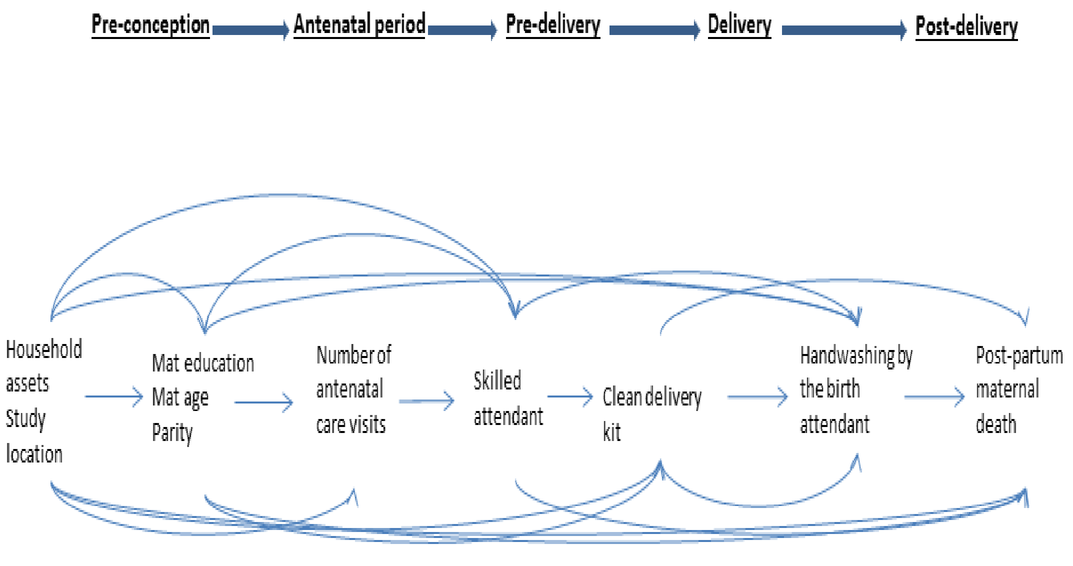
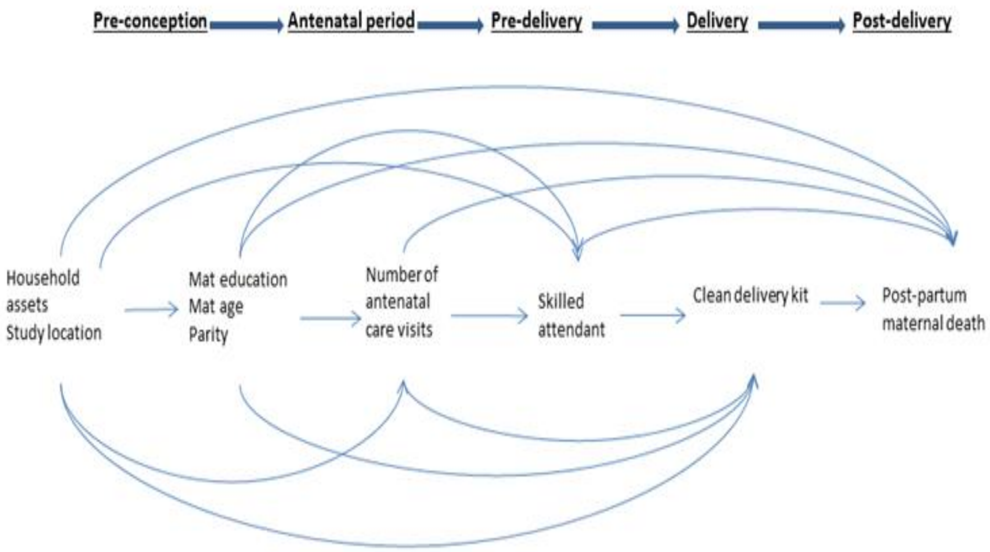


Figure 5.3: DAG showing possible causal relationships between use of a clean delivery kit, maternal mortality, and potential confounders



5.3 Statistical methods

I initially performed univariable analyses comparing deliveries both with and without hand washing and clean delivery kit use. Given the number of multiple significance tests that were performed in this univariable analysis, it is more likely than not, that significant findings will occur.[156] However, results of this analysis are only going to be used to help gain insight into differences between those deliveries where clean delivery practices were used and those deliveries where they were not used. For this reason, no correction factor was applied to account for multiple significance testing. I then fitted logistic regression models using the pooled data to examine the association of kit use and hand washing with postpartum maternal death, controlling for confounders available at all sites. To determine the appropriateness of using a pooled dataset, an interaction term was introduced between each individual clean delivery practice and study site, with results confirming similar associations in the three study sites. I then repeated these analyses separately for the three study sites. Finally, for all models, I tested for modifying effects of confounders on the association between clean delivery practices and maternal death by including a two-way interaction term where there was a plausible explanation for such an effect.

Due to the small number of mothers who died after delivery, low uptake of skilled birth attendance, and large numbers of missing data on clean delivery kit use in Nepal, there were numerical convergence issues when calculating adjusted estimates for the effect of hand washing on maternal mortality. As a result, skilled attendant and clean delivery kit were not included in the adjusted analysis. To provide some information on how excluding these confounders could have affected the estimates, a sensitivity analysis was performed comparing results both with and without skilled attendant and clean delivery kit, separately and simultaneously, using data from India and Bangladesh. Results in Table 5.1 show very small differences in estimates and 95% confidence intervals when comparing adjusted models with skilled attendant and/or kit use to adjusted models without skilled attendant and/or kit use.

Table 5-1: Analysis comparing adjusted odds ratios (aOR) for the effect of hand washing on postpartum maternal mortality in models including kit use and skilled attendance as confounders, and models without them

Confounders present in the adjusted models[b]	**aOR (95% CI)**	***p*-value**[a]
Skilled attendant and clean delivery kit use	0.45 (0.24–0.87)	0.017
Kit use	0.43 (0.22–0.83)	0.012
Skilled attendant	0.44 (0.23–0.85)	0.015
Neither kit use nor skilled attendant	0.43 (0.22–0.84)	0.014

a. *p*-value derived from a Wald test.

b. Adjusted for maternal age, maternal education, parity, number of ante natal care visits, household assets, and study site.

Due to the large numbers of missing data on kit use in Nepal, there were also convergence issues in testing the associations between kit use and postpartum maternal mortality for the complete case analysis. For this reason, logistic regression models for the complete case analysis were fitted to India and Bangladesh data only.

As data were collected from 18 geographic clusters in India, nine in Bangladesh, and 12 in Nepal, maternal mortality could be correlated within clusters. The estimated ICC was <0.0001 using the pooled dataset as well as for the individual study sites, indicating that such correlation was minimal. We therefore fitted logistic regression models with fixed effects only. VIFs showed no evidence of multicollinearity in any of the models.

5.4 Sensitivity analyses

5.4.1 Missing data

Sensitivity analysis on missingness was performed for models testing for the effect of hand washing and clean delivery kit use on maternal mortality, as both had greater than 10% of missing data, either in the pooled dataset, or in the individual study sites.

Demographic, antenatal, and delivery characteristics, including clean delivery practices, maternal and neonatal outcomes were compared between respondents with recorded data on kit use and hand washing and those with missing data on kit use and hand washing, using chi-squared and Fisher's exact tests where appropriate. In India, data on hand washing were missing for 6% (*n*=664) of all home deliveries, in Bangladesh 14.2% (*n*=3639) and in Nepal 41.5% (*n*=1639). In India, data on kit use was missing for 0.9 % (*n*=101) of home deliveries, in Bangladesh 1.5% (*n*=374) and in Nepal 82.5% (*n*=3258).

To reduce bias and loss of information due to missing data, we used MICE as implemented in the MI command in Stata under the assumption that data were missing at random (MAR).[140] Variables used in the MICE models consisted of the key outcome maternal death, previously mentioned confounders, and covariates found to be predictors of missingness that were not already considered, including obstetric haemorrhage.[139, 165] Although it was not possible to include skilled birth attendant and kit use as confounders in the adjusted model testing for the association between hand washing/kit use and postpartum maternal mortality, it was possible to include them as predictors of missingness in the MICE models. In the model testing the association between kit use and maternal death, hand washing was included as a predictor of missingness.

I ran two separate MICE models when performing MI using models examining the association between clean delivery kit use and maternal mortality. To compare with the estimates from the complete case analysis, MI was performed using data from India and Bangladesh only. As was previously discussed, complete case analysis was not possible when including data from Nepal, as there was too much missing information on kit use. I therefore ran MICE models including data from Nepal, to see what estimates would have occurred if complete case analysis had been possible.

To understand the missingness mechanism, logistic regression models were fitted to explore the relationship between missing hand washing and missing kit use, and potential predictors of missingness including maternal death. A multivariable model was fitted with the outcome of missing hand washing, and imputed values of potential predictors of missingness including the study outcome.[147] Results indicated that the missingness mechanism for missing hand washing variable depended on a neonatal death, clean delivery kit use, maternal age, and skilled birth attendant. There was some evidence that the outcome of a maternal death was associated with missing hand washing data. The ROC curve indicated that this model was a poor fit (0.62). This process was also repeated for the outcome of missing kit use. Results indicated that the missingness mechanism is associated with obstetric haemorrhage, number of antenatal care visits, parity, household assets, maternal age, study site, and maternal education. Importantly, the missingness mechanism for missing kit use did not depend on neonatal or maternal death. The ROC curve indicated that this model was a very good fit (0.95).

Patterns of missing data were explored using the *mi misstable patterns* command in Stata, for models estimating the effect of both kit use and hand washing on maternal mortality.

To test modest departures from MAR, a weighted sensitivity analysis using the Selection Model Approach was applied to our findings after MI.[145-147] A similar approach was applied to data in Chapter four. The estimates of the odds ratio of maternal death following hand washing/ kit use compared to without hand washing and kit use from each imputation were weighted and their average then calculated. The weights were determined by the assumed value of the log odds ratio of the probability of hand washing/kit use being observed when hand washing/kit use occurred, compared to when hand washing/kit use did not occur, which is denoted by δ.[145-147] If $\delta=0$ then hand washing/kit use is MAR. Given the potential for social desirability bias in reporting clean delivery practices, I hypothesised that hand washing/kit use data were more likely to be missing in cases in which the birth attendant did not wash her hands/use a kit so that $\delta>0$. Details of this analysis can be found in Chapter three.

5.4.2 Exposure misclassification bias

Chapter three discussed the nature of misclassification bias, and the fact that women's and other respondents' ability to recall clean delivery practices accurately may depend on factors such as neonatal or maternal survival, as well as on different morbidity patterns experienced by mother and infant. Based on this assumption, I used maternal death as a proxy measure to gage the sensitivities and specificities for the hand washing variable. I followed methods developed by Lyles and Lin: I obtained estimated odds ratios accounting for misclassification rates of the main exposure, hand washing, by fitting logistic regression models with appropriate weights based on assumed sensitivities and specificities.[133] Standard errors for these estimates were calculated using a jackknife procedure.[133] Analysis for misclassification bias was carried out in SAS version 9.3.[166]

5.5 Results

5.5.1 Study population

I analysed data from 40 602 mothers who gave birth at home between 2005 and 2011, in India (n=11 063), Bangladesh (n=25 591) and Nepal (n=3948). In total, there were 73 maternal deaths just after delivery and up to 42 days postpartum across all study sites; 18 deaths in India (0.16% of deliveries), 43 deaths in Bangladesh (0.17%), and 12 deaths in Nepal (0.30%). The median maternal age was 25 years in India, 24 in Bangladesh and 26 in Nepal. In India, 5% (590/11063) of mothers had a home delivery assisted by a skilled birth attendant, compared with 3% (900/25591) in Bangladesh, and 0.2% (7/3948) in Nepal. Clean delivery kits were used in 15% of deliveries in India (1684/11 063) and Bangladesh (3901/25 591), but in only 4% of deliveries in Nepal (157/3948). There was substantial variation in the proportion of birth attendants washing their hands before delivery: in India it was 24% (2677/11 063), compared with 69% (17639/25 591) in Bangladesh, and 32% (1258/3948) in Nepal.

Table A5a compares deliveries with and without hand washing by the birth attendant. I found evidence that hand washing was associated with improved maternal survival in India and Bangladesh (*p*=0.057 and *p*=0.048, respectively), but not in Nepal (*p*=0.799); however, in Nepal there were only eight maternal deaths with data on hand washing and four maternal deaths had no information on hand washing. As in the analysis focusing on neonatal mortality, clean delivery kit use was associated with hand washing in all three study sites (*p*<0.001). S4b compares deliveries with and without clean delivery kit use. There was no evidence that clean delivery kit use was associated with improved maternal survival. In Nepal however, each of the 12 maternal deaths had missing data on kit use. Hand washing by the birth attendant was also associated with kit use in each of the three study sites (*p*<0.001).

5.5.2 Clean delivery practices and maternal mortality

Tables 5.2 and 5.3 show estimates from unadjusted and adjusted analysis exploring the associations between clean delivery practices and maternal mortality. The unadjusted pooled analysis showed that hand washing was associated with a 54% reduction in the odds of a postpartum maternal death (OR 0.46, 95% CI: 0.26–0.36) and the adjusted analysis suggested a 49% reduction in the odds of a postpartum maternal death (aOR 0.51, 0.28–0.93). MI had little effect on this estimate (0.48, 0.26–0.90). Use of clean delivery kit was not associated with improved postpartum maternal survival either in the unadjusted or the adjusted models.

Table 5-2: Unadjusted odds ratios [ORs] for association between clean delivery kit use, clean delivery practices, and postpartum maternal mortality

Clean delivery practices	Pooled data [a]		India		Bangladesh		Nepal	
	OR (95% CI)	*p*-value[b]	OR (95% CI)	*p*-value[b]	OR (95% CI)	*p*-value[b]	OR (95% CI)	*p*-value[b]
Use of clean delivery kit[d]	1.19 (0.60–2.36)	0.616	0.69 (0.16–2.30)	0.619	1.46 (0.67–3.18)	0.344	[c]	
Washing hands prior to delivery	0.46 (0.26– 0.36)	0.010	0.17 (0.02–1.27)	0.084	0.49 (0.24–1.01)	0.053	0.83 (0.21–3.35)	0.799

a. Pooled analysis adjusted for study site.

b. Wald test.

c. Unknown due to all mothers who died having missing data on clean delivery kit use.

d. Includes India and Bangladesh data only.

Table 5-3: aORs (95% CI) for the association between clean delivery kit use, clean delivery practices, and maternal mortality obtained from logistic regression models with and without MI

Clean delivery practices	Model type	Pooled data		India		Bangladesh		Nepal	
		aOR (95% CI)	*p*-value[a]	aOR (95% CI)	*p*-value [a]	aOR (95% CI)	*p*-value[a]	aOR (95% CI)	*p*-value[a]
Use of clean delivery kit	logistic regression [b, e]	1.26 (0.62–2.56)	0.519	0.66 (0.15–2.93)	0.587	1.61 (0.71–3.68)	0.256	[f]	
	MI [c, e, d]	1.18 (0.60– 2.24)	0.612	0.68 (0.15–2.99)	0.605	1.45 (0.63–3.30)	0.381	[f]	
	MI [c, g, d]	1.20 (0.63–2.27)	0.581	[h]		[h]		[h]	
Washing hands prior to delivery	logistic regression [b]	0.51 (0.28–0.93)	0.028	0.15 (0.02–1.11)	0.063	0.57 (0.27–1.23)	0.154	0.83 (0.19–3.56)	0.800
	MI [c, d, g]	0.48 (0.26–0.90)	0.022	0.15 (0.02–1.13)	0.066	0.58 (0.27–1.25)	0.162	0.91 (0.23–3.65)	0.898

a. Wald test.

b. Adjusted for maternal age, maternal education, parity, number of antenatal care visits, household assets, and for the pooled analysis, study site.

c. MI models taking into account variables described in b, as well as predictors of missingness including obstetric haemorrhage, and skilled birth attendant

d. MI model also included clean delivery kit or hand washing as predictor of missingness.

e. It was not possible to include Nepal in the pooled analysis due to large numbers of missing data.

f. Model would not converge due large number of deliveries with missing data on kit use

g. MI model using Nepal dataset in addition to India and Bangladesh

h. Not applicable, MI used to calculate aOR of pooled dataset only

5.6 Sensitivity analyses

5.6.1 Missing data

Tables A5c and A5d shows differences in characteristics of mothers with complete data and those with missing data on hand washing and kit use respectively. Overall, 19% (*n*=14) and 23% (*n*=17) of the 73 postpartum maternal deaths had no data on hand washing and kit use respectively.

Results examining patterns of missing data for clean delivery kit use and hand washing were identical and are shown in Table A5e. 76% of the data was complete with the most common pattern of missing data was missing hand washing only: 10% of cases had missing data on hand washing. Missing kit use only was the next most common pattern: information was missing in 5% of cases, followed by missing both kit use and hand washing (4% of cases), and finally missing maternal age only (4% of cases). The remaining patterns of missingness were random and included a combination of various missing variables.

Results from MICE models accounting for missing data under the MAR assumption can be found in Table 5.3, and show that imputed estimates and estimates from the observed data were similar. The adjusted odds ratio from the complete case analysis for the effect of hand washing on maternal mortality was similar (aOR 0.51, 95% CI: 0.28–0.93) to that from MI models assuming data was MAR (0.48, 0.26–0.90). Similarly, the adjusted odds ratio from the complete case analysis for the effect of kit use on maternal mortality was similar (1.26, 0.62–2.56) to that obtained from MI models (1.18, 0.60–2.24). Estimates from the MI model, estimated the effect of kit use on maternal mortality that included Nepal data were similar to estimates from the complete case analysis that didn't use the Nepal data (1.20, 0.63–2.27).

In the analysis assuming that the probability of hand washing being reported when it occurred was greater than the probability of hand washing being reported when it did not, the strength of association between hand washing and maternal mortality was reduced compared to the analysis assuming data were MAR. The aORs ranged from 0.554 (95% CI: 0.321–0.958) to 0.574 (0.338–0.975). As delta moved away from zero, the estimates also moved away from the estimates under the MAR assumption.

Details of these results can be found in Table 5.4. A similar analysis was performed to test the MNAR assumption for kit use and results can be found in Table 5.5. Assuming that the probability of kit use being reported when it occurred was greater than the probability of kit use being reported when it did not occur, the strength of the association between kit use and maternal mortality was reduced compared to that seen in MI analysis assuming the data were MAR. aORs ranged from 1.36 (0.72–2.56) to 1.39 (0.76–2.55). As delta moved away from zero, the estimates also moved away from the estimates under the MAR assumption.

Table 5-4: aOR (95% CI) for different departures from the missing at random assumption (□), for the exposure variable of hand washing, assuming greater probability of hand washing data being missing when hand washing did not occur using 250 imputations

δ	aOR (95% CI)
0.40	0.574 (0.338 – 0.975)
0.30	0.573 (0.337 – 0.975)
0.20	0.572 (0.336 – 0.974)
0.15	0.568 (0.332 – 0.970)
0.10	0.554 (0.321 – 0.958)

Table 5-5: aOR (95% CI) for different departures from the missing at random assumption (□), for the exposure variable of kit use assuming greater probability of kit data being missing when kit use did not occur using 250 imputation

δ	aOR (95% CI)
0.40	1.387 (0.578 – 2.089)
0.30	1.387 (0.574 – 2.085)
0.20	1.387 (0.564 – 2.080)
0.15	1.386 (0.556 – 2.078)
0.10	1.362 (0.544 – 2.093)

5.6.2 Exposure misclassification bias

The sensitivity analysis to assess whether the estimates from the complete case analysis were subject to differential misclassification bias revealed that the strength of the association between hand washing and postpartum maternal death weakened. Table 5.6 provides a range of estimates for different combinations of proposed sensitivities and specificities for the ability to accurately recall hand washing. For example, assuming differential misclassification with sensitivities and specificities of 0.73 and 0.93 in the instance of maternal death, and 0.86 and 0.89 in the instance of survival, yielded aOR=0.68 (0.21–2.25); for respective sensitivities and specificities of (0.90, 0.94) and (0.93, 0.89) we had aOR=0.54 (0.27–1.15). Results indicated that adjusted estimates depended more on sensitivities than on specificities.

Table 5-6: aOR (95% CI) for different combinations sensitivity (SE) and specificity (SP) values, assuming differential misclassification in the instance of maternal death and maternal survival of the exposure variable of hand washing

Assumed sensitivity (maternal death, maternal survival)	**aOR (95% CI)**		
	Assumed specificity (maternal death, maternal survival)		
	0.89, 0.85	0.93, 0.89	0.97, 0.93
0.73, 0.86	0.67 (0.18–2.51)	0.68 (0.21–2.25)	0.69 (0.23–2.06)
0.90, 0.94	0.53 (0.20 –1.20)	0.54 (0.20–1.15)	0.55(0.27–1.11)

a. 95% CI calculated using jackknife standard error

b. Complete case analysis adjusted for maternal age and country only

5.7 Discussion

The pooled, complete case analysis for study sites in India, Bangladesh, and Nepal indicated that hand washing by the birth attendant was associated with a 49% reduction in the odds of postpartum maternal death after adjustment for potential confounders. Use of a clean delivery kit was not associated with a reduction in the odds of postpartum maternal death at individual sites or in the pooled analysis.

These findings need to be interpreted with caution due to limitations imposed by the use of observational data.[125] The analysis testing the sensitivity to the MAR assumption indicated that the association between hand washing and maternal death was an over-estimation of the true effect, providing that data were more likely to be missing in the absence of hand washing.

Clean delivery kit use was missing in 82% of the Nepal dataset, and this limited out study findings for the complete case analysis because missing data created convergence problems in the pooled analysis as well as analysis using the Nepal dataset only. For this reason, the Bangladesh and India data were used in a pooled dataset to arrive at estimates using the complete case analysis, and this was compared to estimates from MI models using the same datasets. MI was also used to obtain estimates using the pooled dataset with the Nepal data, although there were no estimates available from the complete case analysis. The large proportion of missing data on kit use in Nepal made testing the MAR assumption essential for both the analysis testing the effect of hand washing on maternal mortality and the analysis testing the effect of kit use on maternal mortality. As previously mentioned, the surveillance questionnaire surrounding kit use in Nepal was different than in India and Bangladesh. Respondents were initially asked whether they knew what a kit was, and if their response was positive, they were asked whether or not they used a kit. Originally it had been assumed that, respondents who indicated they did not know what a kit was, did not use a kit. It is likely that a small proportion of the women who indicated that they had never seen a kit before, had a birth attendant who used the kit during delivery without informing the woman. This finding was supported in the sensitivity analysis testing the MAR assumption; findings from the analysis testing the proposed MNAR mechanism did not differ substantially compared to the estimates under the MAR assumption.

The sensitivity analyses taking into account differential misclassification for reporting of hand washing by the birth attendant demonstrated that even modest reductions in sensitivity and specificity weakened the estimates obtained from the complete case analysis. Although there were clear associations with reduced odds of postpartum maternal death, confidence intervals based on a jackknife procedure were wide, due to the uncertainty associated with the variability in the observed data, and the fact there were very few maternal deaths. However, as no data were available on the accuracy with which clean delivery practices were recalled, I do not feel that this sensitivity analysis invalidates the main study findings; rather, it suggests the extent to which findings are likely to be biased.

Although the difficulties in studying maternal mortality have been well documented, and include factors such as the requirement for large sample sizes and their associated costs, these obstacles should not act as a deterrent.[167] The availability of observational data alongside recent advances in robust statistical techniques can enable researchers to examine influences on rare outcomes such as maternal deaths.

It was not possible to conduct an analysis using data on cause of death, and physician-led verbal autopsy reports from the India cRCT indicate that only 19 (17%) of the 109 maternal deaths were due to sepsis, and in the Nepal cRCT similar verbal autopsy reports suggested that only two (14%) of the 13 maternal deaths were due to sepsis. Physician-led verbal autopsy reports were not available from Bangladesh. If the above findings on cause of death were similar to our data, we would expect approximately 11 of the 73 maternal deaths to be sepsis-related. In this study, results from the sensitivity analyses converge with those from the above-mentioned analysis of verbal autopsies: it is unlikely that the reduction in the odds of postpartum maternal death was as large as that estimated by the complete case analysis. It is also possible that the large reduction in the odds of postpartum maternal death may be partly the result of hand washing serving as a proxy for other health-promoting behaviours or social support networks. As an example, it is difficult to tease out the effects of one healthy behaviour from another, and often they are inter-linked. A woman, who uses clean delivery practices, may also be more likely to delay bathing her baby as well as practicing exclusive breastfeeding.

If the reductions in the odds of a postpartum maternal death were entirely due to hand washing acting as a proxy measure for unobserved confounders, one might have expected similar findings with the use of a clean delivery kit, which was not the case. In fact, the analysis examining the association between kit use and postpartum maternal mortality showed no significant association. The sensitivity analysis testing the assumption that data on kit use was MAR further supported this lack of association. The fact that kit use was not effective may be due to the fact that hand washing was not used, every time a kit was used. This theory is supported by results from my previous chapter and associated publication looking at associations between clean delivery practices, clean delivery kit use and neonatal mortality. Results from this analysis demonstrated that not all components of the clean delivery kit were being used, suggesting that the birth attendant was not washing her hands with soap in all instances.[75] Results in this chapter were similar to those of previous studies demonstrating that, although kits improved rates of puerperal sepsis, no clear effects on maternal mortality were found.[80, 84]

Despite the sensitivity analyses indicating that results from my analyses should be interpreted with caution, the plausibility of the biological effects of clean delivery practices is irrefutable. As outlined in Chapter one, in the 1840s the Hungarian clinician Ignaz Semmelweis promoted hand washing with a chlorine solution, leading to a subsequent threefold decline in puerperal sepsis mortality rates from more than 900 per 1000 births.[37] Hand washing campaigns have also been shown to improve child health overall.[168] A systematic review found that hand washing with soap has the potential to reduce diarrhoeal disease by 42-47%, with the possibility of saving millions of lives if implemented and scaled up appropriately.[168] Another recent systematic review found that water, sanitation and hygiene (WASH) interventions, including hand washing promotion, have benefits for the growth of children under five.[169] Hygiene campaigns aimed at improving clean delivery practices may have similar benefits. Given the above evidence, conducting clinical trials of clean delivery practices is unethical and we must consider the best available evidence to guide our decision making process on the implementation and recommendation of such clean practices.

Results from the previous chapter found that kit use was associated with a reduction in neonatal mortality and that a combination of clean delivery practices was essential to this improvement.[75] Given the potential for kits to not only improve neonatal survival but also reduce maternal mortality and morbidity, careful consideration needs to be given to their contents and appropriate clean delivery practices. Kits may also be used as a vehicle for components to reduce other causes of maternal mortality, such as misoprostol, a drug known to be effective in reducing the incidence of postpartum haemorrhage.[170] However, it is essential not to discourage women from delivering in institutions while promoting the use of clean delivery kits.

Given the evidence base for hygiene in improving maternal mortality and morbidity associated with puerperal sepsis, the question of how to promote beneficial practices in underserved rural populations in South Asia is an important one. A recent meta-analysis involving seven cRCTs suggested beneficial effects on neonatal and maternal survival of an intervention involving community mobilisation through participatory women's groups.[171] In the three trials where the intervention was most successful and data were available, clean delivery practices, including clean delivery kit use and hand washing by the birth attendant were more common in intervention than control clusters.[99, 101, 114] Working with community-based women's groups may therefore have substantial benefits for maternal survival, partly by improving clean delivery practices during home births in settings where they are common.

5.8 Conclusions

This study draws on a large, population-based dataset with a shorter recall period than DHS surveys (i.e. six weeks vs. up to five years), features an additional indicator unavailable elsewhere for home births (hand washing), and gives careful consideration to potential sources of bias. Its findings demonstrate that improving hygiene through hand washing is likely to improve maternal survival following home births in rural settings in South Asia where there is minimal access to skilled birth attendants. However, the true effect if all forms of bias are removed is difficult to gage, and is most likely to be weaker than the estimate from the complete case analysis.

Chapter 6 Review of integrated community-based interventions to improve clean delivery practices

6.1 Introduction

The previous two chapters have highlighted the importance of a clean delivery to improve newborn and maternal survival among home births in rural, low-resource settings in South Asia. Chapter four examined the association between clean delivery practices and neonatal survival, with results indicating that all clean delivery practices are important in reducing neonatal mortality. Chapter five described the results from analyses on the associations between hygienic delivery practices and postnatal maternal mortality, with results suggesting that hand washing with soap by the birth attendant is the single most effective clean delivery practice affecting the odds of postpartum maternal death. Chapter four also highlighted that simply distributing kits, even with instructions, does not guarantee that all components of the kit will be used appropriately. These results support those from a qualitative study from Nepal, where kit users rarely read the instructions, and when they did, had difficulties understanding them.[159] If clean delivery practices are going to achieve their full potential, interventions that effectively improve a hygienic delivery either through kit use, or through individual clean practices, must be carefully considered.

Many community-based interventions to improve maternal and newborn health tested to date have been complex, integrated packages, aimed at improving survival in rural, low-resource settings. Some of these complex interventions included a component aimed at improving hygiene during delivery. Given that improving maternal and newborn survival involves modifying a complex set of behaviours in order to facilitate change, there is a need for scalable, culturally-sensitive intervention packages aimed at addressing the multiple determinants of maternal and newborn survival, including hygiene in delivery.[172]

As little is known about the most effective means of promoting clean delivery practices, the fourth objective of this thesis is to conduct a literature review of integrated, community-based interventions that include a component aimed explicitly at promoting clean delivery practices. It is anticipated that the results of this review will highlight effective methods for promoting clean deliveries in rural settings of low and middle-income countries.[69] In this chapter, I summarise the results of this review.

6.2 Methods

6.2.1 General

Peer-reviewed publications written in English were identified using the following electronic databases: PubMed, Embase, Medline, Cochrane Reference Libraries, Google Scholar, and Web of Science. The following search terms were used separately and in combination to identify studies: "neonatal mortality, "maternal mortality", "neonatal death", "maternal death", "sepsis", "maternal health", "newborn health", "community-based intervention", "cluster randomised controlled trial", "before after study", "quasi experimental", "essential newborn care", "birth preparedness", "clean delivery", "cord care", "hand wash", "hand hygiene", "hygienic delivery", "delivery surface", "newborn care programmes", "antenatal care programme", "community intervention".

6.2.2 Inclusion criteria

The review included randomised and non-randomised trials with an appropriate comparison group, conducted in rural, low-resource settings, and published between January 1980 and June 2014. Study participants were women of childbearing age (15 to 49 years). I included evaluations of integrated care packages delivered at the community level and aiming to improve overall newborn or maternal health while promoting at least one clean delivery practice and measuring changes in its use.

I did not consider trials promoting the use of clean delivery practices but reporting on sepsis-related outcomes, as this review focused on the effect of different promotion strategies on the reported use of clean delivery practices.

6.2.3 Reported outcomes

The review included trials reporting outcomes for any one of the following clean delivery practices: use of a clean delivery kit, hand washing with soap by the birth attendant, clean instrument to cut the cord, clean thread to tie the cord, use of either dry cord care or application of an antiseptic to the cord, and a clean delivery surface.

6.2.4 Quality of evidence assessment

I assessed the quality of studies using the Cochrane Risk of Bias Tool, and reviewed the appropriateness of statistical methods used.[173] The Risk of Bias Tool covers six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other significant bias. Within each domain, the tool considers the following criteria to be essential: avoiding selection bias requires random sequence generation and allocation concealment; avoiding performance bias requires blinding of participants and personnel; avoiding detection bias requires blinding of personnel conducting the outcome assessment; avoiding attrition bias requires reporting on all incomplete outcome data; diminishing the risk of reporting bias involves selective reporting on outcomes; and avoiding other biases involves reporting any further important concerns about bias. Because community-based interventions are often delivered to entire geographical areas as clusters, it is often impossible for these studies to have a low risk of bias in all six domains. For example, addressing performance bias requires blinding individual participants, which is impossible when interventions are delivered at a cluster level and include socially obvious activities, such as group discussions in the community or antenatal visits by community health workers. Blinding study personnel conducting the outcome assessment can also be logistically difficult in cRCTs taking place in rural, close-knit communities. Therefore, studies were classified as having a high risk of bias if they were found to be at high or unclear risk of bias for at least one of the bias domains: selection bias, attrition bias, reporting bias, and other bias. Studies were classified as having a low risk of bias if they met the following criteria: appropriate randomisation methods; allocation concealment; appropriate description of any incomplete data or losses to follow-up; no selective reporting, and no other major concerns about biases not covered in the tool. Studies deemed to have a high risk of bias were not excluded as long as they met the inclusion criteria, but their limitations are discussed.

6.3 Results

6.3.1 General

In total, 11 studies met the specified inclusion criteria. A summary of the studies is shown in Table 6.1, and includes the following details: country; setting; study period; study type; intervention tested; and primary study outcomes. Table 6.2 describes the clean delivery practices promoted as part of the larger intervention package as well as the associated outcomes. Two studies were excluded as their methods and findings had already been reported in the main study paper and included in the review.[174, 175] Four studies were excluded as they did not report data on clean delivery behaviours, despite promoting clean deliveries in the intervention areas, and instead reported on either sepsis-related morbidity outcomes or overall neonatal or maternal mortality.[80, 176-178] One study was excluded as although they reported on hand washing by the birth attendant, they did not actively promote this practice in the intervention clusters.[115] Other reasons for study exclusion included lack of an appropriate control group.[179]

6.3.2 Study countries and settings

I identified 11 studies eligible for inclusion in the review. 10 of these were carried out in South Asia, and one in sub-Saharan Africa. The study that took place in sub-Saharan Africa was located in Ghana.[1, 81] Of the studies that took place in South Asia, four took place in Bangladesh, four in India, one in Pakistan, and one in Nepal.[10, 99-101, 114, 180-184]

All studies took place in rural settings with limited access to health facilities. The proportion of deliveries occurring in the home varied between settings: on average, the proportion of home deliveries was higher in South Asian studies compared to the study in sub-Saharan Africa. Six of the studies reported clean delivery outcomes for home deliveries only.[1, 10, 99, 100, 114, 184] Five studies did not distinguish between home or facility deliveries for the reported clean delivery practices.[5, 101, 180, 182, 183]

6.3.3 Study designs

Nine studies used a cRCT design, with either a closed or open cohort, and one study used a factorial design.[100] [1, 10, 99, 101, 114, 180, 182-184,] Only one study used a quasi-experimental design.[5]

Table 6-1: Summary of studies included in literature review

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Azad[100] (2010)	Bangladesh	Three rural districts (Bogra, Faridpur, and Moulavibazar)	2005 - 2007	Factorial designed cRCT involving 18 clusters in three rural districts in Bangladesh	Intervention and control arms: Health services strengthening and basic training for TBAs was done in both intervention and control arms. Intervention arm only: Women's groups were run by local female facilitators who were responsible for 18 groups each. Facilitators received five training sessions and covered participatory modes of communication as well as maternal and neonatal health issues. The facilitator's main responsibilities were to activate and strengthen groups, to support women in identifying maternal and neonatal problems, to identify possible strategies and to support the planning, implementation, and monitoring of strategies in the community. Supervisors supported facilitators in preparing for meetings and liaising with community leaders. Training was provided for both intervention and control clusters to doctors, nurses , and paramedical staff about the five cleans. Intervention not delivered as part of existing health infrastructure.	Neonatal mortality
Baqui[5] (2008)	India	The intervention was a part of an integrated nutrition and health programme, implemented in eight states in rural northern India. The study evaluated the effect of the intervention in Uttar Pradesh state only,	2003 - 2006	Quasi-experimental design.in two districts within the chosen state; one acting as the intervention arm, the other as control	Newborn care package aimed at improving behaviours proven to benefit maternal and newborn health. The intervention was delivered through antenatal and postnatal home visits by community-based health and nutrition workers. Intervention was delivered as part of existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Baqui[183] (2008)	Bangladesh	The study was conducted in Sylhet district, which has the highest neonatal mortality rate among Bangladesh's six divisions. Access to health care is poor.	2003 - 2006	cRCT involving three arms, with eight clusters in each arm: a home care arm, a community care arm, and a control arm.	Home care arm: community health workers received six weeks of supervised training in a tertiary care hospital and in households. The training involved skills development for behaviour change communication, provision of essential newborn care, clinical assessment and management of neonates. Community health workers identified pregnancies through routine surveillance, promoted birth and newborn care preparedness through two antenatal visits and three early postnatal home visits. There was also a component of community mobilisation, except with lower coverage than in the community arm, described below. Community care arm: community mobilisation involving training TBAs for two days on cleanliness during delivery, maternal danger signs, and newborn care. Community mobilisers were recruited to hold group meetings for the dissemination of birth preparedness and essential newborn care. Meetings with husbands/heads of household were also held in mosques and markets. Advocacy meetings were held with local leaders. Control arm: received the health services provided by government, non-governmental organisations, and private providers. Intervention was delivered as part of the existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Bhutta[10] (2011)	Pakistan	Took place in Sindh, Hala and Matiari sub-districts, southern Pakistan. The study area was mainly rural and agricultural. Around half of all deliveries took place in the home and were attended by TBAs. .	2006 - 2008	cRCT with 16 clusters: eight clusters in intervention arm and eight clusters in control arm.	The intervention package was designed in collaboration with the Directorate of Health in Sindh. The intervention involved training Lady Health Workers (LHWs) and Dais, as well as promoting coordination between them. LHWs conducted two home visits to women during pregnancy, a visit within 24 hours of birth, and four additional visits in the first month of life. Dais responsible for deliveries also conducted home visits. The intervention also involved the creation of community health committees to promote maternal and newborn health. These voluntary community health committees facilitated community education group sessions. Group sessions aimed to promote antenatal care and maternal health education, use of clean delivery kits, facility births, immediate newborn care, etc. Control clusters received usual care, and LHWs were provided with regular refresher training according to the standard national LHW curriculum, including monthly debriefing sessions in health facilities. Intervention was delivered as part of the existing health infrastructure.	Neonatal and perinatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Darmstadt[184] (2010)	Bangladesh	Tangail District, Mirzapur, Bangladesh. The study was conducted in a rural population with a neonatal mortality rate of 24 per 1000 live births in 2002. There was one private hospital	2004 - 2006	cRCT with 12 unions randomly allocated to intervention or control arms.	The intervention arm received a preventative package aimed at promoting essential newborn care practices through six home visits by CHWs. CHWs were also responsible for routine home-based illness surveillance along with referral of sick newborns to health facilities. CHWs conducted two antenatal home visits and four postnatal home visits. The CHWs promoted delivery in health facilities and, where this was not possible, obtained a birth kit or encouraged families and birth attendants to use appropriate cord care. They also distributed clean delivery kits during the second antenatal visit, for use by the birth attendant. TBAs in the intervention arm attended an orientation session on the aims and activities of the project, essential newborn care practices, and indications for referral of newborns and mothers. In the control arm, mothers and newborns received the usual care provided by governmental and non-governmental services, as well as private providers. Intervention was delivered as part of the existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Fottrell[114] (2013)	Bangladesh	1. Three rural districts, Bogra, Faridpur, and Moulavibazar. 2. Districts were selected using purposive sampling, from different divisions in Bangladesh where the Diabetic Association of Bangladesh (BADAS) was active and had regional offices. 3. Within the district, sub districts and unions were purposefully sampled based on recommendations from BADAS, as being an area with limited access to perinatal health, and feasible travelling distance from BADAS district headquarters.	2009 - 2011	cRCT with nine clusters in intervention arm and nine clusters in control arm (the same as in Azad et al. 2010)	In the intervention arm, 648 women's groups were formed and undertook the same participatory learning and action cycle as in Azad et al. 2010. Both intervention and control clusters received health services strengthening interventions. Intervention was delivered as part of the existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Kirkwood[1] (2013)	Ghana	Seven districts in Brong Ahafo Region. The study was conducted in a largely rural area (only 10% of the study population lived in urban areas). The neonatal mortality rate was 31 per 1000 live births. The study area was originally part of the vitamin A and maternal mortality trial known as "ObaapaVitA trial".	2008 - 2009	cRCT with 98 clusters	The intervention involved training community-based surveillance volunteers (CBSVs) to identify pregnant women in their community, and then carry out two home visits during pregnancy and three home visits on days 1, 3, and 7 after delivery. Community meetings were organised by district health management and trial teams to introduce the importance of newborn care and explain the importance of the intervention. The intervention also involved supportive activities such as sensitisation of health facility staff, community leaders and TBA to the importance of essential newborn care and the trial activities. The control arm benefited from routine maternal and child health care. They also benefited from essential newborn-care strengthening for hospitals as well as and sensitisation activities. Intervention was delivered as part of the existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Kumar [180] (2008)	India	1. Study was conducted in Shivgarh, a rural area in Uttar Pradesh. 2. Socioeconomic indicators are among the lowest in the states. 3. Formal health care system consists of a community health centre and two primary health centres. 4. Health staff includes trained physicians and paramedical staff supported by 18 auxiliary nurse midwives who are outreach workers and trained to deliver babies, provide vaccinations and antenatal check-ups. Care seeking is low in this area.	2003 - 2005	cRCT with 39 clusters (village administrative units), allocated to one of three groups (13 clusters each).	Intervention arm 1: received a preventive package of interventions for essential newborn care (ENC). This included birth preparedness, clean delivery and cord care, thermal care, breastfeeding promotion, and danger recognition. This package was delivered through locally recruited and trained women conducting four antenatal and postnatal home visits, as well as community mobilisation and behaviour change management through group meetings. TBAs were involved in community meetings, and families were encouraged to change practices including avoiding delivering infants on the floor, promoting clean delivery practices, immediate breastfeeding, and skin-to-skin care. Community health workers were also involved in home visits aimed at promoting preventive essential newborn care. Intervention arm 2: received the above mentioned newborn care package plus the use of a liquid crystal hypothermal indicator. Both intervention groups had folk song group meetings with messages that promoted behaviour change. The control arm received usual care from government health facilities and non-governmental organisations in the area. Intervention was delivered as part of the existing health infrastructure.	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Manandhar[101] (2004)	Nepal	Makwanpur district, rural central Nepal. Basic perinatal care was available through the district health system, which included primary health centres, health posts, sub-health posts, and outreach clinics.	2001 - 2003	cRCT with 42 clusters	In the intervention arm, each cluster had a local female facilitator, who was literate and received brief training in perinatal health issues and a facilitation manual. Facilitators supported women's groups through ten monthly meetings using a participatory learning and action cycle and a picture card game that addressed prevention and treatment for typical problems in mothers and infants. The content of identified issues varied, but included topics such as clean delivery practices, intrapartum events, and postpartum haemorrhage. Once the issues were raised, strategies to solve the issues were developed and assessed. Control and intervention clusters received health service strengthening and training of TBAs. Both intervention and control arms also received the following: ENC training for TBAs and local health staff, newborn care kits for community based workers, resuscitation equipment for primary health centres, as well as phototherapy units and warm cots. Intervention was delivered as part of the existing health infrastructure	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Bhandari[182] (2012)	India	Faridab district, Haryana state is rural, and Faridabad city is urban. The trial was carried out in communities with a population of 1.1 million served by 18 primary health centres.	2007 - 2010	cRCT with 18 clusters	This is a cRCT testing the effectiveness of India's Integrated Management of Childhood Illness (IMCI) strategy. This strategy was originally implemented in 2003 and by 2010 it had been implemented in 223 of India's 640 districts. Phase 1 (Jan to Dec 2007): improving skills to promote newborn care practices, improving case management skills, and strengthening health system. Physicians, nurses and community health workers were trained to treat or refer sick newborns and children. Supply of drugs and supervision were strengthened. Phase 2 (Jan 2008 to March 2010): women's groups meetings every 3 months and postnatal home visits on days 1, 3 and 7. The women's group meetings were held to raise awareness about newborn care practices. Postnatal home visits promoted early and exclusive breast feeding, delaying bathing, keeping baby warm, cord care and seeking care for illness. Intervention was delivered as part of the existing health infrastructure	Neonatal mortality

Study	Country	Setting	Study years	Study type	Intervention	Primary study outcome
Tripathy[99] (2010)	India	Three rural districts of Jharkhand and Orissa, eastern India. The two above-mentioned states were among the poorest in eastern India, with 20% of the population living below the poverty line. Neonatal mortality rates were 49 per 1000 live births in Jharkhand and 45 per 1000 live births in Orissa.	2005 - 2008	cRCT with 36 clusters	Each intervention cluster had a local female facilitator, who was literate and who received seven days of training. Facilitators supported women's group's through 20 monthly meetings using a four phase participatory learning and action cycle and a picture card game that addressed prevention and treatment for typical problems in mothers and infants. Stories, participatory games and picture cards were used to facilitate discussions about preventative care and health seeking. Both control and intervention clusters received health service strengthening. Health committees were formed so that community members could meet every two months to express opinions about local health services and discuss maternal and newborn health issues. Workshops using appreciative inquiry were provided to frontline government staff. Intervention was delivered as part of the existing health infrastructure	Neonatal mortality and maternal depression

Table 6-2: Clean delivery practices promoted as part of study and associated outcomes

Study	Clean deliveries promoted as part of the intervention package	Clean delivery outcomes	Sepsis related outcomes
Azad[100] (2010)	Women's groups identified and prioritised problems relating to maternal and newborn health, and implemented strategies to address these problems. Although the main study article did not mention which issues were identified, clean delivery practices including a birth attendant washing their hands and using a clean delivery kit, as well as dry cord care featured in the 'preventive practices' picture cards discussed by women's groups.	Hand washing by the birth attendant prior to delivery Use of clean delivery kit Use of plastic sheet Cord tied with sterilised thread Cord cut with new or sterilised blade Dry cord care or application of antiseptic to the cord Clean delivery practices reported for home deliveries only	None
Baqui [5] (2008)	In the antenatal period, CHWs promoted birth preparedness, including identifying a trained provider and either obtaining a clean delivery kit or making one. CHWs encouraged families to practice the five cleans during delivery. In the postnatal period, women were encouraged to use appropriate cord care and to apply no substances to the cord stump.	Clean cord care including umbilical cord cut with a sterilised blade and tied with a sterile thread Clean delivery practices reported for home and facility deliveries together	None
Baqui [183] (2008)	TBAs in the community care arm had a two-day orientation on cleanliness during delivery. In the home care arm, antenatal visits were used to promote birth preparedness and ENC, but the clean practices promoted were not specifically stated. However, the use of clean instrument to cut the cord was one of the secondary outcomes measured. Clean cord cutting instrument was defined as either a blade from a clean delivery kit or a blade that had been boiled prior to use.	Use of a clean cord cutting instrument defined as a sterilised blade or a blade used from a clean delivery kit Clean delivery practices reported for home and facility deliveries together	None

Study	Clean deliveries promoted as part of the intervention package	Clean delivery outcomes	Sepsis related outcomes
Bhutta[10] (2011)	Clean delivery kits were provided to LHWs in both intervention and control clusters. Appropriate cord care (cleaning and avoidance of traditional maternal application) was recommended in both intervention and control clusters. LHWs promoted the use of clean delivery kits through group sessions.	Clean delivery kit use for home deliveries	None
Darmstadt[184] (2010)	CHWs in the intervention arm recommended the use of a sterilised blade or a blade from a clean delivery kit, as well as dry cord care.	Use of a sterilised blade Dry cord care Clean delivery practices reported for home deliveries only	Infection related neonatal mortality rates
Fottrell[114] (2013)	The study does not mention the specific clean delivery practices that were promoted. The women's groups used picture cards depicting common maternal and newborn health problems, including symptoms of newborn sepsis, as well as strategies to prevent them, including the use of a clean delivery kit and hand washing prior to delivery.	Hand washing by the birth attendant prior to delivery Use of clean delivery kit Use of plastic sheet Cord tied with sterilised thread Cord cut with new or sterilised blade Dry cord care or application of antiseptic Clean delivery practices reported for home deliveries only	Neonatal mortality due to infections (diarrheal disease, meningitis, neonatal pneumonia, and neonatal sepsis).

Study	Clean deliveries promoted as part of the intervention package	Clean delivery outcomes	Sepsis related outcomes
Kirkwood[1] (2013)	During antenatal visits, CBSVs encouraged mothers to plan for a clean home delivery, in particular hand washing with soap by the birth attendant. CBSVs visiting women on the day of delivery encouraged special care for low birth weight babies including hygiene.	Birth attendant washed hands with soap before delivery Clean delivery practices reported for home deliveries only	None
Kumar[180] (2008)	In both intervention arms (i.e. not the control arm), CHWs promoted hand washing with soap by the birth attendant, cutting the cord with a clean blade, tying the cord hygienically (not defined), and discouraged the application of ash or clay to the cord.	Washing hands with soap by the birth attendant. Cord cut with clean blade Clean cord tying Application of ash/clay on the cord. Clean delivery practices reported for home and facility based deliveries together	None
Manandhar[101] (2004)	Women's groups typically made and distributed clean delivery kits.	Use of clean delivery kit Use of a sterilised blade to cut the cord Hand washing by the birth attendant prior to delivery Dry cord care or cord dressed with antiseptic Clean delivery practices were reported for home and facility deliveries together	None

Study	Clean deliveries promoted as part of the intervention package	Clean delivery outcomes	Sepsis related outcomes
Bhandari[182] (2012)	Post-natal care visits promoted appropriate cord care.	Application of nothing or gentian violet on the cord Clean delivery practices reported for home and facility deliveries together	None
Tripathy[99] (2010)	Women's groups discussed clean delivery practices through stories and games.	Hand washing by the birth attendant prior to delivery Use of clean delivery kit Use of plastic sheet Cord tied with sterilised thread Cord cut with new or sterilised blade Dry cord care or application of antiseptic Percentages of early neonatal deaths due to septicaemia Clean delivery practices reported for home deliveries only	Early neonatal mortality due to septicaemia

6.3.4 Intervention packages

All intervention packages were complex in nature, targeting a variety of antenatal, delivery and postnatal practices with the primary objective of reducing neonatal mortality and/or maternal mortality. Broadly, two types of intervention strategies were used: (1) community mobilisation and (2) home visits in the antenatal, delivery, and postnatal period. Four studies used community mobilisation interventions only.[99-101, 114] Five studies used a combination of community mobilisation and home visits.[1, 10, 180, 182, 183] Two studies used home visits only.[5, 184]

Approaches to community mobilisation varied considerably between trials. Four trials used community mobilisation through a participatory learning and action cycle with women's groups.[99-101, 114] Women's groups identified and prioritised problems related to maternal and newborn health, analysed their causes, then discussed and implemented strategies to address these problems and evaluated their progress. The discussions were informed by a picture card game depicting locally relevant maternal and newborn health problems as well as possible options for prevention and treatment. Other trials conceptualised community mobilisation as the dissemination of health education messages to groups, following formative research in the community.[10, 182, 183] In another study in Ghana, district health management staff and trial staff organised community meetings to introduce the importance of newborn care to the community and explain the intervention.[1] One trial disseminated messages aimed at promoting behaviour change through group meetings featuring folk songs.[180]

The interventions featuring home visits initially involved training local TBAs or community health workers who were then responsible for visiting households in the antenatal, delivery, and postnatal periods. TBAs or community health workers used behaviour change messages to promote the following practices: birth preparedness; early and exclusive breastfeeding; appropriate thermal care including delayed bathing; and appropriate cord care. Health workers were also trained to recognise danger signs among mothers and newborns so that they could either be treated in the home or referred to specialist care. Formative research was usually conducted to identify harmful practices that could be modified as part of the intervention. In some instances, TBAs in intervention clusters encouraged women to obtain a kit or were supplied with locally made clean delivery kits to distribute.[183, 184]

6.3.5 Quality of evidence and associated bias

Overall, nine of the studies were considered to be at high risk of bias, due to incomplete reporting of missing data for the secondary outcomes concerning clean delivery practices, which were the main focus of this review.[1, 5, 99-101, 182, 184] However, when considering the bias domains of randomisation, and allocation concealment, most studies were considered to be high quality, with only one study failing to meet the requirements for each of these domains.[5] Two studies were considered at low risk of bias as they met all criteria in the assessment tool including reporting missing data or follow-up data for secondary outcomes.[10, 114] One study was considered at high risk of bias for not using appropriate statistical methods, and not accounting for clustering in the analysis or sample size calculation.[5] Figure 6.1 shows a summary of the findings from the Risk of Bias Assessment Tool and Table 6.3, provides further details of risk of bias assessment.[173]

Figure 6.1: Summary of risk of bias assessment for reviewed studies

Study	Random sequence generation	Allocation concealment	Blinding	Complete outcome	Selective reporting	Other bias	Overall bias rating
Azad (2010) [100]	+	+	-	-	+	-	-
Baqui A (2008 - Bangladesh trial) [183]	+	+	-	-	+	-	-
Baqui A (2008 - India trial)[5]	-	-	?	-	?	-	-
Bhutta Z (2011) [10]	+	+	+	+	+	+	+
Darmstadt (2010) [184]	+	+	-	-	+	-	-
Fottrell (2013) [114]	+	+	-	+	+	+	+
Kirkwood (2013) [1]	+	+	-	-	+	+	-
Kumar V (2008) [180]	+	+	-	-	+	+	-
Manandhar (2004) [101]	+	+	-	-	+	+	-
Bhandari (2012) [182]	+	+	-	-	+	+	-
Tripathy (2010) [99]	+	+	-	-	+	-	-

Legend
+ Low risk of bias
- High risk of bias
? Unknown bias

Table 6-3: Risk of bias assessment for included studies in literature review

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Azad (2010)[100]	Low: Neonatal mortality rates, stillbirth rates, and maternal mortality ratios were calculated using stratified cluster-level analysis because of the small number of clusters in each group. Risk ratios were calculated for each stratum and an overall weighted mean risk ratio was calculated, using a stratified t-test to test the null hypothesis that there was no difference between intervention and control arms. Baseline differences were adjusted for using the two-stage method described by Hayes et al.	Low	Low: Clusters (unions were "randomly allocated to either intervention or control groups stratified by district in the presence of four project staff and two external individuals. Cluster names were written on pieces of paper, which were folded and placed in a bottle."	Low: For each district the first three cluster names drawn from the bottle were allocated to the women's group intervention and the remaining three to control. The project manager drew the papers from the bottle. The allocation sequence was decided upon by the project team before drawing the papers.	High	High	High	High: 1. Analysis was intention to treat at the cluster and individual level. 2. All losses to follow-up were clearly reported for primary outcomes. 3 No mention of numbers available for analysis of the different secondary outcomes. 4. Missing data/non response/unknowns for the individual secondary outcomes not reported.	Low	Low .	High: This is due to lack of reporting for missing data in secondary outcomes.

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Baqui (2008)[183]	Medium: Authors clearly stated how the primary outcomes were calculated. However, authors stated that outcomes for newborn care practices were based on cluster-level averages, and a t-test was used to compare the intervention arm with the control arm at endline. It might have been preferable to use difference and difference methods to account for baseline values, as well as accounting for confounding. 2. Authors did account for clustering, although the exact value for clustering (intra cluster correlation coefficient or design effect) was not mentioned.	Low	Low: 24 clusters were randomly assigned to one of two intervention arms or to the comparison arm with computer-generated pseudo-random number sequence without stratification or matching. The computer-generated randomisation was implemented by a study investigator who had no role in the implementation of the study. The nature of the intervention meant masking was unachievable.	Low: Clusters were allocated randomly with a computer generated number sequence.	High	High	High	High: Analysis was intention to treat at the cluster-level. Authors clearly stated the number of participants who were absent at the time of the survey and the number who declined to participate. However, authors did not specifically state the number who were non-responders or had an unknown response for the specific outcome questions.	Low	High: 1. The recall period for knowledge, practices, and coverage of the intervention was one year, which is likely to accrue some level of recall bias. 2. Results from the control arm suggest that contamination was likely, or that there was a general trend for improved clean delivery practices through other means. Authors clearly state this in the discussion section and state that there is some degree of movement and communication among clusters.	High

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Baqui (2008)[5]	High: 1. Primary and secondary indicators were analysed using difference in difference test to compare the change from baseline to endline for intervention versus comparison districts. 2. There was no mention of methods used to calculate required sample size.	High: did not account for clustering	High: 1. Government intervention was implemented in eight states in India, and only one state was chosen to evaluate, that included one intervention district and one control district. There was no mention why this state was chosen, but we do not know if this is then generalizable to other regions. 2. In each district, a computer programme was used to randomly select nine blocks in intervention district and eight blocks in control district.	High: Within the chosen state, the intervention and control districts were purposefully selected. Only the intervention and control clusters within the intervention or control district were randomly allocated.	High	Unclear	Unclear	High: Data included information collected through a baseline survey as well through an endline survey. The authors reported the number present in each survey, however numbers of respondents who would not participate or who did not have a response to specific questions, were not provided.	Unclear	Medium: An assumption was made that women had a skilled birth attendant if they gave birth in a non-governmental organisation (NGO) or private health facility, or if a skilled provider attended their clinic.	High
Bhutta (2011)[10]	Medium/low: Methods used to determine primary outcomes were described appropriately and in detail. However, when describing methods used to analyse secondary outcomes, very little detail was provided, and authors only stated that they used the svy commands within Stata to account for clustered nature of the data.	Low	Low: Authors used restricted, stratified randomisation to allocate clusters to the intervention or control groups. Three strata were identified on the basis of their size and the number of LHWs per 1000 population.	Low Data collectors and supervisors were blind to cluster allocation. Anthropologists undertaking verbal and social	Low	Low: However unsure if all personnel were blinded. See allocation concealment.	Low: Anthropologists undertaking verbal and social autopsies were masked to cluster allocation.	Low: Complete case analysis. Denominators for the number of participants who were able to report individual outcomes for the care practices were clearly reported.	Low	Low: Authors clearly stated the limitations which were the following. 1. Complete masking of cluster allocation was not feasible. 2. No prospective pregnancy tracking	Low

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
			The research team identified 126 random allocations that resulted in similar population sizes in the two groups (difference <15 000), similar numbers of live births (difference <1000), similar neonatal mortality rates (NMRs; difference <5 deaths per 1000 live births), similar ratios of LHWs to population (difference <0·1 per 1000), and similar proportions of women delivering in hospital (difference <5%). From this list of balanced allocations, one scheme was selected using a computer generated random number.	autopsies were blind to cluster allocation and nature of training of LHWs in their area. Data analysts were not blinded to allocation.						and concerns over Hawthorne effect (behaviour modification in response to the fact they know they are being measured) of repeated home visits. 3. Mother's antenatal and delivery behaviours were based on their reported behaviour. Over reporting of recommended practices is a possibility in this instance as is the improved reporting by mothers of early foetal losses and pregnancy outcomes in the intervention clusters compared to the control. 4. There was also a possibility of differential misclassification of miscarriages and stillbirths between intervention and control clusters.	

Darmstadt (2010)[184]	Low/medium: 1. Detailed description was provided for sample size calculation and sampling methods for both the primary and secondary outcomes. Authors also detailed how baseline and endline samples were arrived at in sufficient detail. 2. Detailed methods for conducting analysis for both primary and secondary outcomes were reported. To investigate changes in knowledge and practices, the authors carried out intention to treat analyses using difference in difference tests with interaction terms for time and study arm. Estimated predicted mean of each knowledge or practice indicator by time and study arm and compared the change between baseline and endline by study arm, controlling for maternal and household background characteristics. Linear probability regression models were used to test the null hypothesis that the difference in difference was zero. Robust standard errors were adjusted for clustering on each union. 3.Authors did not clearly state how prevalence rates for cause specific mortality were arrived at, nor did they state what statistical test was used to determine differences between baseline and control.	Low	Low: 12 unions were randomly allocated to either comparison or intervention arm using a computer generated pseudo random number sequence without stratification or matching.	Low: Intervention and control clusters were allocated using a computer generated random number sequence.	High	High	High	High: 1. Loss to follow-up was not relevant as two independent samples were taken at baseline and endline. 2. Response rates were reported for each survey conducted (baseline surveys, pregnancy outcome surveys, endline surveys, verbal autopsy reports). 3. Coverage rates for antenatal and postnatal visits by community health workers were reported. 4. Change in newborn care practices, was calculated using intention to treat analysis at the study arm level. 5. No clusters were lost to follow-up. 6. Number/percentage of deaths with verbal autopsy data was reported for cause-specific neonatal mortality rates. 7. The number of unknown/missing values for the individual care practices was not reported.	Low	High: 1. There was potential for recall bias in both the endline survey and the verbal autopsy questionnaires. The verbal autopsy questionnaire was conducted on average, 16.5 months between the death and the verbal autopsy collection. The endline survey was conducted between January and May 2006 for births that occurred between 2003 and 2005.	High

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Fottrell (2013)[114]	Low: All analyses assessed using regression techniques for cluster-level summaries that took the stratified and clustered study design into account. To account for potential confounding and to facilitate comparisons with the previous trial, adjustments for confounders were made using a 2-stage analysis.	Low	Low: Same randomisation sequence as in Azad 2010.	Low: Same allocation concealment as in Azad 2010.	High	High	High	Low: 1. Analysis was intention to treat at the cluster and individual level. 2. All losses to follow-up were clearly reported for primary outcomes. 3 The numbers were presented based on numbers of completed interviews. 4. Missing data/non response for the secondary outcomes was reported overall, but not at the individual level.	Low	High: Districts and clusters were purposefully selected so there may be issues around generalisability of findings. The first women's group trial conducted in the same geographical areas could have led to contamination in the intervention clusters.	Low
Kirkwood (2013)[1]	Low: Random effects logistic regression to account for cluster randomised design with relative risks derived by use of the marginal standardisation method and delta method used to calculate 95% CI. These methods were used for each of the primary and secondary outcomes.	Low	Low: Computer generated restricted randomisation was done in a one to one ratio by an independent epidemiologist using stratified sampling to ensure balance within districts and the four large towns.	Low: Computer generated randomised sampling scheme.	High	High	High	High: Intention to treat analysis. Denominators for primary and secondary outcomes were reported. However, the number of missing/unknown/non-response for the clean delivery behaviours in particular, was not reported.	Low	Low	High

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Kumar (2008)[180]	Low: To account for clustering, point estimates for stillbirth rates, neonatal mortality rates, and perinatal mortality rates for each study arm were calculated as the mean of cluster event rates, giving an equal weight to each cluster. Neonatal mortality rates were adjusted for standard of living index, religion, and caste at the cluster level using Poisson regression. The intervention effect was estimated using the rate ratio (RR) and 95% CI for the RR were calculated on the log scale using a Taylor series approximation An unpaired t test on the cluster events rates at 5% significance level was used to test the intervention effect. Authors clearly stated that secondary outcomes were analysed used similar methods.	Low	Low: Stratified cluster randomisation was done at Johns Hopkins University using Stata 7.0 to allocate the 39 cluster units randomly to the three study groups, yielding three allocation sequences of 13 clusters each.	Low: Computer generated cluster randomised allocation was performed.	High	High	High	High: Not reported clearly, however authors stated that they carried out an intention to treat analysis. Authors also stated that coverage of antenatal care was 60% and 65% for postnatal visits in both intervention arms. However, there was no mention of methods to handle missing data for secondary outcomes such as newborn care practices.	Low	Low	High
Manandhar (2004)[101]	Medium/Low: Analysis was intention to treat, taking into account clustering and the paired nature of the data. Multilevel logistic regression models were used to compare differences in primary and secondary outcomes in the intervention clusters compared to the control clusters. No accounting for baseline differences in the analysis, despite differences in poverty, literacy, and education.	Low	Low Matched 42 clusters into 21 pairs based on topographic stratification, ethnic group distributions, and population densities. Random numbers were used to select 12 of the 21 pairs. These 24 clusters formed the intervention and control arms.	Low: Randomly allocated one cluster in each pair to either intervention or control on the basis of a coin toss.	High	High	High	Low: 1. Analysis was intention to treat at the cluster and individual level. 2. All losses to follow-up were clearly reported for primary outcomes. 3 The number of deliveries was reported as numbers available to assess for secondary outcomes.	Low	Low	High

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Bhandari (2012)[182]	Low: Logistic regression using individual patient data, adjusting for clustering and important cluster and individual level differences between intervention and control groups.	Low	Low: 18 clusters were divided into three strata containing six clusters, according to baseline neonatal mortality rates. An independent epidemiologist generated 10 stratified randomisation schemes to allocate the clusters to intervention or control groups. Three of these schemes were excluded due to large differences in neonatal mortality rate, proportion of home births, proportion of mothers who had never been to school, and population size. The authors selected one of the remaining seven allocation schemes by a computer generated random number.	Low: Authors used a computer generated random number to allocate clusters to intervention or control arms.	High	High	High	High: Reported clearly for main outcomes, however a random subset was selected for newborn care practices and it was not clear if there were any missing data. Data were analysed following intention to treat principles.	Low	Low	High

Study	Appropriate statistical methods	Clustering accounted for	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Complete outcome data	No selective reporting	Other bias	Overall bias assessment
Tripathy (2010)[99]	Low: Authors used multivariable logistic regression techniques, accounting for clustering for primary and secondary outcomes. Multiple hypothesis testing was accounted for using the Holms correction factor. Secondary indicators were compared using generalised estimating equations models with semi-robust standard errors at the cluster level. Stratified nature of the trial was accounted for in the analysis.	Low	Low: In the first district, external observers drew folded papers with numbers corresponding to clusters with existing groups from a basket. The first four clusters were allocated to the intervention group, the rest to the control group. This process was repeated in the other two districts in the presence of external observers.	Low: The first clusters drawn from the basket were allocated to the intervention group, the rest to the control group. In each district this was undertaken in the presence of external observers	High	High	High	Low 1. Analysis was intention to treat at the cluster and individual level. 2. All losses to follow-up were clearly reported for primary outcomes. 3 The numbers were presented for number of live births available to assess for secondary outcomes, but unsure how these were arrived at.	Low	High: Intervention/Control areas were purposively selected. Areas such as this are much more likely to see an improvement, in areas with lower neonatal mortality rates, so results have to be interpreted with caution when generalising to other settings with different patterns in neonatal mortality.	High

6.3.6 Study results

6.3.6.1 General

Table 6.4 shows study results for individual clean delivery practices. Results indicate that 10 out of the 11 studies were effective in promoting at least one clean delivery practice in the intervention arm compared to the control arm. One study did not show any difference in the effectiveness of the intervention in promoting clean delivery practices.[100] However, one of the above-mentioned studies repeated the trial whilst increasing the coverage rates of the intervention, resulting in the effective promotion and use of all clean delivery practices in the intervention arm compared to the control arm.[114] In the next chapter, I report results from a pooled analysis of four studies using a similar community mobilisation intervention package with women's groups, and investigate their effects on clean delivery practices.[99-101, 114]

6.3.6.2 Effects on clean cord care

Nine studies assessed the effectiveness of an intervention package in promoting the use clean cord care, including cutting the cord with a new or sterile instrument, tying the cord with a sterile piece of thread, and use of dry cord care or applying some form of antiseptic to the cord. Six studies reporting on the use of a sterile cord-cutting instrument demonstrated that their intervention strategies were effective.[5, 99, 101, 114, 180, 183, 184] Two studies promoting the use of a sterilised blade to cut the cord showed no effect[99].[100] All four studies reporting the effect of interventions in promoting a sterilised thread to tie the cord, reported an improvement in this practice.[5, 99, 114, 180] Four studies showed that their community interventions were effective in promoting the use of either dry cord care or the application of an antiseptic to the cord.[114, 180, 184] [182] However, three studies promoting the same cord care practices found no improvement.[99-101]

Of the seven studies reporting on the use of a sterilised or clean blade to cut the cord, four promoted the clean delivery practice through similar community mobilisation interventions.[99, 100, 114, 163] Two studies used an intervention involving a combination of community mobilisation and home visits.[180, 183] One study used an intervention using home visits only.[184]

Four of the six studies assessing the effectiveness of the intervention on the use of dry cord care or the application of an antiseptic to the cord, used similar community mobilisation techniques.[99-101, 114] There was one study using a combination of community mobilisation and home visits interventions.[182] One study used home visits only.[184]

Two of the four studies reporting on the use of a sterilised thread to tie the umbilical cord, used a similar community mobilisation intervention.[99, 114] One study used a combination of community mobilisation and home visits.[183] There was one study that reported both the use of sterilised blade and sterilised thread, as a single clean delivery practice that used home deliveries only.[5]

6.3.6.3 Effects on hand washing

Clean hands, defined as the birth attendant washing hands with soap prior to delivery, was promoted in six studies. Five studies showed a beneficial effect of the intervention.[1, 99, 101, 114, 180] One study promoting clean hands in delivery, failed to show an effect of the intervention.[100]

Four of the six studies promoting hand washing by the birth attendant used a similar community mobilisation intervention.[99-101, 114] The two remaining studies used a combination of community mobilisation and antenatal care visits. [1, 180]

6.3.6.4 Effects on use of a clean delivery surface

The use of a clean delivery surface is difficult to ascertain, but for the purposes of this review it is defined as use of a new plastic sheet, usually supplied as part of a clean delivery kit. Two studies reported on use of a new plastic sheet which showed that greater use of plastic sheets during delivery in the intervention arm compared to the control arm.[99, 114] One study reporting on the use of a plastic sheet showed no effect.[100] All three of these studies used a community mobilisation intervention to promote the use of a clean delivery surface.

6.3.6.5 Effect on use of a clean delivery kit

For the purposes of this review, a clean delivery kit contained different components to address the six cleans promoted by the WHO, including the following as a minimum:

soap to wash the hands and perineum; a new piece of plastic for a clean delivery surface; a new razor blade to cut the cord; and a piece of sterilised thread to tie the cord. Five interventions promoted the use of a clean delivery kit as part of their package, and all were found to be effective.[100, 101, 114, 163, 185]

Of five studies promoting the use of a kit, four used community mobilisation,[99-101, 114] and one study used a combination of community mobilisation and antenatal and postnatal visits.[10]

Table 6-4: Reported outcomes of reviewed studies on clean delivery practices, maternal and newborn morbidity and mortality

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
Azad[100]	1. Birth attendant washing their hands with soap during home deliveries (intervention verses control)	1. Percentage of singleton home births for which the birth attendant washed hands: 68.4	1. Percentage of singleton home births for which the birth attendant washed hands: 65.3	1. aOR 1.25 (0.88 - 1.75)
	2. aOR for use of a clean delivery kit in intervention arm compared to control arm.	2. Percentage of singleton births that used a clean delivery kit: 27.1	2. Percentage of singleton births that used a clean delivery kit: 18.4	2. aOR clean delivery kit use: 1.28 (0.71 - 2.30)
	3. aOR for use of plastic sheet in intervention arm compared to control arm.	3. Percentage of singleton births for which a plastic sheet was used: 46.7	3. Percentage of singleton births for which a plastic sheet was used: 41.4	3. aOR use of plastic sheet: 1.12 (0.86 - 1.47)
	4. aOR for cutting cord with new or sterilised blade in intervention arm compared to control arm.	4. Percentage singleton births for which a cord was cut with a sterilised blade: 92.4	4. Percentage of singleton births for which a cord was cut with a sterilised blade: 92.1	4. aOR cord cut with sterilised blade: 1.00 (0.97 - 1.03)
	5. aOR for using dry cord care practice or applying antiseptic to the cord in intervention arm compared to control arm.	5. Percentage of singleton births for which dry cord care or antiseptic was used: 68.1	5. Percentage of singleton births for which dry cord care or antiseptic was used: 67.2	5. aOR dried cord care or antiseptic applied to cord: 1.00 (0.80 - 1.26)

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
Baqui [183]	t-test used to determine if there were significant differences at endline, between the intervention arm and control arm for the percentage of deliveries at the cluster level where a clean cord-cutting instrument was used.	Percentage of deliveries for which a clean cord cutting instrument was used at baseline and endline: 1. Home-care arm: baseline, 46%, endline 95%, 2. Community care arm: baseline 49%, endline 76%	Percentage of deliveries for which a clean cord cutting instrument was used at baseline and endline: 1. Control arm: baseline, 46%, endline 61%	Result of t-test at endline: home care arm compared to control arm: $p<0.001$ community care arm compared to control arm: $p<0.001$
Baqui[5]	1. Difference-in-difference test used to determine differences between baseline and endline and intervention groups, for the behaviour of clean cord care including cutting cord with a sterile blade and tying the cord with a sterile thread. Analyses were adjusted for confounding factors.	1. Percentage of deliveries where clean cord care was used: baseline 32.1%, endline 68.4%	1 Percentage of deliveries where clean cord care was used: baseline 36%, endline 41.5%	Adjusted difference-in-difference test for use of sterilised cord cutting and tying: $p<0.001$
Bhutta [10]	*SVY* command within Stata was used to account for the clustered nature of the data, determining if there were significant differences between intervention and control arms for clean delivery kit use by the birth attendant.	Percentage of deliveries for which a kit was used: 35%	Percentage of deliveries for which a kit was used: 3%	$p<<0.0001$.

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
Darmstadt[184]	1. Adjusted difference-in-difference test comparing percentage of deliveries where cord was cut with a sterile instrument between baseline and endline surveys and between control and intervention clusters.	1. Adjusted baseline/endline percentage use of sterile blade: 59.2/ 66.9	1. Adjusted baseline/endline percentage use of sterile blade: 63.3/95.1	1. Use of a sterile blade: significant differential change over time by study arm.
	2. Same as number two, except for use of dry cord care practice.	2. Adjusted baseline/endline percentage use of dry cord care: 95.1/86.0	2. Adjusted baseline/endline percentage use of dry cord care:94.8/94.3	2. Use of dry cord care: significant differential change over time by study arm.
Fottrell[114]	1. Adjusted odds ratio (aOR) comparing birth attendant washing hands with soap in intervention arm compared to control arm.	1. Percentage of newborns delivered where birth attendant washed hands: 91.3	1. Percentage of newborns delivered where birth attendant washed hands: 83.8	1. aOR washed hands: 1.18 (1.02 - 1.35)
	2. aOR for use of a clean delivery kit in intervention arm compared to control arm.	2. Percentage of newborns that were delivered using a clean delivery kit: 29.1	2. Percentage of newborns that were delivered using a clean delivery kit: 15.5	2. aOR used clean delivery kit: 2.26 (1.31 - 3.89)

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
	3. aOR for use of plastic sheet in intervention arm compared to control arm.	3. Percentage of newborns delivered using a plastic sheet: 72.5	3. Percentage of newborns delivered using a plastic sheet was used: 62.1	3. aOR use of plastic sheet: 1.19 (1.06 - 1.34)
	4. aOR for tying cord with sterilised thread in intervention arm compared to control arm.	4. Percentage of newborns where cord was tied with a sterilised thread: 66.8	4. Percentage of newborns where cord was tied with a sterilised thread: 98.9	4. aOR cord tying with a sterilised thread: 1.22 (1.02 - 1.47)
	5. aOR for cutting cord with new or sterilised blade in intervention arm compared to control arm.	5. Percentage of newborns where cord was cut with a sterilised blade: 99.5	5. Percentage of newborns where cord was cut with a sterilised blade:56.2	5. aOR cord cut with sterilised blade: 1.02 (1.00 - 1.04)
	6. aOR for using dry cord care practice or applying antiseptic to the cord in intervention compared arm compared to control arm.	6. Percentage of newborns practicing dry cord care or antiseptic was applied to the cord: 36.9	6. Percentage of newborns practicing dry cord care or applying antiseptic on the cord: 25.4	6. aOR appropriate cord care: 1.58 (1.01 - 2.48)
Kirkwood[1]	Rate ratio comparing whether birth attendant washed hands with soap in intervention arm compared to control arm.	Percentage of deliveries where birth attendant washed hands with soap: 93%	Percentage of deliveries where birth attendant washed hands with soap: 86.9%	Adjusted rate ratio washed hands: 1.05 (1.02 - 1.09)
Kumar [180]	Adjusted rate ratio comparing the following practices in the two intervention arms separately compared to control arm.	Percentage of deliveries using different clean practices in essential newborn care: intervention arm/essential newborn care intervention with thermostat arm.	Percentage of deliveries using different clean practices.	Adjusted rate ratio for the following clean delivery practices in essential newborn care arm/essential newborn care arm with thermostat, compared to control arm.

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
	1. Birth attendant washing hands with soap)	1. Clean hands: 47.2/41.2	1. Clean hands: 16.2	1. Clean hands. Adjusted rate ratio 2.91 (2.39 -3.53) 2.54 (2.08 - 3.10)
	2. Cord cut with clean blade	2. Cut cord with clean blade: 69.1/67.3	2.Cut cord with clean blade: 58.7	2. Clean cord cutting instrument. Adjusted rate ratio 1.18 (1.06 - 1.31) / 1.15 (1.02 - 1.29)
	3. Re-tying cord with clean thread	3.Re-tying the cord with clean thread 46.7/45.5	3. Re-tying cord with clean thread: 78.1	3. Clean cord tying. Adjusted rate ratio 0.60 (0.47 - 0.76) / 0.58 (0.49 - 0.70)
	4. Application of ash/clay on cord	4. Application of ash/clay on cord: 38.9/36.1	4. Application of ask/clay to cord: 60.9	4. Application of ash/clay to cord. Adjusted rate ratio 0.64 (0.52 - 0.79) / 0.59 (0.51 - 0.70)
Manandhar[101]	1. Adjusted odds ratio (aOR) for birth attendant washing hands with soap in intervention arm compared to control arm.	1. Percentage of newborns delivered where birth attendant washed hands: 68%	1. Percentage of newborns where birth attendant washed hands: 33%	1. aOR washed hands: 5.5 (2.40 - 12.6)

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
	2. aOR for use of a clean delivery kit in intervention arm compared to control arm.	2. Percentage of newborns that were delivered using a clean delivery kit: 19%	2. Percentage of newborns that were delivered using a clean delivery kit: 5%	2. aOR used clean delivery kit: 4.59 (2.83 - 7.45)
	3. aOR for cutting cord with new or sterilised blade in intervention arm compared to control arm.	3. Percentage of newborns whose cord was cut with a sterilised blade: 54%	3. Percentage of newborns whose cord was cut with a sterilised blade: 26%	3. aOR cord cut with sterilised blade: 3.47 (1.39 - 8.69)
	4. aOR for dressing cord using dry cord care practice or applying antiseptic to the cord in intervention arm compared to control arm.	4. Percentage of newborns practicing dry cord care practices or antiseptic use on the cord: 81%	4. Percentage of newborns practicing dry cord care or antiseptic was applied on the cord: 73%	4. aOR appropriate cord care: 1.62 (0.58 - 12.6)
Bhandari[182]	Adjusted odd ratio (aOR) comparing use of dry cord care or the application of gentian violet paint to cord in intervention arm compared to the control arm.	Percentage of deliveries with dry cord care or gentian violet applied to cord. All deliveries: 84.1% Home deliveries: 87.7%	Percentage of deliveries with dry cord care or gentian violet applied to cord. All deliveries: 39.5% Home deliveries: 35.3%	All deliveries using dry cord care of gentian violet applied to the cord aOR 8.20 (6.43 - 10.45) Home deliveries using dry cord care of gentian violet applied to the cord aOR 4.50 (3.01 - 6.71)
Tripathy[99]	1. Adjusted odds ratio (aOR) for birth attendant washing hands with soap in intervention arm compared to control arm.	1. Percentage of newborns delivered where birth attendant washed hands: 41%	1. Percentage of newborns delivered where birth attendant washed hands 23%	1. aOR washed hands: 2.50 (1.35 - 4.62)

Study	Outcomes measured	Intervention results (%)	Control results (%)	Outcome estimates
	2. aOR for use of a clean delivery kit in intervention arm compared to control arm.	2. Percentage of newborns that were delivered with a clean delivery kit: 32%	2. Percentage of newborns that were delivered with a clean delivery kit: 18%	2. aOR used clean delivery kit: 2.28 (1.27 - 4.09)
	3. aOR for use of plastic sheet in intervention arm compared to control arm.	3. Percentage of newborns delivered using a plastic sheet: 26/%	3. Percentage of newborns delivered using a plastic sheet 8%	3. aOR use of plastic sheet: 2.98 (1.84 - 4.81)
	4. aOR for tying cord with sterilised thread in intervention arm compared to control arm.	4. Percentage of newborns whose cord was tied with a sterilised thread: 32%	4. Percentage of newborns whose cord was tied with a sterilised thread: 11%	4. aOR cord tying with a sterilised thread: 4.33 (2.06 - 9.11)
	5. aOR for cutting cord with new or sterilised blade in intervention arm compared to control arm.	5. Percentage of newborns whose cord was cut with a sterilised blade: 83%	5. Percentage of newborns whose cord was cut with a sterilised blade: 79%	5. aOR cord cut with sterilised blade: 1.55 (0.96 - 2.51)
	6. aOR for using dry cord care practice or antiseptic to the cord in intervention arm compared to control arm	6. Percentage of newborns practicing dry cord care or antiseptic was applied to the cord: 84%	6. Percentage of newborns practicing dry cord care or antiseptic was applied to the cord: 89%	6. aOR appropriate cord care: 1.01 (0.39 - 2.62)

6.4 Discussion

The findings of this review suggest that community-based interventions are effective in promoting clean delivery practices in rural, low-resource settings. This review has also revealed that three main types of intervention packages have been used to promote clean deliveries, all of which have been successful to varying degrees: community mobilisation; home visits in the antenatal and postnatal period; and a combination of community mobilisation and home visits.

Overall, this literature review suggests that a meta-analysis assessing the effects of community mobilisation on different clean delivery practices is feasible, as four of the studies reviewed used similar interventions and reporting strategies. Conducting a meta-analysis of interventions using a combination of community mobilisation and home visits is not possible, due to the low numbers of studies and high levels of heterogeneity in the study designs and reporting methods. Of the studies that used a combination of home visits and community mobilisation, there were two studies available assessing the effect of the intervention on use of a sterilised blade, one study testing the effect of dry cord care, two studies testing the effect of hand washing and one study testing the effect of the intervention on uptake of clean delivery kit use. The high degree of heterogeneity amongst the community mobilisation techniques used for these small numbers of studies, as well as the variability in the behaviour change messages promoted in the home visits, made conducting a meta-analysis inadvisable in this instance. Likewise, as there were only two studies using an intervention involving home visits only, a meta-analysis is inadvisable in this instance as well.

Overall, the studies included in this review were considered to have high levels of bias, due to all studies failing to report on missing or unknown data for the secondary outcomes of interest. Although it is likely that many of these outcomes had acceptable levels of missing data, this is still largely unknown, so it is difficult to determine the level of bias this may have introduced.

The studies were generally considered to be of high quality, with the majority using appropriate statistical methods, accounting for clustering, and minimising bias through appropriate randomizing methods and allocation concealment. Only one study was quasi-experimental with questionable statistical methods and high levels of bias due to lack of randomisation and allocation concealment.[5] Due to the nature of cRCTs, most of the studies did not blind participants or the personnel conducting the intervention to allocation. Although it is feasible to blind staff assessing the study outcomes, the nature of settings in which these studies are conducted make this logistically quite difficult. Community-based interventions in low-resource settings are generally conducted in small to medium-sized communities, where many people would be aware about whether or not an intervention is being delivered in their community. Blinding the assessors to the outcomes would involve employing staff who reside outside the study location, but even then there is a substantial risk that staff assessing the outcomes will be aware of whether or not they are interviewing participants in a control or intervention cluster. Given the above information, it is unsurprising that only two studies reported on blinding for outcome assessment.[10, 114]

The statistical methods used in the different trials were overall, adequate. However, when assessing effects of the intervention on secondary outcomes, there were no studies that adjusted for baseline differences in clean delivery practices for the intervention and control clusters. For studies where there were no apparent differences between the intervention and control arms, this would be acceptable practice, but in studies where this was not the case, differences in baseline characteristics should be accounted for in the analysis.[5, 183, 184]

Strategies aimed at improving clean delivery practices include community mobilisation, home visits promoting clean deliveries including appropriate cord care and treatment and referral of sick newborns. Comparing the effectiveness of the different strategies is difficult due to the heterogeneity in the study designs as well as the methods used to promote the different clean practices. Overall, it appears that trials that either included an intervention aimed at home visits only, or an intervention including a combination of a community mobilisation intervention and home visits during antenatal, delivery and postnatal period, were more effective, compared to trials using community mobilisation intervention on its own. However, this finding may be misleading as community mobilisation trials may not have been specifically promoting all the clean delivery practices being assessed.

Other contextual factors that may have affected the outcomes in question are the use of skilled birth attendants. Levels of deliveries assisted by skilled attendants vary considerably between the different studies and skilled attendants are more likely not only to use clean delivery practices, but to use them effectively.[75 83] When promoting clean delivery practices, it is important to educate and train both skilled and unskilled attendants on how to appropriately use them, as was done in the trial by Bhandari et al.[182]

Sustainability and scalability are paramount for the long-term success of any intervention involving behaviour change in low-resource settings. For these reasons, community mobilisation using women's groups is an attractive intervention strategy. Additionally, women's groups are low-cost and in many settings there are pre-existing women's groups or similar organisations, making scale-up feasible. Alongside community mobilisation, evidence from this review suggests training both skilled and unskilled birth attendants is effective in ensuring all clean delivery practices are applied. With both types of intervention strategies, continuing inputs must be provided through women's groups meetings involving expectant parents, as well as training for both traditional and skilled attendants. Further evidence will be required as to the scalability of community mobilisation packages and home visits in promoting clean deliveries.

An important caveat to interventions aimed at improving clean deliveries in the home, is that this should not discourage women from having a facility-based delivery. However, the proportion of facility-based deliveries has increased substantially over the past ten years, so it seems unlikely that the promotion of clean deliveries in the home will deter from this practice.

Findings from this review are encouraging, as the use of clean delivery practices has increased using the two main intervention strategies found in the literature. More research will be required on how to implement these strategies within existing health systems, as well as methods to ensure their long-term sustainability.

Chapter 7 Influence of women's groups on the use clean delivery practices in rural South Asia: meta-analysis of individual patient data from four cRCTs

7.1 Introduction

Chapter six featured a literature review of studies analysing the effectiveness of community intervention packages that included a component that focused on the promotion of clean delivery practices, on newborn and maternal survival in South Asia. The review identified two broad types of interventions: community mobilisation with participatory women's groups, and home visits in the antenatal and postnatal period. The review also found high levels of heterogeneity within each of the two types of intervention strategies, the components of the intervention package delivered, as well as the clean delivery practices targeted for improvement. There were four trials testing the effects of community mobilisation through participatory women's groups, seven trials testing an intervention that consisted of a combination of community mobilisation and home visits, and two trials testing the effects of home visits only.

The main objective of this chapter is to analyse the effect of community mobilisation through women's groups on the uptake of individual clean delivery practices with data from four cRCTs conducted in South Asia. This chapter also seeks to assess individual-level factors that potentially modify the effect of women's groups on clean delivery practices.

7.2 Methods

7.2.1 General

For reasons previously discussed in Chapter six (page 182), it is not possible to carry out a meta-analysis using the trials that tested the effects of the combined intervention of community mobilisation and home visits, or home visits only, on the use of clean delivery practices. I therefore performed a meta-analysis using trials that tested the effects of community mobilisation through women's groups on the use of clean delivery practices.

Section 3.2.2, provide details of the individual studies included in the meta-analysis, including information on the study populations, surveillance systems, outcome definitions, exposure definitions, statistical methods, and ethical approval. The sections below discuss methods specific to this analysis.

7.2.2 Study population

The study population includes data from 55 344 home deliveries from both the intervention and control arms of four separate cRCTs. One trial took place in India between 2005 and 2008 (n=15 101), two trials took place in one single geographical area in Bangladesh, the first from 2005 to 2008 (n=25 311) and the second from 2009 to 2011 (n=9114), and one trial took place in Nepal between 2000 and 2003 (n=5818). It is important to emphasise that, in line with previous analyses in this thesis, this analysis includes home deliveries only, as the community mobilisation intervention would only realistically be able to improve clean delivery practices in home deliveries.

7.2.3 Outcome ascertainment and exposures

This analysis focused on the effect of the women's group intervention on the following clean delivery practices: clean delivery kit use, hand washing with soap by the birth attendant, use of gloves by the birth attendant to ensure clean hands, use of a plastic sheet as a clean delivery surface, use of a sterilised blade to cut the cord, use of sterilised thread to tie the cord, use of dry cord care, and use of antiseptic on the cord. The India and Bangladesh cRCTs had data on all clean delivery practices, however the Nepal cRCT did not have data available on the use of sterilised thread, plastic, and gloves. When examining the effect of clean delivery kit use, hand washing, gloves, and a plastic sheet, I have included stillbirths in the study population. However, when examining the effect of the intervention on cord care (i.e. use of a sterilised blade, use of a sterilised thread, dry cord care, and antiseptic to clean the cord) only live born infants are included in the study population.

7.2.4 Baseline differences between intervention and control arms

One of the purposes of conducting a randomised trial is to ensure that factors influencing the treatment effect are equally distributed between the intervention and control arms at baseline. However, a perfect balance between these factors is not always achievable and should be accounted for in subsequent analyses. To determine if any adjustments were required due to baseline differences between and within trials, I compared demographic, antenatal, and delivery characteristics between intervention and control arms for all studies.

Initially, the data were examined for significant (defined here as $p<0.05$) baseline differences between the intervention and control arms in the pooled dataset, as well as within the individual cRCTs, using data made available from the first six months for each of the cRCTs. A six-month period was chosen as a conservative baseline "window period" as it has been shown that 14 months is a realistic time period for the effects of such complex interventions to take place.[186] Baseline differences that were compared were: type of birth attendant (skilled, unskilled but trained, unskilled and untrained); maternal age (15 – 49 years); maternal education (no education, primary, secondary and above); number of antenatal care visits (0-4+); parity (1-4+); and household assets (none, some, or all). Besides examining baseline differences, I also examined the proportion of deliveries where the mother had attended a women's group meeting between the intervention arms for the four separate trials. Given the number of multiple significance tests that were performed in this univariable analysis of baseline differences, it is more likely than not, that significant findings will occur.[156] However, results of this analysis are only going to be used to help gain insight into differences that could potentially bias study findings. For this reason, no correction factor was applied to account for multiple significance testing. A full description of how baseline differences and women's group attendance could bias the estimates of association between the intervention and clean delivery practices can be found in Box 7.1.

7.2.5 Modifying effects of individual level characteristics on the intervention

It is possible that the association between the women's group intervention and use of clean delivery practices vary according to a level of another exposure (i.e. an effect modifier).[127] In other words, the effect of the women's group intervention was different in different sub-populations, such as socioeconomic status. Potential effect modifiers were identified *a priori* and included: the type of birth attendant; number of antenatal care visits; maternal age; maternal education; parity; and household assets. I also hypothesised that the effect of women's group attendance, in the use of clean delivery practices, was different for the separate trials. A full description of mechanisms through which the above-mentioned covariates could potentially behave as effect modifiers can be found in Box 7.1.

Box 7-1: Description of the mechanisms through which either baseline differences in the intervention and control arms or effect modifiers could create bias in the association between the women's group intervention and the uptake of clean delivery practices

Description of the covariate of interest	Effect of baseline differences on relationship between intervention and use of clean delivery practices	Mechanism by which covariate acts as an effect modifier
Type of birth attendant: There were three main types of birth attendants: (1) a skilled attendant formally trained in the importance of hygiene in delivery and more likely to use clean delivery practices; (2) an unskilled but trained birth attendant who may have received informal training in the importance of clean deliveries; (3) an unskilled and untrained attendant with no formal or informal training in clean deliveries.	Bias is a possibility where there is an imbalance in the proportion of deliveries assisted by skilled attendants between the intervention and control arms. As an example, if the intervention arm had a higher proportion of skilled attendants than the control arm, this could potentially bias the association between the intervention and uptake of clean deliveries away from the null.	The type of birth attendant present at delivery has the potential of modifying the effect of the intervention on the outcome, as the intervention is more likely to have a greater effect in birth attendants with no formal training, than in attendants who are already trained in the importance of clean delivery practices.
Number of antenatal care visits: Attendance to antenatal care appointments is essential to educate the mother on factors such as birth preparedness and essential newborn care. Antenatal care providers offer educational advice to women on the importance of factors such as clean delivery practices and exclusive breastfeeding. The more antenatal care visits a mother receives, the more likely she is to influence the birth attendant in using clean deliveries.	An imbalance between the intervention and control arms in the number of antenatal care visits women receive can potentially create bias. As an example, if women in the intervention arm have more antenatal care visits than women the control arm, this could bias this association away from the null.	It is hypothesised that the number of antenatal care visits will modify the effectiveness of an intervention, whereby the fewer antenatal care visits a woman has, the more effective the intervention is in improving use of clean delivery practices.
Maternal age: The age of a mother is thought to affect her use of clean delivery practices. Younger women may be more open and receptive to new ideas, such as using antiseptic on the cord, compared to older women who may be more likely to use traditional birth practices that are potentially harmful to the newborn.	An imbalance in the proportion of younger or older women, between the intervention and control arms, could potentially bias the association between the intervention and the uptake of clean practices. The direction of the bias will be determined by the influence that maternal age has on the use of clean delivery practices.	Maternal age can potentially modify the effectiveness of the intervention in the uptake of clean delivery practices. If younger women are more receptive to messages relayed in the group meetings, the intervention may have a greater effect in this group compared to older women.
Maternal education: Education can influence a woman's ability and willingness to acquire knowledge on important healthy behaviours, such as clean delivery practices.	Differences in the level of maternal education between the intervention and control arms could potentially provide a biased estimate for the effect of the intervention on uptake of clean delivery practices. As an example, if the control arm had a greater proportion of women with higher education levels than the	Assuming more educated women are already knowledgeable in the importance of clean deliveries, it is likely that the intervention will have a greater effect in women with less education.

Description of the covariate of interest	Effect of baseline differences on relationship between intervention and use of clean delivery practices	Mechanism by which covariate acts as an effect modifier
	intervention arm, the association between the intervention and clean delivery practices could be biased towards the null.	
Household assets: the wealth of a family is thought to improve access to health care such as skilled birth attendants, and the ability to purchase items such as a clean delivery kit.	An imbalance between the intervention and control arms in the proportion of mothers with more household assets, could potentially bias the association between the intervention and use of clean delivery practices. As an example, if the intervention arm has a greater proportion of women with "all" household assets, a bias could occur where the estimates for the association moves away from the null, showing a greater effect than actually exists.	Household assets can potentially modify the effect of the intervention in the use of clean delivery practices whereby women with fewer household assets are more likely to benefit from the intervention, than women with more household assets.
Parity: nullliparity and grand parity both have the potential to influence a women's use of clean delivery practices. Nulliparous women are potentially more likely to use clean delivery practices due to apprehension surrounding the delivery and trying to ensure that they are doing as much as possible to ensure a healthy pregnancy. A mother who has delivered several babies may be more likely to have more confidence surrounding the delivery and may be less likely to use "new techniques" compared to traditional practices that have proved successful in the past.	A disproportionate proportion of women who are nulliparous in either the intervention or control arm can bias the association between the intervention and use of clean delivery practices. Controlling for this imbalance will help to remove this bias.	Parity has the potential to modify the effect of the intervention on the use of clean deliveries. As an example, the intervention may not have as much of an effect in grand parity women who have had several deliveries in the past and may not be as receptive to educational messages trying to influence traditional practices. Nulliparous women may be more receptive to the educational messages relayed in the intervention and practice clean deliveries.
Woman's attendance to community mobilisation meetings: women who attend the group meetings were more likely to use clean delivery practices promoted as part of the intervention compared to women who did not attend the meetings.	Women's group attendance is not included in the model due to baseline differences, but due to the fact there were important differences in attendance that could create confounding bias. It is hypothesised that women who attended group meetings were more likely to use clean delivery practices compared to women who did not attend the meetings.	The effect of women's group attendance on the uptake of separate clean delivery practices was expected to differ between studies. To test this hypothesis, an interaction term between women's group attendance and study will provide study-specific odds ratios for the effect of women's group attendance on the uptake of clean delivery practices.

7.2.6 Statistical methods

7.2.6.1 General

I used individual patient data (IPD) to carry out a one-stage meta-analysis, as opposed to a meta-analysis using aggregate data at the trial level. I considered that the IPD analysis would be more appropriate than an analysis of aggregate data as it would be less subject to bias, have greater power, and also allow for the use of statistical methods required to answer the questions associated with this chapter's objectives.[187, 188] The IPD analysis also allowed for the adjustment of important baseline differences between and within trials, which may have helped to remove bias. Importantly, a meta-analysis using IDP allowed for the identification of potential patient-specific characteristics that modify the effect of the intervention in improving the use of clean delivery practices (i.e. sub-group analysis). Often meta-analyses using aggregate-level data have low power to examine potential effect modifiers, and meta-analyses using IPD increases power to detect such differences. A study by Lambert et al, 2002, demonstrated that the IPD approach was the only method that provided sufficient power to detect true intervention-covariate interactions.[189] One such example demonstrated that a meta-analysis using aggregate-level data achieved only 11% power, while an IPD approach reached 91% power.[189]

7.2.6.2 Model selection procedure

I carried out a one-stage meta-analysis using IPD by pooling data from the four separate trials into one dataset, and applying appropriate mixed-effects models to test the effect of women's groups on the use of separate clean delivery practices using Stata's *xtmelogit* command. The mixed-effects random intercept models accounted for the unobserved effects of 96 geographical clusters within four separate trials. Mixed-effects models assume that the distribution of the residuals at each level come from a multivariate normal distribution. To test this assumption, level two residuals were graphed using a normal score plot. The appearance of the level two residuals occurring in a straight line indicated the normality assumption had been fulfilled.[157] The fixed effects terms in the model included the following covariates: treatment allocation, individual attendance to at least one women's group meeting, and previously mentioned baseline differences. The covariate representing the four cRCTs was also treated as a fixed effect.

Besides allowing the mixed-effects models having a random intercept, we also tested the appropriateness of allowing some covariates of having a random slope. Allowing a covariate to have a random slope assumes that it varies across the different geographical clusters in its ability to influence the uptake of the different clean delivery practices. The appropriateness of treatment allocation being included as a random slope was tested using the likelihood ratio statistic. Using similar methods, I also explored whether the effect of the previously mentioned covariates including individual attendance to a women's group meeting, number of antenatal care visits, and type of birth attendant, vary across geographical clusters and would therefore more appropriately be treated as a random effect.

I used Stata's default independent covariance matrix structure that allows for a distinct variance for each random effect within a random-effects equation and assumes that all covariances are zero.[190] The most complex covariance structure is the unstructured covariance matrix that allows for all variances and covariances to be distinct.[190] Longitudinal data often uses an unstructured covariance matrix to account for the structure of follow-up data.[190] It was assumed that within-cluster correlation was not an issue with this analysis and to ensure that results do not differ substantially between the different possible covariance matrices, I compared estimates using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) with the more conservative unstructured covariance matrix and the covariance matrix assuming complete independence.

I explored the effect of the following modifiers on the ability of the intervention to improve the use of clean delivery practices: type of birth attendant, number of antenatal care visits, maternal age, maternal education, parity, and household assets. I also explored the effects of the separate cRCTs on the association between women's group attendance and use of clean delivery practices. Finally, I tested whether or not the effect of the interventions differed between the different studies in the use of the different clean delivery practices. To determine the appropriateness of the effect modifier, I used a likelihood ratio statistic to compare models with and without the interaction term, with an interaction considered significant if $p<0.05$. As stated in the first paragraph of the statistical methods of this chapter, it was difficult to detect effect modifiers in individual studies because of the lack of statistical power. Therefore, in order to obtain robust estimates, I only used the pooled dataset for this part of the analysis.

7.2.6.3 Missing data

I used MI when data were missing in more than 10% of cases for any of the clean delivery practices in any of the cRCTs. In India, data on hand washing were missing in 5% (*n*=744) of cases, in the first Bangladesh study 13.5% of cases (*n*=3,406), in the second Bangladesh study, 13.1% of cases (*n*=1,192), and in Nepal 31.9% of the cases (*n*=1,853). Data on kit use were also missing: in India, data on kit use were missing in 0.5% (*n*=64) of cases; in the first Bangladesh study data, they were missing in 1.7% (*n*=433) instances; in the second Bangladesh study data were missing in 1.2% (*n*=111) cases. In contrast, in the Nepal study, data on kit use were missing in 70.9% (*n*=4,126) of cases. All other clean delivery practices had data missing for fewer than 10% of cases. Due to the above findings, I performed MI for models examining the effect of the intervention on kit use and hand washing only, in order to minimise bias and loss of information due to missing data. I also used MI for models testing for effect modification, to ensure that possible bias associated with the missing data was accounted for. Missing data patterns were explored for models investigating the effect of women's groups on clean delivery kit use and hand washing.

As with other MI analyses in this thesis, I assumed that the missing data mechanism differed across trials due to differences in data collection methods, predictors of missing data, and the amount of missing data. For these reasons, data were imputed separately for the different trials, and a pooled dataset of imputed data was created to provide estimates under the assumption that data were missing at random (MAR).

Due to the hierarchical nature of the data (96 geographical clusters within four cRCTs), it was necessary to impute the data taking this data structure into account. REALCOM-impute software was used to impute 10 separate datasets whilst taking into account this data structure for each study site and for the clean delivery practices of hand washing and kit use.[141] The imputed dataset for each trial was then uploaded from REALCOM-impute to Stata to create a pooled dataset, where the *mi estimate* command was then used to provide estimates and standard errors calculated using Rubin's rules.[139] Variables included in the models were the outcomes of interest (i.e.

the different clean delivery practices), previously mentioned baseline differences, and covariates found to be predictors of missingness that had not already been considered.

7.3 Results

7.3.1 General

Table A6a compares potential baseline differences between the intervention and control arms for the pooled dataset as well as separately for each trial. This analysis included data collected in the first six months of each trial. Comparison of type of birth attendant, number of antenatal care visits, maternal age, maternal education, and household assets between the intervention and control arms, indicate there were important baseline differences for these variables.

Besides baseline differences, Table A6a shows differences in women's group attendance for the intervention arms of the separate trials: in the first Bangladesh trial only 3.1% of the women reported attending at least one women's group meeting, compared to 37.8% in India, 29.3% in the second Bangladesh trial, and 35.8% in the Nepal trial.

7.3.2 Effect of women's group intervention on the use of clean delivery practices

7.3.2.1 IPD meta-analysis

Unadjusted estimates shown in Table 7.1 suggests that the women's group intervention was associated with an increased use of the following clean delivery practices: use of a clean delivery kit (OR 2.35, 95% CI: 1.70–3.24); hand washing by the birth attendant (2.57, 1.77–3.72); use of a sterilised blade to cut the cord (2.30, 1.46–3.63); use of sterilised thread to tie the cord (2.26, 1.42–3.58); and use of a plastic sheet (2.69, 1.93–3.75). The women's group intervention was also associated with a decreased use of gloves in delivery (0.50, 0.33 – 0.76). The intervention did not have a significant effect of improving the use of dry cord care or the application of antiseptic to the cord.

Although results from the adjusted analyses shown in Table 7.2, also indicate a significant effect for the same clean delivery practices, estimates moved towards the null hypothesis; clean delivery kit use (aOR 2.07, 95% CI: 1.55–2.77), hand washing (1.71, 1.28–2.29), sterilised blade to cut the cord (1.66, 1.20–2.30), sterilised thread to tie the cord (1.54, 1.11–2.13), and use of a plastic sheet (1.75, 1.36–2.26). The women's group intervention was shown to reduce the use of gloves in delivery (0.65, 0.42–0.99). Like the unadjusted analysis, the intervention had no effect in improving dry cord care practices, nor the application of an antiseptic to the cord.

7.3.2.2 Individual cRCTs

Table 7.2 show that the India and second Bangladesh cRCTs gave results similar to the adjusted analysis in that the women's group intervention had a strong effect in improving the uptake of clean delivery kit use (India aOR 2.00, 95% CI: 1.26–3.17), (Second Bangladesh trial 4.49, 2.82–7.16), and hand washing by the birth attendant (India 2.20, 1.29–3.75), (Second Bangladesh trial 2.15, 1.34–3.45). Whilst the intervention in India was successful in improving the uptake of use of a sterilised blade (4.26, 2.59–7.00), use of sterilised thread (3.12, 1.86–5.23), and use of a plastic sheet (4.82, 3.33–6.96), the second Bangladesh intervention was effective in improving use of dry cord care (1.84, 1.09–3.13) and use of antiseptic to clean the cord (1.79, 1.22–2.63). The women's group intervention in the first Bangladesh trial demonstrated no effect in improving the use of any clean delivery practices. The women's group intervention in Nepal showed significant improvements in kit use (2.03, 1.04 –3.97), and in hand washing by the birth attendant (2.88, 1.38–6.01).

Table 7-1: Unadjusted odds ratios [OR] (95% CI) for the effect of women's group intervention on uptake of clean delivery practices

Practices	Pooled dataset[b]	India[b]	Bangladesh 2005[b]	Bangladesh 2011[b]	Nepal[b]
Use of a clean delivery kit[c]	2.35 (1.70 - 3.24)	2.35 (1.39 - 3.97)	1.66 (0.84 - 3.28)	3.64 (1.85 - 7.18)	2.18 (1.06 - 4.49)
Birth attendant washing hands prior to delivery[c]	2.57 (1.77 - 3.72)	2.46 (1.30 - 4.67)	1.22 (0.67 - 2.22)	2.62 (1.63 - 4.21)	4.90 (1.90 - 12.60)
Use of sterilised blade to cut the cord[d]	2.30 (1.46 - 3.63)	3.18 (1.60 - 6.30)	1.10 (0.53 -- 2.28)	1.45 (0.57 - 3.67)	3.54 (1.08 - 11.56)
Use of sterilised thread to tie the cord[,d]	2.26 (1.42 - 3.58)	3.44 (1.61 - 7.33)	1.29 (0.67 - 2.49)	1.74 (0.80 - 3.76)	[a]
Use of plastic sheet as a delivery surface[,c]	2.69 (1.93 - 3.75)	4.63 (2.94 - 7.28)	1.30 (0.72 - 2.36)	1.95 (1.07 - 3.59)	[a]
Use of gloves[c]	0.50 (0.33 - 0.76)	0.40 (0.18 - 0.86)	0.67 (0.36 - 1.25)	0.58 (0.35 - 0.94)	[a]
Use of dry cord care[d]	1.08 (0.63 - 1.85)	0.80 (0.29 - 2.23)	1.13 (0.60 - 2.12)	1.87 (0.74 - 4.70)	1.05 (0.29 - 3.84)
Use of antiseptic to clean the cord[d]	1.07 (0.74 - 1.57)	0.63 (0.24 - 1.62)	0.71 (0.44 - 1.15)	1.53 (0.92 - 2.54)	5.67 (1.78 - 18.04)

a. Variables not collected for Nepal cRCT.
b. Adjusted for clustering accounting for the different population clusters.
c. Includes stillbirths.
d. Excludes stillbirths.

Table 7-2: aOR (95%CI) for the effect of the women's group intervention on clean delivery practices, with and without MI

Practices	Model type	Pooled dataset[b,c,d]	India[b,c,d]	Bangladesh 2005[b,c,d]	Bangladesh 2011[b,c,d]	Nepal[b,c,d]
Use of a clean delivery kit[f]	Mixed-effects logistic regression	2.07 (1.55 - 2.77)	2.00 (1.26 - 3.17)	1.40 (0.85 - 2.30)	4.49 (2.82 - 7.16)	2.03 (1.04 - 3.97)
	MI[e]	1.93 (1.43 – 2.59)	1.86 (0.17 - 1.08)	1.42 (0.87 - 1.57)	4.53 (2.86- 7.24)	1.73 (0.94 - 3.16)
Birth attendant washing hands prior to delivery[f]	Mixed-effects logistic regression	1.71 (1.28 - 2.29)	2.20 (1.29 - 3.75)	1.13 (0.74 - 1.71)	2.15 (1.34 - 3.45)	2.88 (1.38 - 6.01)
	MI[e]	1.65 (1.23 – 2.16)	1.84 (1.09 - 3.10)	1.16 (0.79 - 1.72)	2.12 (1.32 - 3.42)	2.89 (1.38 - 5.99)
Use of sterilised blade to cut the cord[g]	Mixed-effects logistic regression	1.66 (1.20 - 2.30)	4.26 (2.59 - 7.00)	0.98 (0.53 - 1.81)	0.87 (0.48 - 1.57)	1.92 (0.95 - 3.89)
Use of sterilised thread to tie the cord[g]	Mixed-effects logistic regression	1.54 (1.11 - 2.13)	3.12 (1.86 - 5.23)	1.02 (0.61 - 1.70)	1.07 (0.63 - 1.84)	[a]
Use of plastic sheet as a delivery surface[af]	Mixed-effects logistic regression	1.75 (1.36 - 2.26)	4.82 (3.33 - 6.96)	0.77 (0.51 - 1.16)	1.52 (0.97 - 2.37)	[a]
Use of gloves[,f]	Mixed-effects logistic regression	0.65 (0.42 - 0.99)	0.45 (0.26 - 0.81)	0.77 (0.49 - 1.20)	0.53 (0.32 - 0.88)	[a]
Use of dry cord care[g]	Mixed-effects logistic regression	1.01 (0.75 - 1.37)	0.55 (0.32 - 0.92)	1.20 (0.73 - 1.95)	1.84 (1.09 - 3.13)	1.29 (0.57 - 2.91)
Use of antiseptic to clean the cord only[g]	Mixed-effects logistic regression	1.24 (0.95 - 1.51)	1.01 (0.53 - 1.95)	0.81 (0.54 - 1.21)	1.79 (1.22 - 2.63)	2.98 (0.84 - 9.24)

a. Variables not collected for Nepal cRCT.
b. Clustering accounting for different population clusters.
c. Adjusted for women's group attendance, type of birth attendant, number of antenatal care visits, parity, maternal age, household assets, maternal education, and cRCT.
d. Random slope for women's group attendance, type of birth attendant, and number of antenatal care visits.
e. MI models were used for the outcomes of kit use and hand washing where greater than 10% of the data were missing.
f. Include stillbirths.
g. Excludes stillbirth.

7.3.3 Influence of effect modifiers on the intervention in the use of clean delivery practices

7.3.3.1 General

Table 7.3 describes the influence of potential effect modifiers on the intervention and its impact on the uptake of clean delivery practices. Briefly, the type of birth attendant was significant in modifying the effect of the intervention in the uptake of clean delivery kit use, hand washing, and use of a plastic sheet. Maternal education was significant in modifying the effect of the intervention on clean delivery kit use and hand washing. Household assets significantly modified the relationship between the intervention and use of a sterilised blade and thread, as well as the use of a plastic sheet.

7.3.3.2 Type of birth attendant

The effect of the intervention on the use of a clean delivery kit differed depending on the type of birth attendant present at delivery: there was a greater effect of the intervention when an unskilled attendant was present compared to a skilled attendant. When a skilled birth attendant was responsible for the delivery, the intervention had a significant positive effect on use of a kit (aOR 1.66, 95% CI: 1.17–2.39). A significant positive effect was also present when an unskilled but trained attendant was used in delivery (2.57, 1.85–3.56). When an unskilled and untrained attendant was present at delivery, the intervention had its greatest impact (3.40, 2.06–5.60).

The type of birth attendant also had a significant positive influence in modifying the effect of the intervention on the uptake of hand washing by the birth attendant. A similar trend was seen with the clean delivery kit use. The intervention had no effect on the use of hand washing by a skilled birth attendant (aOR 0.95, 95% CI: 0.57–1.57). However, the intervention had a significant positive effect on the uptake of hand washing when an unskilled but trained birth attendant was present (2.24, 1.64–3.04). The intervention also had a significant positive effect on hand washing when an unskilled and untrained attendant was present (3.40, 2.14–5.40).

Similar findings were also present where the birth attendant modified the effect of the intervention on the use of a plastic sheet in delivery, with the intervention having a greater effect with unskilled attendants compared to skilled attendants. The intervention had no effect on the use of a plastic sheet by a skilled birth attendant (aOR 1.23, 95% CI: 0.88–1.72). However, the intervention had a significant positive effect on the use of a plastic sheet, when an unskilled but trained birth attendant was used (2.50, 1.90 – 3.29). The intervention also had a significant positive effect on the use of a plastic sheet when an unskilled and untrained attendant was used (4.34, 2.85–6.62).

7.3.3.3 Maternal education

The effect of the intervention on the uptake of kit use and hand washing varied depending on levels of maternal education. When a woman had at least secondary education, the adjusted odds ratios of using a kit and hand washing were aOR 1.89 (95% CI: 1.39–2.55) and 1.48 (1.09–2.01) respectively. In the instance of woman having a primary level of education, the odds of using a kit and the birth attendant washing her hands were 2.04 (1.51–2.77) and 1.54 (1.14–2.08) respectively. The greatest effect of the intervention was observed among women with no education, where the odds ratios of using a kit and hand washing were 2.18 (1.62–2.93) and 1.86 (1.39–2.49) respectively.

7.3.3.4 Household assets

The modifying effect of household assets on the intervention showed a less consistent trend than for maternal education and type of birth attendant. In households with all assets, the intervention had a significant effect on the use of a sterilised blade, sterilised thread, and plastic sheet: (aOR 1.59, 95% CI: 1.14–2.21), (1.43, 1.03–1.99), and (1.97, 1.51–2.56), respectively. In households with some assets, there was also a positive effect on the above-mentioned clean delivery practices: (1.81, 1.31–2.52), (1.79, 1.29–2.49) and (1.61, 1.23–2.11) respectively. Finally, in households with no assets, the intervention also had a positive effect on the use of a sterilised blade, sterilised thread, and plastic sheet: (1.53, 1.10–2.14), (1.33, 0.95–1.85), and (1.61, 1.23–2.11) respectively.

Table 7-3: aOR, (95% CI) for effect of intervention within strata of effect modifier on use of individual clean delivery practices with and without MI

Effect modifier	Model type	Clean delivery kit	Hand washing	Sterilised blade	Sterilised thread[d]	Plastic sheet[d]
Type of birth attendant[a]						
Skilled	mixed-effects	1.66 (1.17 - 2.39)	0.95 (0.57 - 1.57)	b	b	1.23 (0.88 - 1.72)
	MI	1.52 (1.06 - 2.18)	0.95 (0.58 - 1.54)	c	c	c
Unskilled, but trained	mixed-effects	2.57 (1.85 - 3.56)	2.24 (1.64 - 3.04)	b	b	2.50 (1.90 - 3.29)
	MI	2.44 (1.75 - 3.35)	1.97 (1.45 - 2.69)	c	c	c
Unskilled, untrained	mixed-effects	3.40 (2.06 - 5.60)	3.40 (2.14 - 5.40)	b	b	4.34 (2.85 - 6.62)
	MI	3.28 (1.91 - 5.61)	2.91 (1.84 - 4.62)	c	c	c
Maternal education						
Secondary and above	mixed-effects	1.89 (1.39 - 2.55)	1.48 (1.09 - 2.01)	b	b	b
	MI	1.77(1.31 - 2.41)	1.45 (1.08 - 1.96)	c	c	c
Primary	mixed-effects	2.04 (1.51 - 2.77)	1.54 (1.14 - 2.08)	b	b	b
	MI	1.90 (1.39 - 2.59)	1.47 (1.10 - 1.97)	c	c	c
None	mixed-effects	2.18 (1.62 - 2.93)	1.86 (1.39 - 2.49)	b	b	b

Effect modifier	Model type	Clean delivery kit	Hand washing	Sterilised blade	Sterilised thread[d]	Plastic sheet[d]
	MI	2.08 (1.52 - 2.80)	1.80 (1.36 - 2.38)	c	c	c
Household assets						
All assets	mixed-effects	b	b	1.59 (1.14- 2.21)	1.43 (1.03 - 1.99)	1.97 (1.51 - 2.56)
	MI	b	b	c	c	c
Some assets	mixed-effects	b	b	1.81 (1.31 - 2.52)	1.79 (1.29 - 2.49)	1.68 (1.29 - 2.19)
	MI	b	b	c	c	c
No assets	mixed-effects	b	b	1.53 (1.10 - 2.14)	1.33 (0.95 - 1.85)	1.61 (1.23 - 2.11)
	MI	b	b	c	c	c

a. Different categories of birth attendants: skilled (country specific definitions defined by Demographic Health Survey data, most recent version for country in question: India and Nepal, doctor, nurse or trained midwife; Bangladesh: doctor, nurse, trained midwife, family welfare visitor, community skilled birth attendant)[15-17]; unskilled but trained birth attendant includes people with informal training in how to conduct a delivery such as TBAs or village doctors; an untrained and unskilled attendant includes people with neither formal nor informal training in how to conduct a delivery such as a mother in law, sister, or husband.

b. Results of likelihood ratio test indicate interaction term was not significant (p>0.05).

c. Not applicable: MI analysis was not required on those clean practices with less than 10% of the data were missing.

d. India and Bangladesh data only.

7.3.4 Modifying effects of women's group attendance in individual cRCTs on the use of clean delivery practices

Table 7.4 shows that the effect of women's groups attendance on the use of different clean delivery practices, differed significantly for the separate cRCTs. Attendance to women's group meetings in India had a greater effect on the odds of using a clean delivery kit, sterilised blade, sterilised thread and dry cord care, than attendance to women's groups meetings in the other cRCTs. As an example, the aOR for the use of a kit in the India cRCT was 1.80, 95% CI 1.40–2.33, compared to in the first Bangladesh trial of 1.04, 0.69–1.60. Attendance to women's groups in the India cRCT also had a positive impact in improving the use of a sterilised blade (2.50, 1.86 – 3.36), use of sterilised thread (2.83, 2.15 – 3.74) and dry cord care (1.80, 1.29– 2.51). Attendance to women's groups meeting for the first Bangladesh trial had a significant positive effect on the use of a sterilised blade (2.26, 95% CI: 1.37–3.74), and sterilised thread (2.21, 1.40–3.49). Attendance to women's groups meeting had little effect on the use of clean delivery practices for the second Bangladesh trial. In Nepal, attendance to women's group meeting improved kit use only (1.75, 1.15–2.66). Women's group attendance had no significant effect on the use of hand washing by the birth attendant, use of a plastic sheet, use of gloves, and the application of antiseptic to the cord (results not shown).

Table 7-4: aOR (95% CI) showing the effect of women's group attendance on the use of clean delivery practices with and without MI by individual cRCT

		aOR (95% CI)			
Study	**Model type**	**Clean delivery kit**	**Sterilised blade[a]**	**Sterilised thread[a]**	**Dry cord care[a]**
India	mixed-effects[c]	1.80 (1.40 - 2.33)	2.50 (1.86 - 3.36)	2.83 (2.15 - 3.74)	1.80 (1.29 - 2.51)
	MI [d]	1.75 (1.38 - 2.61)	b	b	b
Bangladesh 1	mixed-effects[c]	1.04 (0.69 - 1.60)	2.26 (1.37 - 3.74)	2.21 (1.40 - 3.49)	1.04 (0.68 - 1.59)
	MI [d]	1.05 (0.70 - 1.57)	b	b	b
Bangladesh 2	mixed-effects[c]	0.96 (0.66 - 1.39)	1.00 (0.65 - 1.54)	1.03 (0.70 - 1.52)	0.83 (0.56 - 1.23)
	MI [d]	0.97 (0.68 - 1.38)	b	b	b
Nepal	mixed-effects[c]	1.75 (1.15 - 2.66)	1.37 (0.91 - 2.08)	a	1.06 (0.71 - 1.58)
	MI [d]	1.32 (0.90 - 1.93)	b	b,a	b

a. Nepal data not included

b. Not applicable: MI analysis was not required on those clean practices with less than 10% of the data were missing.

c. All models were adjusted for type of birth attendant, intervention allocation, maternal age, maternal education, household assets, parity, number of antenatal care visits, and study site.

d. All models had random slope for women's group attendance, type of birth attendant, and number of antenatal care visits.

7.3.5 Missing data

Table A6b shows differences between intervention and control arms for the pooled dataset, as well as the individual studies, in missing data for key baseline characteristics as well as individual clean delivery practices. There were significantly more missing data for both use of clean delivery kit and hand washing in the intervention arm, than in the control arm of the pooled dataset (p<0.001). This difference was mainly driven by the Nepal study where there were substantially more missing data in the intervention arm than in the missing arm for both kit use and hand washing (p<0.001). Although there were differences in baseline characteristics, between intervention and control arms, these differences were negligible in comparison to the differences in missing kit use and hand washing between the intervention and control arms. Briefly, in the pooled dataset there were more missing data in the intervention arms for sterilised blade (p=0.004), sterilised thread (p<0.001), use of gloves (p<0.001), and a skilled birth attendant (p=0.016). There were more missing data in the control arms of the pooled dataset for use of dry cord care (p<0.001), use of a plastic sheet (p=0.025), number of antenatal care visit (p=0.026), and maternal age (p=0.026).

Table A6c shows missing data patterns for models with clean delivery kit use and demonstrates that 89% of the variables had complete data. Kit use had the majority of the missing values (8%), followed by maternal age (2%). Although there were only 8% of the values missing with kit use, the majority of the missing data arose in Nepal (70%). Table A6d demonstrates missing data patterns for the model with hand washing and indicates that 20% of the data was missing, the majority due to hand washing by the birth attendant (9%) followed by kit use (5%), and hand washing combined with kit use (3%).

Results of the MI analysis on the effect of the women's group intervention on the uptake of the kit use and hand washing indicated that imputed estimates and estimates from the complete case analysis were similar (Table 7.2). The MI analysis examining the modifying effects of type of birth attendant, maternal education and household assets also indicated that although imputed estimates moved towards the null, compared to estimates from the complete case analysis, results were still significant (Table 7.3).

7.4 Discussion

Results from the IDP meta-analysis examining data from four cRCTs in India, Bangladesh, and Nepal, indicate that community mobilisation through women's groups was effective in improving the use of clean delivery practices, including the use of clean delivery kits, hand washing by the birth attendant, use of a sterilised blade and thread to cut and tie the cord, and the use of a plastic sheet as a clean delivery surface.

Importantly, results from this analysis indicate that women's groups were more effective in improving the use of clean delivery practices in the most disadvantaged groups. For instance, women's groups were more effective in improving kit use, hand washing by the birth attendant, and use of a plastic sheet in deliveries assisted by birth attendants with little or no formal training. These results are not surprising, given that skilled attendants receive training in the importance of hygiene in delivery as part of their formal education. Birth attendants such as TBAs, who have no formal training, stand to benefit from the women's group intervention where information about the importance and appropriate use of individual clean delivery practices is communicated. The women's group intervention was also more effective in improving kit use and hand washing by the birth attendant among women who had little or no education, compared to women with secondary or higher education. These findings also indicate that the intervention is more effective among women who are more disadvantaged, and supports a secondary analysis from the Indian trial, which found that women's groups were more effective in reducing mortality in the most marginalised groups.[191]

The effect of women's group attendance on the use of the different clean delivery practices differed for the separate cRCTs. Attending women's groups meetings in India appeared to have a greater effect on the odds of using clean delivery practices, than in Bangladesh and Nepal. The exact reasons for this are unknown, but it is possible the women's groups in India had a greater focus in improving clean delivery practices than in the other studies. It is also possible, that the women in the Indian trial were more deprived than women in the other trials, resulting in a greater impact of women's group attendance on the use of clean delivery practices.

Results from this analysis help to gain insight into the different mechanisms through which women's group improve clean delivery practices. For instance, it is already known that women's groups made and distributed clean delivery kits, which explains why the intervention had such a pronounced effect in improving the use of this practice.[99] However, women's groups were also effective in improving the use of other clean practices such as the use of a plastic sheet as a clean delivery surface. Given results from a crude analysis indicate the majority of deliveries where plastic was used, also used a kit, it is not unreasonable to assume kits were acting as a medium to promote the use of practices such as a plastic sheet. If this were the case, then it is realistic to assume that kits could also act as a vehicle to promote other low-cost interventions such as misoprostol to prevent postpartum haemorrhage.[170]

Results of this analysis suggest that community mobilisation through women's groups is both a feasible and effective method to achieve considerable improvements in the use of clean delivery practices. Women's groups addressed problems that they identified as being important in their area.[99] We do not know whether groups addressed all issues that could improve newborn and maternal health. If groups were to receive more direction, in promoting educational messages concentrating on specific behaviours that were known to be harmful, then the groups could improve the uptake of all clean delivery practices. For instance, given recent evidence from two cRCTs indicates that cleansing the umbilical cord with antiseptic may be beneficial at improving neonatal sepsis in certain settings.[77, 78] then directing women's group discussions to specifically target this behaviour may be of benefit.

This study is not without limitations, due to biases associated with the type of data collected. The outcome measures in question were collected approximately six weeks after delivery and are therefore subject to a degree of recall bias. This is a common issue in surveillance data, and needs to be recognised when interpreting the study findings. Although the trials included in the meta-analysis were randomised, and one would expect bias to occur equally in the intervention and control arms, this is not always the case. For instance, Chapter five of this thesis, which analyses the effect of hand washing by the birth attendant on maternal mortality, highlights the dangers of differential misclassification bias in recalling whether hand washing by the birth attendant was used in delivery, as well as bias associated with data that was not missing at random. If these biases were imbalanced between the intervention and control arms for this analysis, this in turn could affect the results. For instance, given maternal deaths were more likely to occur in the control arms, than the intervention arms, and given there is a reduced sensitivity in reporting hand washing in the instance of a maternal death, this could have resulted in differential misclassification bias moving the estimates away from the null. However, it is anticipated that this would have minimal effects on the estimates mainly due to the fact maternal mortality is a rare event in this context, and not the primary outcome as was the case in the analysis in Chapter five. The same reasoning applies to the possibility of bias arising due to data not being missing at random, where missing data is more likely to occur in the instance of a maternal or neonatal death. It is anticipated that missing not at random bias would move estimates away from the null, and most likely this change would be minimal as mortality outcomes occur at a low prevalence and are not the main study outcomes as was the case in Chapter four and Chapter five.

Recently, there have been government incentives to increase the use skilled birth attendants, in the hope of improving birth outcomes for mothers and newborns. Although the use of skilled attendants is increasing for home deliveries, this coverage is certainly not universal, and the most disadvantaged women remain the most vulnerable.[36] Discussing the importance of clean delivery practices with informal birth attendants and other community members through women's groups will help to achieve more hygienic deliveries. In turn, it is anticipated that this will help in improving neonatal and maternal survival due to reduced rates of puerperal and neonatal sepsis.

Given that clean deliveries improve maternal and newborn survival, and that community mobilisation through women's groups can improve the use of clean delivery practices, women's groups may be part of the solution in reducing maternal and newborn morbidity and mortality due to neonatal and puerperal sepsis. Women's groups are by no means a complete solution to complex problem, but they can help to alleviate some of the burden of poor health outcomes at birth, associated with unhygienic deliveries. Ultimately, women must have access to skilled care in the antenatal and delivery period, as well as access to facility-based deliveries.

Chapter 8 Clean delivery practices and the future of home deliveries

8.1 Introduction

This final chapter outlines the overall evidence on the effectiveness of clean delivery practices in improving neonatal and maternal survival, and on successful interventions aimed at improving their use. I discuss the strengths and limitations of this evidence in turn in the following sections. Finally, the conclusions of this chapter bring together interpretations of the evidence presented with research and policy implications for future interventions.

8.2 Main study findings

Details of main results for each of the thesis' study objectives can be found in Table 8.1. The key public health messages conveyed through my analyses is that all clean delivery practices, except the use of gloves, increased neonatal survival, and that hand washing was an important practice in promoting maternal survival.

Another key finding was the results of the literature review and meta-analysis of complex interventions with a component aimed at improving the use of clean delivery practices. Results from the literature review suggested that there was potential for two broad types of interventions including community mobilisation and home visits in the antenatal and postnatal periods. Results from the meta-analysis examining the effect of community mobilisation through women's groups demonstrated that this was a feasible method to improve the use of all clean delivery practices. Sub-group analyses indicated that the groups who benefited most from this intervention were the most vulnerable: women with little or no education and women who used unskilled birth attendants. Due to the heterogeneity of studies, conducting a meta-analysis on the effectiveness of home visits on the uptake of clean delivery practices was not possible.

Table 8-1: Summary of key findings, by study objective

Study objective	Main findings	Estimates from my analyses (where applicable)
1. Review the literature on the effect of clean delivery practices, including kit use, on maternal and neonatal health outcomes.	• Authors of a literature review assessing the effects of clean delivery kits and clean delivery practices on neonatal health outcomes concluded that there was no real evidence to support the independent effects of kits, since most studies where reductions in mortality were observed included kits as a broader intervention package.[68] • The limited evidence suggested that kit use was associated with a reduction in neonatal mortality.[68] • One trial assessed the impact of kit use on maternal mortality, but the sample size was not large enough to detect an effect with sufficient precision.[80] • Recent cRCTs show that application of chlorhexidine to the umbilical cord was associated with reduced neonatal mortality.[71, 77-79] • There is no up to date evidence available on the benefits of hand washing and maternal mortality.	• Literature review, please refer to references
2. Examine the associations of clean delivery kit use and clean delivery practices with neonatal mortality among home births in three rural sites in India, Bangladesh and Nepal.	• Use of all clean delivery practices, except wearing gloves, was associated with a reduction in neonatal mortality. • Use of each additional clean delivery practice was associated with a linear reduction in neonatal mortality. • Cause of death analysis raised doubts about the main study results because hand washing, use of a plastic sheet and application of antiseptic to the cord were associated with a reduction in neonatal mortality due to an intrapartum event	• Kit use (aOR: 0.64, 95% CI: 0.53 – 0.76); hand washing (0.74, 0.64 – 0.85; sterilised blade (0.79, 0.69 – 0.89); sterilised thread (0.83, 0.73 – 0.96); antiseptic to clean the cord (0.18, 0.12 – 0.28); plastic sheet (0.69, 0.59 – 0.81); gloves (0.85 – 1.39). • Each additional clean delivery practice (0.85, 0.80 – 0.90) • See Table 4.3, too many results to display here.
3. Evaluate the contribution of unsafe delivery practices to maternal mortality among home births in the same three rural sites.	• Handwashing, but not kit use, was associated with a reduction in maternal mortality. • Results from the sensitivity analysis testing the assumption that data were missing at random (MAR), indicated that findings from the complete case analyses and findings from the MI analysis assuming data were MAR, may have been biased. Assuming data were MAR, would result in an over-estimation of the effect of hand washing on maternal mortality. The results	• Handwashing (aOR; 0.51, 95% CI 0. 28 – 0.93); kit use (1.26, 0.62 – 2.56) • See Table 5.4 and 5.5, too many results to display here.

Study objective	Main findings	Estimates from my analyses (where applicable)
	from the sensitivity analysis that assumed data were not missing at random, were still highly significant. • Results from the sensitivity analyses testing for misclassification bias indicated that the association between hand washing and maternal mortality needs to be treated with caution, but this was largely due to the small number of maternal deaths.	• See Table 5.6, too many results to display here.
4. Review the literature on community-based interventions to improve clean delivery practices and clean delivery kit use in low and middle-income countries.	• The review concluded that two main types of interventions improved the use of clean delivery practices: community mobilisation and home visits. • The studies included in this review were heterogeneous in design, making it difficult to conduct a meta-analysis. • All studies were effective in the promotion of at least one clean delivery practice in the intervention arm, compared to the control arm. • All studies showed improved kit use in the intervention arm compared to the control arm. • Improved hand washing by the birth attendant was seen in four of the six studies.	• Not applicable
5. Assess the impact of one of these community-based interventions, community mobilisation through participatory women's groups, on clean delivery practices and clean delivery kit use.	• Community mobilisation through women's groups was effective in improving the use of kits, hand washing by the birth attendant, use of a sterilised blade, use of a sterilised thread and use of a plastic sheet. • Women's groups were more effective at improving the use of selected clean delivery practices in those deliveries assisted by an unskilled and untrained attendant compared to those deliveries assisted by a skilled birth attendant. • Women's groups were also more effective at improving the use of selected clean delivery practices in women who were less educated.	• Kit use (aOR: 2.07, 95% CI: 1.55 – 2.77); hand washing (1.71; 1.28 – 2.29); sterilised blade (1.66 (1.20 – 2.30); plastic sheet (1.75, 1.35 – 2.26) • See table 7.3, too many results to display here.

8.3 Strengths and limitations of the thesis

8.3.1 Strengths

The thesis has several strengths, which are listed below:

1. Analyses were conducted using a large dataset drawn from four separate cRCTs in three south Asian countries, which are similar, but also have distinct characteristics, between 2000 and 2012.
2. Although Chapter four and Chapter five used analyses testing associations between clean delivery practices and mortality were carried out using observational data (i.e. data from the control arms only), using data from randomised trials helped to ensure that the data had been collected systematically and to a high standard.
3. Results of the literature review on the associations of clean delivery practices and neonatal and maternal morbidity and mortality indicated a significant gap in high quality evidence on clean delivery practices. To the best of my knowledge, this is the first time that estimates on associations between clean delivery practices and mortality have been obtained using appropriate statistical techniques. Confounders were carefully selected using up to date causal inference techniques. The robustness of the study findings were assessed using appropriate sensitivity analyses. Estimates from these analyses can be used in the LIST tool, to help better inform public health decisions in the scaling up of interventions that promote clean deliveries.
4. Results of the literature review on clean delivery practices also indicated that there was paucity of evidence on the effect of clean delivery practices and maternal mortality. To the best of my knowledge, this is the first time it was possible to test for associations between kit use and hand washing with maternal mortality using an adequate sample size. This was made possible by the large dataset, which was drawn from four separate trials that used similar surveillance systems to collect data on maternal mortality and information on clean delivery practices.
5. Appropriate analysis of observational data testing for associations between clean delivery practices on neonatal and maternal health outcomes is rare. I attempted to use different sensitivity techniques to demonstrate that results

obtained through methods using complete case analysis with observational data are not always what they seem. I hope that this can be used as a cautionary example on the dangers of drawing erroneous conclusions using observational data without appropriately examining for the robustness of the study findings through sensitivity analyses.

6. Data used in the separate analyses were drawn from trials in three separate countries in South Asia, allowing for relative generalisability of study findings to rural areas of this region.

8.3.2 Limitations

The main limitation of this study is the observational nature of the data used for the analyses on clean delivery practices and mortality. This section will briefly review the implications of using observational data in this study, and demonstrate how it may have affected the study findings.

8.3.2.1 Residual confounding

Results from the analyses on associations between clean deliveries and neonatal and maternal mortality demonstrated large reductions in the odds of death with use of selected clean delivery practices. For example, results suggested that use of a clean delivery kit was associated with a 36% reduction in the odds of a neonatal death (aOR 0.64, 95% CI: 0.53–0.76). If published estimates on the rates of cause-specific neonatal mortality due to sepsis are accurate, then the size of the reduction in mortality seen in these analyses seems unlikely. Furthermore, a comparison of use of a plastic sheet in reducing the odds of a neonatal death to the same extent as a clean delivery kit seems implausible (aOR 0.69, 95% CI: 0.59–0.81).

If current estimates are accurate in suggesting that puerperal sepsis is responsible for between 3% of maternal deaths in Bangladesh to 10% of maternal deaths in India, then the association between hand washing by the birth attendant and a 51% reduction in the odds of a maternal death also seems highly unlikely.[25]

A possible explanation for these findings is the use of clean delivery practices served as a proxy indicator for a type of healthy behaviour that improved overall neonatal and maternal survival. It is possible that participants who reported using clean delivery practices exhibited a collective group of behaviours that was difficult to measure. For example, in a widely-read article discussing possible explanations for conflicting results in the reduction of cardiovascular disease, cancer and all-cause mortality with antioxidant use, suggested that residual confounding caused by inadequate adjustment for the complexity of social and environmental exposures acting across the life course.[155] In these analyses, data were cross-sectional in nature and it was therefore not possible to capture confounding variables that occurred throughout the mother's life and could potentially influence the use of different clean delivery practices as well as the mother's and infant's outcome in delivery.

8.3.2.2 Missing data

The presence of missing data was identified as a limitation in the methods section and in individual analyses, with missing data on clean delivery practices raising particular concerns. The Nepal dataset contained an exceptionally large proportion of missing data on clean delivery kit use in the analysis examining associations between kit use and neonatal mortality (82.7%), and in the analysis examining associations between kit use and maternal mortality (82.5%). However, results from MI analysis, under the MAR assumption, verified results from the complete case analyses. Although sensitivity analyses testing the MAR assumption demonstrated estimates for the associations between clean delivery practices and maternal mortality were slightly biased, the effects were still highly significant. Sensitivity analyses testing the same assumptions for the neonatal mortality outcome did not suggest the presence of bias. It is also important to note that those clean delivery practices for which data were missing in less than 10% of cases were associated with reductions in neonatal mortality similar to those found with kit use. Finally, similar analyses conducted using data from Bangladesh and India only, found results similar to analyses that included the Nepal data. The above findings suggest that missing data may have biased the study findings slightly, but not to the extent that this would change the conclusions drawn from this thesis.

8.3.2.3 Misclassification bias (measurement error)

Sensitivity analyses for the associations between hand washing and maternal mortality showed that even small deviances in the ability to accurately recall whether the birth attendant washed her hands prior to delivery, could create bias by moving estimates away from the null. However, a similar sensitivity analysis for associations between kit use and hand washing with neonatal mortality, indicated misclassification bias was not an issue. The discrepancies between the neonatal and maternal mortality analyses may have arisen because women who died were not present to complete the survey questionnaire and therefore the use of clean delivery practices were not verified. Instead someone who was present at delivery was responsible for answering these questions. If no one present at the time of delivery was available to answer the questionnaire, this was left up to a close relative. It is reasonable to assume that someone who was not present at the time of the delivery would not be able to accurately complete the questionnaire.

Since the questionnaires had not been validated, it is not possible to determine the sensitivity and specificity of questions relating to clean delivery practices, making it difficult to ascertain the extent to which study estimates were biased. Most likely findings were biased away from the null; nonetheless it is equivocal if this bias changed the main conclusions drawn from the analysis on hand washing and maternal mortality.

8.3.2.4 Confounding bias

Although modern causal inference techniques were employed to identify potential confounders using directed acyclic graphs (DAGs), it is still possible that not all confounders were accounted for. As previously discussed, there is a possibility of residual confounding due to inaccuracies in the measurement of confounders, and a possibility of uncontrolled confounding where not all confounders were included in the adjusted analyses.

Residual confounding may have occurred for the variable “household assets”, which was used as a proxy indicator to measure socioeconomic status. The separate trials collected different information on household items, making a variable that was sensitive marker of socioeconomic status difficult to obtain. One trial may have collected information on whether a television was present, and another trial may have collected information on whether a motorcycle was present. It is not possible to determine how residual confounding for this variable may have affected the study estimates. It is likely that more socially disadvantaged mothers did not use clean delivery practices, and the variable of household assets did not adequately capture this. Indeed, analyses on the effect of women's groups on the uptake of clean delivery practices support this argument as sub-group analyses showed that the intervention was more effective in socially disadvantaged groups, suggesting that women who were less educated or who did not have a skilled birth attendant present at delivery, were less likely to use clean delivery practices.

Residual confounding is also a possibility for the variable "study site". The purpose of including this variable in the separate models was to control for the differences between the trials that were potentially biasing the relationship in question. Without controlling for differences between the studies that were both causal for the exposure and outcome in question, could lead to an over or under-estimation of the relevant estimate. In my analyses, I found when I removed the term "study" from the different models, the estimate in question moved away from the null. The issue with the term "study site" is that it's general term, encompassing all differences between the different studies, and does not capture the specific disparities that are potentially contributing to confounding bias. A possible difference between the trials that could lead to confounding bias in the analyses of mortality and clean delivery practices is the presence of non-governmental organisations (NGOs) that may have been actively promoting clean delivery practices and other behaviours to improve survival in pregnancy and childbirth.

8.3.2.5 Validity and reliability of survey questionnaires

The survey questionnaires used for the different cRCTs from which data for this thesis is drawn did not validate the questions on clean delivery practices and, for this reason, the sensitivity and specificity for these different exposures is largely unknown. Accurate measurement of key indicators related to maternal, newborn and child health is essential to their improvement.[192] A recent publication reviewed the accuracy of maternal, newborn and child health indicators used in DHS and Multiple Indicator Cluster Surveys, and found a high degree of accuracy for some indicators such as caesarean section, but a moderate or low degree of accuracy for other indicators such as events occurring shortly after delivery.[193] Validation of the survey questionnaires will ensure that questions on clean delivery practices are measuring what they intend to measure.

8.3.2.6 Sample size and power issues

Studies using maternal mortality as the main outcome measure are uncommon, given it is a relatively rare event, requiring a large sample size. Although I calculated there was 100% power to determine the observed effect of hand washing by the birth attendant on maternal mortality at the 95% significance level, there was only 30% power to determine the observed effect with kit use on maternal mortality. The dangers of using a post-hoc power calculation have been well documented, however this estimate demonstrates even a modest reduction for a rare event such as maternal mortality, requires a sample size much larger than was available for the analysis involving the association of kit use on maternal mortality.[194-197]

8.4 Comparison of similarities between this study and other studies

8.4.1 Clean delivery practices and neonatal and maternal mortality

Previous research supports my findings that clean delivery practices are effective in reducing neonatal mortality. Results from a recent systematic review that used a Delphi panel of experts to arrive at estimates on the overall expected effect of clean delivery practices on neonatal mortality, concluded that clean delivery practices could reduce deaths due to neonatal sepsis in the home (15% (IQR 10 – 20)) and through the use of clean postnatal care practices such as cleaning the umbilical cord with chlorhexidine (40% (IQR 25 – 50)).[68]

Also consistent with the study findings are results from a trial in Nepal which demonstrated that hand washing by the birth attendant prior to delivery reduced neonatal morality.[104] Previous research also identified the application of chlorhexidine to the umbilical cord as an effective means of reducing neonatal mortality.[77, 78, 89] No other studies have tested for the individual associations between a sterilised blade to cut the cord, a sterilised thread to tie the cord, use of plastic sheet as a clean delivery surface, and use of gloves to improve hand hygiene, and neonatal mortality.

Although the overall findings from the above-mentioned systematic review and other studies agree that clean delivery practices improve neonatal survival, results from my analyses showed a much stronger association than results from other studies. For instance, cRCTs showed the application of disinfectant to the umbilical cord had a smaller effect in reducing neonatal morality than was demonstrated in my findings.[77-79] More specifically, a recent factorial cRCT demonstrated that applying chlorhexidine to the umbilical cord reduced the odds of neonatal mortality by 38% (RR 0.62, 95% CI: 0.45–0.85).[78] This is compared to the 82% reduction seen in my analysis (aOR 0.18, 95% CI: 0.12–0.28). In part, the greater reduction in neonatal mortality seen with my results may be due to the observational nature of the data. As previously discussed, it is conceivable that the use of clean delivery practices served as a proxy indicator for other behaviours that were also responsible for reducing neonatal mortality.

Only one previous study attempted to measure the effect of kit use on maternal mortality; however it was not adequately powered.[74, 80] Furthermore, it was not possible to disentangle the effect of kit use from that of the broader intervention package.[74] Although there were no studies that examined the associations between clean delivery practices and maternal mortality, there were two studies that tested for associations between kit use and puerperal sepsis that showed promising results.[80, 84]

8.4.2 Meta-analysis showing the effect of community mobilisation through women's groups at improving the use of clean delivery practices

Results from the meta-analysis, demonstrating improved use of clean delivery practices with community mobilisation through groups, were largely in agreement with those of the individual studies. Details of the individual studies are provided in Chapter six.

8.5 Discussion on selected important findings

The main findings from the first part of my thesis, that clean deliveries improved neonatal and maternal survival, were unsurprising given their biological plausibility. What was surprising was the extent to which clean deliveries improved survival, suggesting that bias was possibly present. Although the large reduction in mortality observed is a limitation of my work, it also has important implications. As discussed in section 8.3.2.1, residual confounding is a likely explanation for the over-estimation of the association between clean delivery practices and mortality. The same section also reviewed the possibility that use of clean delivery practices, were potentially serving as a proxy indicator, for a type of healthy behaviour that was representative of complex traits acquired throughout a lifetime that was impossible to account for using cross-sectional data. If the use of clean delivery practices, are serving as a proxy indictor for a set of complex behaviours acquired throughout the life course, this is suggestive of the fact that an intervention that is successful in improving the use of clean deliveries, will have to target these complex behaviours.

Another important public health message conveyed through my thesis was that not only do women's groups improve the uptake of a majority of clean delivery practices, but they also improve the use of these practices in populations who are most in need. Sub-group analyses showed that women with little or no education benefited the most from community mobilisation thought women's groups in both the improvement of kit use and hand washing by the birth attendant. Moreover, community mobilisation was more effective in improving the use of clean delivery practices in women whose deliveries were assisted by an unskilled birth attendant, compared to women whose deliveries were assisted by a skilled birth attendant. A possible explanation for this finding is that women, who benefited the most, were not using the clean delivery practices in the first place.

8.6 Conclusions and recommendations for policy and future research

8.6.1 Conclusions

The main findings from this thesis are the following: clean delivery practices improve both neonatal and maternal survival although the extent to which this occurs remains difficult to quantify with great precision. Community interventions were shown to be successful in improving the use of clean delivery practices and should be scaled up to resource-poor rural settings where a large proportion of mothers still deliver at home.

8.6.1.1 Clean delivery practices are associated with improved survival

Results from the separate analyses on clean delivery practices and mortality showed improved survival and, given the biological plausibility of clean deliveries in improving survival, suggests that clean deliveries reduced sepsis-related maternal and neonatal deaths. However, in light of the results from the cause of death analyses on neonatal mortality as well as results from the sensitivity analyses on maternal mortality, the extent to which clean deliveries improve survival remains uncertain.

8.6.1.2 Community interventions are effective in improving the use of clean delivery practices, especially in disadvantaged populations

Chapters six and seven of this thesis demonstrated that community interventions involving either community mobilisation through women's groups or home visits, were effective in improving the use of clean delivery practices. Results from the meta-analysis showed that women's groups were more effective at improving the use of clean delivery practices in less educated women and those who did not have access to a skilled birth attendant.

8.6.1.3 Appropriate promotion of clean delivery kit use and other clean delivery practices

Findings from the analyses on neonatal mortality found that distributing a clean delivery kit did not guarantee that all the clean delivery practices were used.[75] These findings were similar to those of a qualitative study from Nepal where kit users were found to rarely read the instructions on how to correctly use the different components of the kit.[159] If all the contents of the kits were being used appropriately, then the reduction in neonatal mortality with kit use would be similar to the reduction found when combinations of different clean delivery practices were used simultaneously. As another example, if all the components of the clean delivery kit were being used appropriately, then one would expect the same association found between hand washing and maternal mortality, with kit use and maternal mortality. Instead, there was no significant association found with kit use and maternal mortality. This is suggestive of the fact that if kit use and hand washing were reported accurately, when a woman reported using a kit, she was not necessarily using the soap.

These findings demonstrate how promoting the appropriate use of kits and other clean delivery practices must take into account the context in which they will be used. A 'one size fits all' approach to distributing kits and promoting clean delivery practices will not be effective. As shown in this thesis, women's groups may be an effective means of ensuring that kits and other clean delivery practices are used appropriately.

8.6.1.4 Behaviours associated with hygiene in delivery are complex

The greater than expected reductions in mortality observed with the use of clean delivery practices suggest that the use of these practices may also have been serving as a proxy for a set of complex behaviours that were too complex to account for in the adjusted analyses. Furthermore, the analyses on interventions aimed at improving the use of clean delivery practices suggested that women who benefited the most from the women's group intervention were among the most disadvantaged.

The above findings indicate that behaviours governing hygiene in delivery are not straight forward and require interventions aimed at complex household behaviours that can also serve to empower women. For instance, even if a woman is aware of the importance of hygiene in delivery, if she does not have a say in her delivery allowing her to insist that the birth attendant wash her hands, or that the umbilical cord should be cleaned with a disinfectant, little can be done to ensure clean delivery practices are used.

These results are consistent with findings from a recent publication that found women's groups to be most effective in reducing neonatal mortality in the most socio-economically marginalised groups.[191] Authors elaborate further to discuss how neonatal mortality is a complex event that results from a combination of different causes and not one isolated behaviour.[191] If this is the case, the use of clean delivery practices could indeed be serving as a proxy measure for the combination of different behaviours that are used to prevent a neonatal death.

8.6.2 Recommendations for future research

The main findings from this thesis can help to guide future research. Essentially what is needed is research in the following areas*:* accurate estimation of the associations between clean delivery practices and neonatal and maternal mortality; studies that help to determine the most effective and feasible methods to promote clean deliver*y* practices in rural community settings; studies that determine the most appropriate content of clean deliver kits; and methods to monitor the effect of kit use in facility-based deliveries.

8.6.2.1 How can we accurately measure the effects of clean delivery practices?

Given the above conclusions, the question remains of how to accurately measure the effect of different clean delivery practices on neonatal and maternal mortality. The first issue to consider are appropriate outcome measures that will accurately capture the effect of clean delivery practices on sepsis. Mortality was used as the main outcome measure in this thesis as information was not available on sepsis-related measures. Given the difficulties associated with measuring the rare event of maternal mortality, using the measure of puerperal sepsis as an outcome would be a more effective means of capturing any effects of the clean deliveries. Outcomes for neonatal sepsis need to be considered, such as the morbidity measure of omphalitis as well as the cause specific mortality indicator of neonatal sepsis. It is essential that questions relating to the outcomes of interest have been validated to ensure the outcomes are being measured accurately with known sensitivities and specificities.

It is not ethical to conduct randomised trials on the effect of clean deliveries on sepsis given the following; the known evidence on the improvement in survival with clean delivery practices, the biological plausibility of clean delivery practices in reducing neonatal and maternal mortality, and the acceptability of clean deliveries as a standard practices in delivery. However, conducting a purposely designed cross-sectional study would not only be ethical but if designed correctly could provide accurate estimates on the effect of clean deliveries and sepsis-related outcomes. If issues that arose in this analysis are taken into consideration in future research, it would be possible to remove much of the bias present in these analyses. Key to doing this will be the validation of questions relating to the use of the different clean delivery practices as well as sepsis-related outcomes. Another important design issue will be asking women on the use of clean practices as close to the delivery date as possible. This will help to remove measurement error, commonly known as misclassification bias due to recall bias and social desirability bias. Questions could also be designed so as to minimize the proportion of missing data.

A main issue encountered with the analyses in this thesis, is the possibility of the clean delivery practices serving as a proxy measure for other healthy behaviours. Potential ways of reducing this bias will need to be carefully considered, including the inclusion of appropriate confounders to measure socio-economic status as well as measures that adequately capture differences between study sites.

8.6.2.2 What are the best strategies to promote clean delivery practices?

The complexity of behaviours associated with clean delivery practices has been discussed previously and needs to be considered when promoting their use. Evidence from the literature review on the effects of community mobilisation through women's groups and home visits in promoting clean delivery practices, suggests that both of these methods are effective.

One possibility of determining effective and feasible means of promoting clean deliveries would be a factorial trial that measured not only the use of clean delivery practices as an outcome, but also sepsis-related morbidity and mortality. Potentially, one treatment arm could use community mobilisation through women's groups, the second treatment arm could use home visits in the antenatal and postnatal period, the third arm could be a combination of the previous two arms, and the final arm could serve as a control group. The trial could also seek to measure other cause-specific mortality and morbidity outcomes, care-seeking behaviour, essential newborn care practices, postnatal care, and the costs associated with each type of intervention.

Another possibility of gaining insight into effective mechanisms of promoting clean delivery practices would be to examine DHS data to see which geographical areas, have succeeded in increasing the uptake of clean delivery practices. Contextualising regions where clean delivery practices are the norm, through the examination of local health care systems and community interventions, could provide important lessons for other settings where using clean delivery practices is not as commonplace.

8.6.2.3 What contents should go into the clean delivery kit?

The WHO promotes the use of 'six cleans', which are addressed in the contents of a typical clean delivery kit. Normally, a kit includes soap to wash the hands, a clean thread to tie the cord, a new blade to cut the umbilical cord, and a piece of plastic for a clean delivery surface. Given the simplicity by which hygiene in delivery can be maintained through appropriate kit use, consideration should also be given to other contents to include in the kit that could address other major determinants of neonatal and maternal morbidity and mortality. For instance, misoprostol has the potential for averting unnecessary deaths due to obstetric haemorrhage.[170] Another possibility is the inclusion of antibiotics for women who exhibit signs of infection or for women suffering from pre-labour rupture of membranes, as a way of reducing the incidence of an intrapartum event.[198]

Randomised trials are needed to determine the effectiveness of different combinations of items in improving survival in rural, community based settings. Initially the inclusion of many components may be appealing, however the associated costs of these items will need to be taken into consideration.[68]

8.6.2.4 Facility-based deliveries

Lastly, we need to ensure that the promotion of clean delivery kits does not deter women from facility-based deliveries. Efforts need to be put into monitoring whether the promotion of kits is potentially influencing women's uptake of facility-based deliveries. One possibility would be to include appropriate questions in the DHS questionnaire that could monitor the influence of kits in women attending facility based deliveries.

Facility-based deliveries are on the rise in South Asia, particularly in India. The increased demand is in part due to *Janani Suraksha Yojana* (JSY), a conditional cash transfer programme aimed at increasing births in health facilities.[162] A mechanism through which kit use could be promoted without deterring from facility-based deliveries, would be to encourage their use alongside campaigns to promote facility-based deliveries. A take home message for women could be that kit use is appropriate for home deliveries, where facility-based deliveries is not possible and where facility hygiene and other services such as the supply of medicines are compromised.

8.7 Final concluding remarks

Improving the appropriate use of clean delivery practices in rural, community-based settings in South Asia has the potential of averting many unnecessary deaths and disabilities. Although a recent Delphi expert opinion process suggested that clean birth practices has the ability of reducing neonatal deaths due to sepsis for home deliveries, by 15% (IQR: 10 – 20) and clean postnatal practices has the possibility of reducing these deaths by 40% (IQR 25 – 40%), results from my analyses suggested this was an underestimation of the true effect.[68] If this is the case, then the number of lives saved by clean delivery practices would be even greater than initially expected. Additionally, a recent publication estimated that 90% of births attended by unskilled attendants, will occur in rural areas and most of these will be home deliveries for the foreseeable future.[36] The above information indicates that action is required to ensure that home deliveries, in rural, underserved populations in South Asia are carried out in safe and hygienic condition, and that women's groups appear to be an effective method to promote this.

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APPENDICIES

Appendix 1: SAS code used to calculate estimates for sensitivity analysis testing for misclassification bias

The following SAS code was used to calculate estimates for different combinations of sensitivities and specificities for the variable "hand washing by the birth attendant with soap prior to delivery". Several different combinations of sensitivities and specificities were used to gain insight into how different degrees of misclassification bias may have affected the study findings.

The first file is the executive file entitled *"exepvw"* that is a macro that runs off of two other SAS files, entitled *"PVW code"* and *"JACK"*. Estimates are calculated based on different combinations of specificities and sensitivities for the main exposure variable on handwashing.

The second file entitled *"pvw"* is a macro that uses the specified combination of sensitivities and specificities, to calculate the weights in order to obtain estimates for the weighted logistic regression.

The third file entitled *"jack"* uses the jackknife procedure to calculate the standard errors.

The code was originally developed by Marine Corbine, and modified for purposes of this analysis.

EXEPVW Macro

```
libname handwash "h:\misclassification\analyses2012\handwash\thesis";

data handwash.mat;

set handwash;

run;

proc freq data=handwash.mat;

tables mumdied handwash country /missing;

run;
```

```
proc freq data=handwash.mat;
table mumdied*country*handwash /missing list;
run;

data handwash.mat_complete;
set handwash.mat;
where (mum_age ne . and handwash ne .);
if country=1 then do;
bangladesh=0;
nepal=0;
end;
if country=2 then do;
bangladesh=1;
nepal=0;
end;
if country=3 then do;
bangladesh=0;
nepal=1;
end;
keep mumdied mum_age handwash bangladesh nepal;
run;
```

```
data mat_complete;

length mumdied mum_age handwash bangladesh nepal 3;

set handwash.mat_complete;

run;

%include "h:\misclassification\analyses2012\handwash\PVWcode.sas";

options nonotes nosource;

proc printto print="D:\misoutput.lst";

run;

libname bigdata "D:\";

%pvwnopriorcov(mat_complete,0.5,0.7,0.6,0.6,resmat);
```

PVW Code

```
%macro pvwnopriorcov(misclassdata,seca,seco,spca,spco,results);

/*This macro runs PVW on a datset where:

        - dichotomous outcome=mumdied

        - dichotomous misclassified exposure=handwash

        - covariate=mum_age

        - covariate=country

        I assume here that the misclassification is differential according to maternal death


misclassdata=misclassified dataset

seca=sensitivity cases

seco=sensitivity controls
```

spca=specificity cases

spco=specificity controls*/

%macro analyze(data=,out=,num=);/*The content of the analyse macro is used by the jack macro and run for the original dataset and for all the

jackknifed datasets

data=input dataset

out=results

num=number of observations of the input dataset*/

/*Fits the logistic regression model to estimate the association between handwash and the other covariates in the data*/

proc logistic data=&data descending OUTEST=EST(drop=_type_ _name_ _LINK_ _STATUS_ _LNLIKE_) noprint;

model handwash=mumdied mum_age bangladesh nepal/maxiter=5000;

%bystmt;

run;

/*Repeats the estimates of the logistic model for &num rows*/

data est2;

set est;

do k=1 to #

output;

end;

rename mumdied=bmumdied mum_age=bmum_age bangladesh=bbangladesh nepal=bnepal;

```
drop k;

run;

/*adds the values of sensitivities and specificities in the input dataset*/

/*data outboot1;

set &data ;

seca0=&seca;

seco0=&seco;

spca0=&spca;

spco0=&spco;

run;*/

/*add the estimates of the logistic model coefficients in the input dataset and adjusts the values for sensitivities and specificities*/

data bigdata.mis_pvw;

merge &data est2;

pistar=exp(intercept+bmumdied*mumdied+bmum_age*mum_age+bbangladesh*bangladesh+bnepal*nepal)/(1+exp(intercept+bmumdied*

mumdied+bmum_age*mum_age+bbangladesh*bangladesh+bnepal*nepal));

maxse=pistar+0.01;

maxsp=1-pistar+0.01;

drop intercept bmumdied bmum_age bbangladesh bnepal;

run;
```

```
/*calculates the min for se and sp*/

proc means data=bigdata.mis_pvw noprint;

var maxse maxsp;

class mumdied;

output out=maxsesp(drop=_FREQ_ _TYPE_) max=;

run;

data maxsesp1;

retain maxseco maxseca maxspco maxspca;

set maxsesp;

if mumdied=0 then do;

maxseco=maxse;

maxspco=maxsp;

end;

if mumdied=1 then do;

maxseca=maxse;

maxspca=maxsp;

end;

run;


data maxsesp2;

length correctionseca correctionspca correctionseco correctionspco 3;

set maxsesp1;
```

```
where mumdied=1;
seca0=&seca;
seco0=&seco;
spca0=&spca;
spco0=&spco;
seca=max(seca0,maxseca);
seco=max(seco0,maxseco);
spca=max(spca0,maxspca);
spco=max(spco0,maxspco);
if seca=seca0 then correctionseca=0;
else if seca ne seca0 then correctionseca=1;
if seco=seco0 then correctionseco=0;
else if seco ne seco0 then correctionseco=1;
if spca=spca0 then correctionspca=0;
else if spca ne spca0 then correctionspca=1;
if spco=spco0 then correctionspco=0;
else if spco ne spco0 then correctionspco=1;
call symput('seca1',seca);
call symput('spca1',spca);
call symput('seco1',seco);
call symput('spco1',spco);
run;
```

```
/*calculation of ppv and npv*/

data bigdata.mis_pvw;

set bigdata.mis_pvw;

seca=&seca1;

seco=&seco1;

spca=&spca1;

spco=&spco1;

ppvca=(seca*(pistar+spca-1))/(pistar*(seca+spca-1));

ppvco=(seco*(pistar+spco-1))/(pistar*(seco+spco-1));

npvca=(spca*(seca-pistar))/((1-pistar)*(seca+spca-1));

npvco=(spco*(seco-pistar))/((1-pistar)*(seco+spco-1));

drop pistar seca seco spca spco maxse maxsp;

run;

/*duplication of the records and computation of the weights*/

data bigdata.mis_pvw1;

length T 3;

set bigdata.mis_pvw;

do T=0 to 1;

if handwash=0 then do;

if T=0 then do;

if mumdied=0 then w=npvco;

else if mumdied=1 then w=npvca;
```

```
end;

if T=1 then do;

if mumdied=0 then w=1-npvco;

else if mumdied=1 then w=1-npvca;

end;

if handwash=1 then do;

if T=0 then do;

if mumdied=0 then w=1-ppvco;

else if mumdied=1 then w=1-ppvca;

end;

if T=1 then do;

if mumdied=0 then w=ppvco;

else if mumdied=1 then w=ppvca;

end;

output;

end;

run;

/*weighted logistic regression*/

proc logistic data=bigdata.mis_pvw1 outest=or_pvw(rename=(_type_=stat2 _name_=name2)) covout descending noprint;

model mumdied=T mum_age bangladesh nepal /maxiter=5000;

weight w;

%bystmt;
```

```
run;

data &out;

set or_pvw;

where (stat2='PARMS' and _STATUS_ eq '0 Converged');

run;

%mend;

%inc "h:\misclassification\jack.sas";

%jack(data=&misclassdata,biascorr=0);

data &results;

informat method $4.;

set jackstat;

where name eq 'T';

OR_corr=exp(value);

lower_corr=exp(alcl);

upper_corr=exp(aucl);

seca=&seca;

seco=&seco;

spca=&spca;

spco=&spco;

method='pvw';

keep method seca seco spca spco OR_corr lower_corr upper_corr; run;

 %mend;
```

JACK code

The code used to calculate the jackknife standard errors was developed by SAS.

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%macro jack (/* Jackknife resampling analysis */

data=, /* Input data set. If the data set does not support direct access via the POINT= option, do NOT use

the %BYSTMT macro in the %ANALYZE macro. */

stat=_numeric_,/* Numeric variables in the OUT= data set created by the %ANALYZE macro that contain the values

of statistics for which you want to compute jackknife distributions. */

id=, /* One or more numeric or character variables that uniquely identify the observations of the OUT=

data set within each BY group. No ID variables are needed if the OUT= data set has only one

observation per BY group. The ID variables may not be named _TYPE_, _NAME_, or _STAT_. */

biascorr=1, /* 1 for bias correction; 0 otherwise. */

```
alpha=.05,    /* significance (i.e., one minus confidence) level for confidence intervals;
blank to suppress

confidence intervals. */

print=1,      /* 1 to print the jackknife estimates;

0 otherwise. */

chart=1       /* 1 to chart the jackknife resampling distributions;

0 otherwise. */);

%if %bquote(&data)= %then %do;

%put ERROR in JACK: The DATA= argument must be specified.;

%goto exit;

%end;

%global _jackdat; %let _jackdat=&data;

%global vardef;

%let vardef=DF;

 %local jack by useby;

 %let useby=0;

*compute the actual values of the statistics;

%let by=;

%analyze(data=&data,out=JACKACT,num=33030);

%if &syserr>4 %then %goto exit;
```

***find number of observations in the input data set;**

```
%local nobs;

data _null_;

call symput('nobs',trim(left(put(_nobs,12.))));

if 0 then set &data nobs=_nobs;

stop;

run;

%if &syserr>4 %then %goto exit;

%if &useby %then %do;

%jackby(data=&data,print=0);

%if &syserr>4 %then %goto exit;

%let by=_sample_;

%analyze(data=JACKDATA,out=JACKDIST,num=33029);

%if &syserr>4 %then %goto exit;

%end;

%else %do;

%jackslow(data=&data);

%if &syserr>4 %then %goto exit;

%end;

%if &chart %then %do;

%if %bquote(&id)^= %then %do;

proc sort data=JACKDIST; by &id; run;
```

```
proc chart data=JACKDIST(drop=_sample_);
vbar &stat;
by &id;
run;
%end;
%else %do;
proc chart data=JACKDIST(drop=_sample_);
vbar &stat;
run;
%end;
%end;
%jackse(stat=&stat,id=&id,alpha=&alpha,biascorr=&biascorr,print=&print)
%exit:;
%mend jack;
%macro jackby( /* Jackknife resampling */
data=&_jackdat,
print=0);
data JACKDATA/view=JACKDATA;
length _sample_ 4;/*added*/
do _sample_=1 to &nobs;
do _i=1 to &nobs;
if _i^=_sample_ then do;
```

```
_obs_=_i;

set &data point=_i;

output;

end;

end;

end;

stop;

drop _obs_ ;/*added*/

run;

%if &syserr>4 %then %goto exit;

%if &print %then %do;

proc print data=JACKDATA; id _sample_ _obs_; run;

%end;

%exit:;

%mend jackby;

%
```

***JACKSE**

```
%macro jackse( /* Jackknife estimates of standard error, bias, and

normal confidence intervals */

stat=,

id=,

alpha=.05,
```

```
biascorr=1,

print=1

);

%global _jackdat;

%if %bquote(&_jackdat)= %then %do;

%put ERROR in JACKSE: You must run JACK before JACKSE;

%goto exit;

%end;

%if %bquote(&alpha)^= %then %do;

*compute confidence level;

%local conf;

data _null_;

conf=100*(1-&alpha);

call symput('conf',trim(left(put(conf,best8.))));

run;

%end;

%if %bquote(&id)^= %then %do;

*sort the actual statistics;

proc sort data=JACKACT;

by &id;

run;

%if &syserr>4 %then %goto exit;
```

```
%end;
```

***transpose the actual statistics in each observation;**

```
proc transpose data=JACKACT out=JACKACT2 prefix=value;

%if %bquote(&stat)^= %then %do;

var &stat;

%end;

%if %bquote(&id)^= %then %do;

by &id;

%end;

run;

%if &syserr>4 %then %goto exit;

proc sort data=JACKACT2;

by %if %bquote(&id)^= %then &id; _name_ ;

run;

%if &syserr>4 %then %goto exit;

%if %bquote(&id)^= %then %do;

proc sort data=JACKDIST;

by &id;

run;

%if &syserr>4 %then %goto exit;

%end;
```

***compute mean, std, min, max of resampling distribution;**

```
proc means data=JACKDIST(drop=_sample_) noprint vardef=n;

%if %bquote(&stat)^= %then %do;

var &stat;

%end;

output out=JACKTMP2(drop=_type_ _freq_);

%if %bquote(&id)^= %then %do;

by &id;

%end;

run;

%if &syserr>4 %then %goto exit;
```

***transpose statistics for resampling distribution;**

```
proc transpose data=JACKTMP2 out=JACKTMP3;

 %if %bquote(&stat)^= %then %do;

var &stat;

%end;

id _stat_;

%if %bquote(&id)^= %then %do;

by &id;

%end;

run;

%if &syserr>4 %then %goto exit;
```

```
proc sort data=JACKTMP3;

by %if %bquote(&id)^= %then &id; _name_ ;

run;

%if &syserr>4 %then %goto exit;

data JACKSTAT;

retain &id name value jackmean

%if &biascorr %then bias;

stderr

%if %bquote(&alpha)^= %then alcl;

%if &biascorr %then biasco;

%if %bquote(&alpha)^= %then aucl confid method;

min max n;

merge JACKACT2(rename=(_name_=name value1=value))

JACKTMP3(rename=(_name_=name mean=jackmean std=stderr));

by %if %bquote(&id)^= %then &id; name;

%if %bquote(&alpha)^= %then %do;

length method $20;

retain z; drop z;

if _n_=1 then do;

z=probit(1-&alpha/2); put z=;

confid=&conf;

method='Jackknife';
```

```
end;
%end;
stderr=stderr*sqrt(&nobs-1);
%if &biascorr %then %do;
bias=(jackmean-value)*(&nobs-1);
biasco=value-bias;
%if %bquote(&alpha)^= %then %do;
alcl=biasco-z*stderr;
aucl=biasco+z*stderr;
%end;
%end;
%else %if %bquote(&alpha)^= %then %do;
alcl=value-z*stderr;
aucl=value+z*stderr;
%end;
label name  ='Name'
value ='Observed Statistic'
jackmean='Jackknife Mean'
%if &biascorr %then %do;
bias  ='Estimated Bias'
biasco='Bias-Corrected Statistic'
%end;
```

```
stderr='Estimated Standard Error'
%if %bquote(&alpha)^= %then %do;
alcl  ='Estimated Lower Confidence Limit'
aucl  ='Estimated Upper Confidence Limit'
method='Method for Confidence Interval'
confid='Confidence Level (%)'
%end;
min   ='Minimum Resampled Estimate'
max   ='Maximum Resampled Estimate'
n     ='Number of Resamples';
run;
%if &syserr>4 %then %goto exit;
%if &print %then %do;
proc print data=JACKSTAT label;
id %if %bquote(&id)^= %then &id; name;
run;
%end;
%exit:;
%mend jackse;
%macro bystmt;
%let useby=1;
by &by;
```

```
%mend bystmt;

%macro vardef;

%let usevardf=1;

vardef=&vardef

%mend vardef;
```

Appendix 2: Stata do file for sensitivity analysis using selection model approach testing missing at random assumption

****
****

* Program: do-file for sensitivity analysis using selection model approach testing missing at random assumption

* This do file was specifically used for analysis on the associations between handwashing and maternal mortality

* Name:SMA.do

* Author: Nadine Seward (modified from do file created for short course in missing data analysis from LSHTM)

****
****

*Initially I run the multiple imputation model, under the MAR assumption, using 250 separate imputations

mi set wide

mi register imputed mumdied handwash cdk educ assetCAT del_skill mum_age anc_num parity del_bleed

mi impute chained (logit) mumdied handwash cdk del_skill del_bleed(ologit) educ assetCAT (regress) parity mum_age anc_num, add(250) rseed (1389) by(country) augment

mi estimate: logit mumdied i.handwash i.educ i.assetCAT mum_age anc_num i.country parity

save imputehw, replace

use imputehw, clear

mi estimate: logit mumdied i.cdk i.educ i.assetCAT mum_age anc_num parity

```
save impuations052015, replace

use impuations052015, clear



* calculate estimates and SE for imputed handwashing variable

postfile ests est se using ests, replace

quietly forvalues i=1(1)250 {

	dis 1

	logit _`i'_mumdied _`i'_cdk _`i'_educ _`i'_assetCAT _`i'_del_skill
	_`i'_mum_age _`i'_anc_num _`i'_parity

	post ests (_b[_`i'_cdk]) (_se[_`i'_cdk])

}

postclose ests



* calculate the weight for each imputation

gen delta=-0.4

postfile wts w using wts, replace



* sum the weights for each imputation

quietly forvalues i=1(1)250 {

gen w=-delta*handmiss*_`i'_handwash

summ w

post wts (r(sum))

drop w
```

```
}

postclose wts


* use previously saved estimates, and merge with the weights

use ests, clear

merge using wts


* calculate the weights:

* first we centre the weights

egen mw=mean(w)

gen cw=w-mw

* exponentiate the weights

gen ecw=exp(cw)

* calculate weighted average (the mean is the MNAR parameter estimate):

summ est [w=ecw]
```

Appendix 3: copy of paper published in PLOS Medicine entitled: association between clean delivery kit use, clean delivery practices, and neonatal survival: pooled analysis of data from three study sites in South Asia.

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3 Ekjut, Chakradharpur, Jharkhand, India,

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Running title: Clean Delivery Kits and Neonatal Mortality

Abbreviations: cRCT, cluster-randomised controlled trial; OR, odds ratio; TBA, traditional birth attendant; WHO, World Health Organization

Abstract

Background: Sepsis accounts for up to 15% of an estimated 3.3 million annual neonatal deaths globally. We used data collected from the control arms of three previously conducted cluster-randomised controlled trials in rural Bangladesh, India, and Nepal to examine the association between clean delivery kit use or clean delivery practices and neonatal mortality among home births.

Methods and Findings: Hierarchical, logistic regression models were used to explore the association between neonatal mortality and clean delivery kit use or clean delivery practices in 19,754 home births, controlling for confounders common to all study sites. We tested the association between kit use and neonatal mortality using a pooled dataset from all three sites and separately for each site. We then examined the association between individual clean delivery practices addressed in the contents of the kit (sterilised blade and thread, plastic sheet, gloves, hand washing, and appropriate cord care) and neonatal mortality. Finally, we examined the combined association between mortality and four specific clean delivery practices (sterilised blade and thread, hand washing, and plastic sheet). Using the pooled dataset, we found that kit use was associated with a relative reduction in neonatal mortality (adjusted odds ratio 0.52, 95% CI 0.39–0.68). While use of a clean delivery kit was not always accompanied by clean delivery practices, using a plastic sheet during delivery, a sterilised blade to cut the cord, a sterilised thread to tie the cord, and antiseptic to clean the umbilicus were each significantly associated with relative reductions in mortality, independently of kit use. Each additional clean delivery practice used was associated with a 16% relative reduction in neonatal mortality (odds ratio 0.84, 95% CI 0.77–0.92).

Conclusions: The appropriate use of a clean delivery kit or clean delivery practices is associated with relative reductions in neonatal mortality among home births in underserved, rural populations.

Introduction

Every year, an estimated 3.3 million newborn infants worldwide die in the first month of life, 99% of them in low- and middle-income countries, and 35% of them in South Asia [1–4]. The fourth Millennium Development Goal set a target to reduce mortality in children by two-thirds between 1990 and 2015 [5]. Although neonatal mortality rates declined by 31% in South Asia between 1990 and 2009, they remain high in many countries: 34.3 (27.7–40.8) per 1,000 live births in India, 31.3 (25.4–36.9) in Bangladesh, and 25.4 (20.5–30.9) in Nepal [3, 4].

Direct cause-of-death data suggest that sepsis, defined as a systemic bacterial infection, could be responsible for up to 15% of neonatal deaths [1]. An estimated 30%–40% of infections leading to neonatal sepsis are transmitted at the time of birth, and early-onset sepsis can manifest within the first 72 h of life [6]. Preventing infections through clean delivery practices is an important strategy to reduce sepsis-related deaths [7]. The World Health Organization (WHO) promotes the observance of "six cleans" at the time of delivery: clean hands, clean perineum, clean delivery surface, clean cord and tying instruments, and clean cutting surfaces [7]. A recent expert consensus suggested that uptake of these practices could reduce neonatal sepsis deaths by 15% for home births (interquartile range [IQR] 10–20) and 27% for facility births (IQR 24–36) [8].

In South Asia, around 65% of deliveries occur at home, most (59%) without skilled birth attendance. Maintaining clean delivery practices in home environments can be challenging for mothers and their birthing companions [2]. A recent analysis suggests that locally made kits linked with programmes to improve clean delivery practices are highly cost effective, at an estimated US$215 per life saved [9]. Kits usually include soap for washing the birth attendant's hands and mother's perineum, a plastic sheet to provide a clean delivery surface, a clean string for tying the umbilical cord, a new razor blade for cutting the cord, and pictorial instructions to illustrate the sequence of events during a delivery [7].

A recent systematic review on clean birth practices suggested that empirical evidence on the impact of clean delivery kits and clean delivery practices on neonatal mortality or sepsis-related neonatal deaths from community-based studies is surprisingly scarce [8]. A cluster-randomised controlled trial (cRCT) in rural Pakistan examined the effect on neonatal mortality of training traditional birth attendants (TBAs) and supplying them with clean delivery kits [10]. At the end of the study, neonatal mortality was 35 per 1,000 in the intervention clusters and 49 per 1,000 in control clusters (odds ratio [OR] 0.71, $p < 0.001$). The specific contribution of kit use to the mortality reduction could not be estimated because the trial evaluated the impact of a broad antenatal care and delivery package. However, kits were used in 35% of deliveries in intervention clusters compared with only 3% in control clusters. Other studies included a cross-sectional survey from Egypt, which found an independent association between kit use and reduced cord infection (OR 0.42, $p = 0.041$), and a stepped-wedge randomised community trial in Tanzania in which cord infection was 12.6 times more likely ($p < 0.001$) among neonates whose mothers did not use a kit [11,12]. Four other studies of the effect of clean birth kits on cord infection summarised in a recent review had heterogeneous results [8]. In all, kits were included in larger integrated packages to improve neonatal and maternal outcomes. Other studies showed that, while kits modify practices directly linked to their physical components, for example use of a clean, sterilised blade, they often do not affect more distal caring practices depicted in accompanying instructions and educational leaflets, for example early breastfeeding and wrapping the newborn infant [13]. Research evaluating the effectiveness of kits needs to take into account the effects of other interventions (e.g., concurrent kit promotion activities), as well as potential confounders that could influence their impact on neonatal mortality.

In this study we used data from the control arms of three cRCTs conducted by the authors among rural, underserved populations in South Asia, to explore associations between neonatal mortality, the use of clean delivery kits, and individual clean delivery practices. We had full access to individual participant data from these trials. Data from other previously conducted trials on clean delivery practices and kit use were not included as the heterogeneity of designs employed in other studies, which was noted in a recent systematic review, made it inadvisable to combine our estimates [8]. Our analysis had three objectives: first, to examine the association of kit use with neonatal mortality; second, to assess the association of neonatal mortality with individual clean delivery practices (hand washing, using a plastic sheet, use of gloves, sterilizing the blade, sterilizing the string, applying antiseptic to the umbilical stump, and dry cord care); third, to determine the cumulative effect on neonatal mortality of using four clean delivery practices, irrespective of kit use. The analyses were conducted for each site separately as well as using the pooled dataset for all sites, controlling for country of origin.

Methods

Ethical Approval

Ethical approval for the trials during which data for this study were collected came from the Institute of Child Health and Great Ormond Street Hospital for Children (UK) and the following in-country research ethics committees: the ethics committee of the Diabetic Association of Bangladesh (Perinatal Care Project, Bangladesh Diabetes Somity or BADAS); an independent ethics committee in Jamshedpur, India (Ekjut trial); and the Nepal Health Research Council. All trials were conducted in disadvantaged areas with high levels of female illiteracy. All participants gave consent in writing, by thumbprint, or verbally.

Study Populations and Interventions

We used data from 19,754 home births available from the control arms of three community-based cRCTs carried out between 2000 and 2008 in India (*n* = 6,841), Bangladesh (*n* = 7,041), and Nepal (*n* = 5,872) [14–16]. Figure 1 shows their locations. Table 1 describes the characteristics of each study population, the timeline of studies, the contents of clean delivery kits available in each site, and baseline neonatal mortality rates. In Nepal, we used surveillance data from an additional six control clusters that were not part of the original cRCT. These clusters were located in the same district as the other clusters, were similar to them, and identical surveillance methods were used. In each of the cRCTs, clusters were randomised to intervention or control arms. Intervention clusters received a community-based participatory intervention within women's groups, aimed at improving maternal and newborn health. As these clusters received a complex intervention with the potential to confound or modify the association between kit use and clean delivery practices and mortality, we restricted our analysis to the control arms.

In all study areas, kits were promoted and distributed through the health system as part of government initiatives to improve birth outcomes. In all sites, kits included the following as a minimum: soap, clean string, a razor blade, and a plastic sheet. Sterilisation of string and blade was recommended. In India, mothers received kits from health facilities, made some themselves, and also purchased some from each other as well as from TBAs. In Nepal, kits included a plastic disc against which the cord could be cut. Instructions on kit use were included in Nepal and Bangladesh, and in government manufactured kits in India. Data on kit use and individual clean delivery practices were collected in each of the studies. Our analysis was limited to live-born singleton infants delivered at home in control areas, for whom data on kit use were available.

Surveillance Systems and Outcome Ascertainment

The sites had similar surveillance systems to monitor birth outcomes, and the same data collection procedures were followed in control clusters (included in this study) as in intervention clusters (excluded from this study) at all sites. Details of the individual surveillance systems can be found in previous publications [14–16, 17]. Briefly, in Nepal community-based monitors identified all pregnancies then followed up pregnant women to ascertain any births and deaths. In India and Bangladesh, one key informant per 250 households identified all births and reported birth outcomes and maternal deaths. Following an identification, an interviewer met with all mothers to verify the birth and/or death and administer a structured questionnaire to the mother, or, in case of a maternal death, to a relative. Following ICD 10, we defined a neonatal death as death to a newborn infant within the first 28 d of life [18]. All sites gathered information about the antenatal, delivery, and postnatal periods through a structured questionnaire administered to mothers in a non-blinded manner around 6 weeks after delivery. In India and Bangladesh, interviewers asked about kit use and described its contents to mothers at the time of interview. In Nepal, interviewers showed a picture of a clean delivery kit to the respondent. If the respondent recognised it, they were asked if a kit had been used during delivery. Independent of mothers' knowledge and use of kits, information was collected on the following clean delivery practices: using a boiled instrument to cut the cord, hand washing, use of dry cord care, and antiseptic cord dressing. The WHO defines “dry cord care” as the practice of putting nothing on the newly cut umbilical cord, or cleaning soiled skin in the periumbilical area with soap and water, wiping it with a dry cotton swab or cloth, and allowing the area to air dry [19]. In our study sites, mothers were asked whether any substance was placed on their newborn’s umbilical cord during their interview around 6 weeks after delivery, and we coded their response as “dry cord care” if no substance had been applied. Information on the use of a boiled string to tie the cord, use of gloves and a plastic sheet was collected in Bangladesh and India, but not in Nepal.

Data Collection and Management

Data were collected on paper, checked by auditors, entered by separate data entry operators, and cross-checked by data managers for data quality purposes. Databases were created in Microsoft Access or SQL Server. Separate datasets for each study and a pooled dataset consisting of information common to the three sites were then prepared for analysis in Stata, release 11.0 [20].

Statistical Methods

We considered variables that might potentially confound or modify the association between kit use, clean delivery practices, and neonatal mortality on the basis of a priori knowledge. These confounders included; maternal age (years), education and reading ability, household assets, number of antenatal care visits, obstetric haemorrhage, preterm delivery, delivery assisted by a skilled birth attendant (doctor, nurse, or trained midwife), delivery assisted by a TBA, exclusive breastfeeding, fever in the 3 d preceding delivery, malpresentation, and season of birth. In site-specific analyses for Bangladesh and India, we adjusted for additional confounders including: cord wrapped around the infant’s neck at birth, infant in poor condition at 5 min (poor or no cry, blue limbs, infant poorly active or no movement), maternal ability to independently access a health care facility, and parity. We compared differences in these potential confounders and effect modifiers between kit users and nonusers.

Neonatal and maternal characteristics and clean delivery practices were compared between respondents with complete and those with missing information on clean delivery kit use using chi-square statistics, to establish whether missing data could potentially bias subsequent analyses. As kit uptake was relatively low, data from three separate study sites were combined into a pooled dataset to increase the power to detect accurate estimates.

Analyses exploring the association of clean delivery kits with neonatal mortality were carried out using the pooled dataset and separately for the three sites. For each analysis, we examined the association of kit use with neonatal death using hierarchical logistic regression, controlling for all confounders common to the study sites to ensure comparability of results. Maternal age, parity, and number of antenatal care visits were treated as continuous variables. Two-way interaction terms were fitted between all potential confounders, kit use, and neonatal mortality where there was a plausible explanation.

We used similar methods for analyses of the association of clean delivery practices with neonatal mortality. First, we examined the individual association of each clean delivery practice with neonatal mortality in separate hierarchical logistic regression models, controlling for kit use and all other confounders. The Nepal dataset did not contain information on boiling the thread, use of a plastic sheet, or use of gloves, so these practices were evaluated using the pooled data from Bangladesh and India only, and separately for each of the two sites. Second, to determine if the four clean delivery practices documented in India and Bangladesh had an augmented collective benefit, we introduced into the model a covariate for the number of practices followed, along with kit use and potential confounders. A linear test for trend for number of clean delivery practices was applied to the hierarchical model, and a likelihood ratio statistic with $p < 0.05$ considered significant. Antiseptic use was not included as limited incidence led to difficulties in model convergence.

We used data from 18, 18, and 5 population clusters in India, Nepal, and Bangladesh respectively, and we assumed that delivery practices would be more similar for births that occurred in the same cluster, than for births in other clusters. Likelihood ratio tests confirmed the clustered nature of the data on delivery practices in all three datasets (*p*

< 0.05), and we addressed it in the hierarchical models by using the Stata "xtmelogit" command, which provides maximum likelihood estimation using adaptive quadrature. There was no evidence of multicollinearity in any model.

Results

Study Population Characteristics

Univariable analyses revealed that kits were used for 18.4% (1,256) of home births in India, 18.4% (1,294), in Bangladesh, and 5.7% (335) in Nepal. The mean maternal age was 25.8, 24.7, and 27.2 y in India, Bangladesh, and Nepal, respectively. There was substantial variation in female literacy: in India, 76.4% (5,224) of mothers were illiterate, in Bangladesh 37.4% (2,634), and in Nepal 68.8% (3,896). In India, 4.9% (337) of home-delivered infants had a skilled birth attendant, compared with 1.1% (78) in Bangladesh and 0.4% (24) in Nepal.

Data on kit use were missing for 0.5% (38) of births in India and 2.1% (159) in Bangladesh. There were no missing data on kit use in Nepal because of the interview sequence described earlier. Because there were few missing data, we do not present differences between infants with missing data for kit use and those with complete data.

Table 2 presents a comparison of births with and without clean delivery kit use. Using a clean delivery kit was associated with neonatal survival in India and Bangladesh, but not in Nepal. Infants breastfed exclusively for the first 6 weeks of life were more likely to have been delivered using a kit than nonexclusively breastfed infants in Bangladesh ($p < 0.001$), but not in Nepal. Term infants were also more likely to have been delivered using a kit than preterm infants in India and Bangladesh ($p < 0.001$), but not in Nepal. Kits did not necessarily guarantee clean delivery practices: in India, for example, hand washing with soap prior to delivery occurred in only 40% (480/1,256) of births at which a kit was used. Gaps in other clean delivery practices were found in all three sites for births at which a clean delivery kit was used, though in general clean delivery practices were more likely to be observed when a kit had been used.

Clean Delivery Kits, Clean Delivery Practices, and Risk of Neonatal Mortality

Table 3 presents results of analyses examining the association between kit use and neonatal mortality, within and across study sites. Kit use was associated with a 48% relative reduction in neonatal mortality in the pooled dataset (OR 0.52, 95% CI 0.39–0.68), and the association did not differ significantly between sites. Use of a kit was associated with a 57% relative reduction in neonatal mortality in India (OR 0.43, 95% CI 0.29–0.63), 32% in Bangladesh (OR 0.68, 95% 0.44–1.04), and 49% in Nepal (OR 0.51, 95% CI 0.17–1.51).

Table 3 also describes the association of seven individual clean delivery practices with neonatal mortality for all sites combined and separately. The use of a sterilised blade to cut the cord, antiseptic to clean the cord, a sterilised thread to tie the cord, and a plastic sheet for a clean delivery surface were all associated with significant relative reductions in mortality when controlling for kit use and confounders common to all sites in the pooled dataset. Dry cord care was associated with significantly increased odds of death in the pooled dataset, as well as in India and Bangladesh. However, in Nepal, dry cord care was associated with significant relative reductions in neonatal mortality (OR 0.48, 95% CI 0.32–0.73).

Finally, Table 3 shows results for a pooled analysis combining data from all three countries to explore the association of between one and four clean delivery practices with neonatal mortality. With each additional clean delivery practice, we found a 16% relative reduction in mortality (OR 0.84, 0.77–0.92).

Findings from Cause-of-Death Data

To check the plausibility of the effect sizes, we used cause-specific mortality data available from the control arms of the Indian cRCT to examine the association of kits with sepsis-related neonatal death, and with death due to the other two primary causes of newborn mortality (consequences of preterm birth and intrapartum-related deaths, or birth asphyxia). This analysis accounted for clustering, and used data drawn from 366 verbal autopsies analysed by physician review. Kit use was associated with strong relative reductions in sepsis-related mortality (OR 0.28, 95% CI 0.12–0.65), but also with relative reductions in mortality ascribed to prematurity and birth asphyxia (OR 0.51, 95% CI 0.35–0.76).

Discussion

Results from our pooled analysis across study sites indicated a significant association between kit use and reduced mortality in rural South Asian communities. The non-significant results found in Nepal may be due to the small number of kit users in this sample, resulting in lack of power. The results also indicate the importance of individual clean delivery practices: a combination of hand washing, use of sterilised blade, use of sterilised thread and plastic sheet was linearly associated with a reduction in neonatal deaths with each additional clean delivery practice used.

Many governments and nongovernmental organisations encourage the use of clean delivery kits, both with and without accompanying promotion programmes. Our study shows that distributing kits, even with instructions, does not guarantee that life-saving clean delivery practices will be used. These findings concur with those of a qualitative study from Nepal in which 51 mothers and TBAs were interviewed about their perceptions of clean delivery kits [21]. Few users took out the instructions for the kit, and when they did, they had difficulties understanding them. Delivery and postnatal practices—for example, cord care and immediate breastfeeding—are culturally patterned, and understanding the context in which kits are used is key to developing and evaluating culturally appropriate promotion activities [22].

Given the potential of kits to improve neonatal survival following home births, how can their use be promoted? Programmes have employed several approaches, including dissemination through health facilities, community health workers, and private providers such as pharmacists, but few of these initiatives have been evaluated. In our study sites, an intervention involving community mobilisation through participatory women's groups was used to improve birth outcomes. Women's groups discussed clean delivery and care-seeking behaviour through stories and games that facilitated discussions about prevention and care for typical problems in mothers and newborn infants. As a result of these discussions, some groups made and promoted clean delivery kits, resulting in significant increases in kit use within intervention clusters in Nepal and India. [14,15] In a recent Pakistani trial, Lady Health Workers (LHWs) conducted participatory group sessions with mothers to promote beneficial practices in the antenatal, delivery, and postnatal period. Clean delivery kits were available from

LHWs in both intervention and control clusters, but kit use for home deliveries was more common in the intervention clusters (35% versus 3%; $p < 0.0001$). [23] Findings from these trials suggest that group-based community interventions can significantly increase the use of clean delivery kits for home births.

The content and cost of kits also need consideration. Most kits do not currently contain antiseptic to clean the umbilical cord, and the WHO recommends dry cord care. In our study, dry cord care was associated with an increased likelihood of neonatal death in Bangladesh and India, but not in Nepal, a finding that needs to be interpreted with caution. A cRCT in Sarlahi district, Nepal, compared topical applications of chlorhexidine to the umbilical cord to dry cord care in reducing cord infections and neonatal mortality. Mortality was reduced by 34%, from 21.6 to 14.4 per 1,000, (OR 0.66, 95% CI 0.46 – 0.95) for those infants enrolled and treated within 24 h. [24] Other studies are underway.

At the time during which the trials included in this study took place, the cost of a clean delivery kit was US$0.44 in India (20 Indian rupees), US$0.40 in Nepal (30 Nepalese rupees), and US$0.27 in Bangladesh (20 Bangladesh taka). While the kit can be considered a low-cost intervention, there have been no studies on willingness to pay for kits, and these costs may still be prohibitive for the poorest women.

Our analysis was limited to home births. Initiatives to promote access to skilled care at birth in South Asia have already resulted in substantial increases in institutional deliveries. [25,26] Since this trend is likely to continue in the future, further research is needed to understand the possible population-level impact on neonatal mortality of promoting kits through different channels, for example through women's groups, for community-based skilled birth attendants and in health facilities. In particular, we need to understand whether the promotion of clean delivery kits and clean delivery practices for home births dis-incentivises institutional deliveries, whether promoting kits for home births in the context of increasing institutional deliveries is cost-effective, and the potential of kits to prevent infections during institutional deliveries. [8]

Study Limitations

The associations found between kit use, other clean delivery practices, and neonatal mortality were greater than expected based on previous estimates of cause-specific neonatal mortality due to sepsis. We are circumspect about our findings, particularly in view of the possibility of residual confounding. It is likely that women who used kits and whose birth attendants adopted clean delivery practices were different from women who did not. For example, kit users may have performed other postnatal caring practices unaccounted for in our list of confounders, and these could have reduced the risk of neonatal death. Results from the analysis of cause-specific mortality data from India are encouraging in that they confirm the association of kit use with reduced sepsis deaths, but also puzzling in that they suggest that kit use was associated with reduced deaths from prematurity and birth asphyxia, albeit to a lesser extent. This result could be due to residual confounding, or a reflection of the limitation of verbal autopsies, and in particular of single-cause diagnoses; infection may further aggravate the consequences of prematurity and birth asphyxia. Recall bias is a further potential limitation, as women were not interviewed until about 6 weeks after delivery. Recall bias following a neonatal death could lead to both under and over-reporting of kit use, and therefore to both over and under-estimation of the effect sizes seen in this study. There is also a possibility of social desirability bias, in that women may have reported desirable practice to interviewers. Over-reporting of kit use would tend to lead to an under-estimation of its true effect. Finally, women with missing data were significantly more likely to have experienced a neonatal death; excluding them from the analysis would also tend to reduce the observed magnitude of the effect.

Conclusions

Our findings suggest that the use of clean delivery kits and clean delivery practices are associated with an increased likelihood of neonatal survival in rural settings where access to formal care and institutional deliveries are limited. The use of kits may not always be accompanied by clean delivery practices, and the latter should be emphasised when promoting them. Further research should explore the context of kit use in order to develop and test locally appropriate promotion strategies, as well as examine the potential of kits to improve neonatal survival in the context of increasing institutional delivery rates.

Acknowledgments

We would like to thank our colleagues at MIRA (Nepal), Ekjut (India), and the Perinatal Care Project (BADAS, Bangladesh), members of the partner communities, and the mothers and relatives who agreed to be interviewed.

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Editors' Summary

Background.

Worldwide, around 3.3 million babies die in the first month of life, according to data for 2009 from the World Health Organization. Although the global neonatal mortality rate declined by 28% (from 33.2 deaths per 1,000 live births to 23.9) between 1990 and 2009, the proportion of child deaths that are now in the neonatal period has increased in all regions of the world, and currently stands at 41%. This figure is concerning and neonatal mortality remains a big obstacle to the international community in meeting the target of Millennium Development Goal 4—to reduce deaths in children under 5 years by two-thirds from 1990 levels by 2015. At least 15% of all neonatal deaths are due to sepsis (systematic bacterial infection) and an estimated 30%–40% of infections are transmitted at the time of birth. Therefore preventing infections through clean delivery practices is an important strategy to reduce sepsis-related deaths in newborns and can contribute to reducing the overall burden of neonatal deaths.

Why Was This Study Done?

In South Asia, around 65% of deliveries occur at home, without skilled birth attendants, making practices around clean delivery particularly challenging. To date, evidence on the impact of clean delivery kits and clean delivery practices on neonatal mortality or sepsis-related neonatal deaths from community-based studies is scarce. In this study the researchers explored the associations between neonatal mortality, the use of clean delivery kits, and individual clean delivery practices by using data from the control arms of three cluster-randomised controlled trials conducted among rural populations in South Asia.

What Did the Researchers Do and Find?

The researchers used data from almost 20,000 (19,754) home births available from the control arms of three community-based cluster-randomised trials conducted between 2000 and 2008 in India (*n* = 6,841, 18 clusters), Bangladesh (*n* = 7,041, 5 clusters), and Nepal (*n* = 5,872, 18 clusters). The researchers did not include data from other previously conducted trials on clean delivery practices because of the mix of designs used in these studies and limited their analysis to live-born singleton infants delivered at home in control areas, for whom data on birth kit use were available. The researchers conducted a separate analysis for each country on kit use and clean delivery practices and also analyzed the pooled dataset for all countries while controlling for factors about the mother, the pregnancy, the delivery, and the postnatal period.

Using these methods, the researchers found that kits were used for 18.4% of home births in India, 18.4% in Bangladesh, and 5.7% in Nepal. Importantly, according to the pooled analysis, kit use was associated with a 48% relative reduction in neonatal mortality (odds ratio/chance 0.52), which was similar across all countries: 57% relative reduction in neonatal mortality in India, 32% in Bangladesh, and 49% in Nepal. Delivery practices were also important: in the pooled country analysis, the use of a sterilised blade to cut the cord, antiseptic to clean the cord, a sterilised thread to tie the cord, and a plastic sheet for a clean delivery surface were all associated with significant relative reductions in mortality after controlling for kit use and confounders common to all sites. The researchers found a 16% relative reduction in mortality with each additional clean delivery practice used.

What Do These Findings Mean?

These findings show that the appropriate use of a clean delivery kit and clean delivery practices could lead to substantial reductions in neonatal mortality among home births in poor rural communities with limited access to health care. The results also reinforce the importance of each clean delivery practice; hand washing and use of a sterilised blade, sterilised thread, and plastic sheet were linearly associated with a reduction in neonatal deaths with each additional clean delivery practice used. Costs of such kits are low (US$0.44 in India, US$0.40 in Nepal, and US$0.27 in Bangladesh, although these costs may still be prohibitive for the poorest women), and given the impact of clean delivery kits and clean delivery practices in reducing neonatal practices, such strategies should be widely promoted by the international community.

Additional Information.

Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001180.

- A recent *PLoS Medicine* study by Oestergaard et al. has the latest figures on neonatal mortality world-wide http://dx.doi.org/10.1371/journal.pmed.1001080
- UNICEF has information about progress towards Millennium Development Goal 4 http://www.childinfo.org/
- The United Nations Population Fund has more information about safe birth practices http://www.unfpa.org
- The following website describes ongoing work on socio-economic inequalities in newborn and maternal health in Asia and Africa by some of the study authors: http://equinam.global-health-inequalities.info/

Table 1. Characteristics of the studies and populations included in the analysis.

Characteristics	India	Bangladesh	Nepal
Location	Three districts of Jharkhand and Orissa (eastern India): Keonjhar, West Singhbhum, and Saraikela	Three districts: Bogra, Maulvibazaar, and Faridpur	Makwanpur district
Study period	July 31, 2005 to July 30, 2008	Feb 1, 2005 to Dec 31, 2007	cRCT: Nov 1, 2001 to Oct 31, 2003. Intervention roll-out: 2003–2007
Study design	cRCT, open cohort.	Factorial design, cRCT, open cohort.	cRCT, matched design and closed cohort. Post cRCT, roll-out of intervention into control clusters.

Characteristics	India	Bangladesh	Nepal
Cluster characteristics	8–10 villages with residents classified as tribal or OBC.	Villages making up a union.	Village Development Committees.
n clusters analysed	18	5	18
Participants	Women aged between 15 and 49 y who had given birth in study period and their infants.	Women aged between 15 and 49 y who had given birth in study period and their infants.	Women aged between 15 and 49 y, married, and with potential to become pregnant in study period and their infants.
n births analysed	6,841	7,041	5,872
Neonatal mortality rate prior to intervention (per 1,000 live births)	58[a]	41[b]	60[b]
Contents of clean delivery kits	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Plastic coin to use as surface to cut the cord. Instructions available in government kits only.
Individual clean delivery practices recorded separately from kit use	Hand washing, use of sterilised blade to cut cord, type of cord care (dry or other), use of sterilised thread to tie the cord, use of plastic sheet, and use of gloves.	Hand washing, use of sterilised blade to cut cord, type of cord care (dry or other), use of sterilised thread to tie the cord, use of plastic sheet, and use of gloves.	Hand washing, use of sterilised blade to cut cord, type of cord care (dry or other).
Concurrent activities to promote clean delivery practices and kit use	In both intervention and control areas, strengthening the activities of village health and sanitation committees.	Training was provided to nurses, doctors, and paramedical staff in essential newborn care, including the six cleans.	Health service strengthening across intervention and control areas included training of all health workers on the six cleans.

[a]Neonatal mortality rate from cRCT baseline data.

[b]Neonatal mortality rate from demographic health survey data.

OBC: Other backward class

Table 2. Comparison of deliveries with and without clean delivery kit use.

Factors Associated with Use of a Clean Delivery Kit	India (*n* = 6,841)		Bangladesh (*n* = 7,041)		Nepal (*n* = 5,872)	
	Used a Kit (*n* = 1,256)	Did Not Use a Kit (*n* = 5,585)	Used a Kit (*n* = 1,294)	Did Not Use a Kit (*n* = 5,747)	Used a Kit (*n* = 335)	Did Not Use a Kit (*n* = 5,537)
Newborn health						
Neonatal death, *n* (%)						
No	1,221 (97.2)	5,254 (94.1)*	1,267 (97.9)	5,550 (96.6)*	329 (98.2)	5,374 (97.1)
Yes	35 (2.8)	331 (5.9)	27 (2.1)	197 (3.4)	6 (1.8)	163 (2.9)
Baby exclusively breastfed, *n* (%)						
Yes	862 (68.6)	3,839 (68.8)	910 (70.3)	3,497(60.9)*	289 (86.8)	5,186 (94.4)*
No	394 (31.4)	1,745 (31.2)	384 (29.7)	2,248 (39.1)	44 (13.2)	307 (5.6)
Missing	0	1 (0.0)	0	2 (0.0)	2 (0.6)	44 (0.8)
Clean delivery practices						
Hand washing before assisting delivery, *n* (%)						
No	712 (59.7)	4,255 (80.2)*	72 (6.4)	1,482 (29.9)*	38 (12.5)	1,792 (48.8)*
Yes	480 (40.3)	1,054 (19.8)	1,056 (93.6)	3,478 (70.1)	267 (87.5)	1,878 (51.2)
Missing	64 (5.1)	276 (4.9)	166 (12.8)	787 (13.7)	30 (9.0)	1,876 (33.7)
Use of plastic sheet, *n* (%)						
No	775 (61.7)	5,520 (98.8)*	66 (5.1)	3,880 (67.5)*	na[a]	na
Yes	481 (38.3)	65 (1.2)	1,228 (94.9)	1,867 (32.5)	Na	na
Use of sterilised blade to cut cord, *n* (%)						
No	918 (77.9)	4,699 (87.0)*	288 (23.5)	2,101 (38.1)*	70 (21.1)	4,025 (73.2)*
Yes	260 (22.1)	699 (13.0)	938 (76.5)	3,408 (61.9)	262 (78.9)	1,475 (26.8)
Missing	78 (6.2)	187 (3.4)	68 (5.3)	238 (4.1)	3 (0.9)	37 (0.7)
Use of sterilised thread to tie the cord, *n* (%)						
No	970 (80.5)	4,879 (89.8)*	306 (25.1)	2,417 (44.2)*	na	na
Yes	235 (19.5)	557 (10.2)	912 (74.9)	3,048 (55.8)	Na	na

Factors Associated with Use of a Clean Delivery Kit	**India (*n* = 6,841)**		**Bangladesh (*n* = 7,041)**		**Nepal (*n* = 5,872)**	
	Used a Kit (*n* = 1,256)	**Did Not Use a Kit (*n* = 5,585)**	**Used a Kit (*n* = 1,294)**	**Did Not Use a Kit (*n* = 5,747)**	**Used a Kit (*n* = 335)**	**Did Not Use a Kit (*n* = 5,537)**
Missing	51 (4.1)	149 (2.7)	76 (5.9)	282 (4.9)	Na	na
Use of gloves to assist delivery, *n* (%)						
No	1,041 (82.9)	5,513 (98.7)*	1,085 (83.8)	5,545 (96.5)*	na	na
Yes	214 (17.1)	72 (1.3)	209 (16.2)	202 (3.5)	na	na
Use of antiseptic to clean the cord, *n* (%)						
No	1,212 (96.5)	5,543 (99.2)*	1,223 (95.0)	5,509 (96.6)*	309 (95.1)	5,462 (99.8)*
Yes	44 (3.5)	42 (0.8)	64 (5.0)	192 (3.4)	16 (4.9)	12 (0.2)
Missing	0	0	7 (0.5)	46 (0.8)	10 (34.0)	63 (1.1)
Use of dry cord care practice, *n* (%)						
No	148 (11.8)	626 (11.2)	445 (34.6)	2,191 (38.4)*	109 (33.4)	1,332 (24.3)*
Yes	1,108 (88.2)	4,959 (88.8)	842 (65.4)	3,510 (61.6)	217 (66.6)	4,142 (75.7)
Missing	0	0	7 (0.5)	46 (0.8)	9 (2.7)	63 (1.1)
Maternal characteristics						
Maternal education, *n* (%)						
No education	376 (29.9)	1,011 (18.1)*	359 (27.7)	2,002 (34.8)*	93 (28.4)	314 (5.9)*
Primary	62 (4.9)	262 (4.7)	435 (33.6)	2,033 (35.4)	85 (25.9)	788 (14.7)
Secondary	818 (65.1)	4,312 (77.2)	500 (38.6)	1,712 (29.8)	150 (45.7)	4,237 (79.4)
Missing	0	0	0	0	7 (2.1)	198 (3.6)
Maternal reading ability, *n* (%)						
Unable to read	833 (66.3)	4,391 (78.6)*	632 (48.9)	2,339 (40.7)*	146 (44.5)	766 (14.4)*
Reads with difficulty	83 (6.6)	281 (5.0)	234 (18.1)	1,199 (20.9)	78 (23.8)	781 (14.6)
Reads with ease	340 (27.1)	913 (16.4)	426 (33.0)	2,204 (38.4)	104 (31.7)	3,792 (71.0)
Missing	0	0	2 (0.1)	5 (0.2)	7 (2.1)	198 (3.6)
Maternal age in years, *n* (%)						
<20	143 (12.0)	620 (12.0)*	237 (18.3)	903 (15.7)*	46 (13.7)	610 (11.0)*

Factors Associated with Use of a Clean Delivery Kit	India (*n* = 6,841)		Bangladesh (*n* = 7,041)		Nepal (*n* = 5,872)	
	Used a Kit (*n* = 1,256)	**Did Not Use a Kit (*n* = 5,585)**	**Used a Kit (*n* = 1,294)**	**Did Not Use a Kit (*n* = 5,747)**	**Used a Kit (*n* = 335)**	**Did Not Use a Kit (*n* = 5,537)**
20–29	766 (64.4)	3,131 (60.5)	822 (63.5)	3,671 (63.9)	225 (67.2)	3,249 (58.7)
30–39	269 (22.6)	1,355 (26.2)	224 (17.3)	1,098 (19.1)	57 (17.0)	1,381 (25.0)
40+	11 (0.9)	71 (1.4)	11 (0.9)	73 (1.3)	7 (2.1)	296 (5.3)
Missing	67 (5.3)	408 (7.3)	0	2 (0.0)	0	1 (0.0)
Caste or tribal group, *n* (%)						
Scheduled tribe[b]	880 (70.1)	4,190 (75.0)*	na	na	na	na
Scheduled caste[b]	53 (4.2)	214 (3.8)	na	na	na	na
Other backward class[b]	316 (25.2)	1,160 (20.8)	na	na	na	na
Household assets, *n* (%)						
All	216 (17.2)	1,093 (19.6)*	505 (39.0)	2,856 (49.7)*	62 (18.5)	2,531 (45.7)*
Some	810 (64.5)	3,570 (63.9)	228 (17.6)	1,084 (18.9)	114 (34.0)	1,912 (34.5)
None	230 (18.3)	922 (16.5)	561 (43.4)	1,807 (31.4)	159 (47.5)	1,094 (19.8)
Parity, *n* (%)						
1	308 (24.5)	1,195 (21.4)*	483 (37.3)	1,765 (30.7)*	na	na
2	313 (24.9)	1,304 (23.3)	360 (27.8)	1,558 (27.1)	na	na
3	241 (19.2)	1,079 (19.3)	200 (15.5)	1,062 (18.5)	na	na
4	152 (12.1)	742 (13.3)	116 (9.0)	632 (11.0)	na	na
5	105 (8.4)	494 (8.9)	67 (5.2)	370 (6.4)	na	na
6	137 (10.9)	771 (13.8)	68 (5.2)	360 (6.3)	na	na
Mother can access a health facility independently, *n* (%)						
Always	125 (10.0)	661 (11.8)*	43 (3.3)	296 (5.1)*	na	na
Sometimes	376 (29.9)	1,470 (26.3)	328 (25.3)	2,026 (35.3)	na	na
Never without company	731 (58.2)	3,194 (57.2)	887 (68.6)	3,298 (57.4)	na	na
Never even with company	24 (1.9)	260 (4.7)	36 (2.8)	127 (2.2)	na	na
Antenatal period						

Factors Associated with Use of a Clean Delivery Kit	India (*n* = 6,841)		Bangladesh (*n* = 7,041)		Nepal (*n* = 5,872)	
	Used a Kit (*n* = 1,256)	**Did Not Use a Kit (*n* = 5,585)**	**Used a Kit (*n* = 1,294)**	**Did Not Use a Kit (*n* = 5,747)**	**Used a Kit (*n* = 335)**	**Did Not Use a Kit (*n* = 5,537)**
Number of antenatal care visits, *n* (%)						
0	263 (21.0)	1,765 (31.6)*	292 (22.6)	2,478 (43.1)*	51 (15.2)	3,389 (61.1)*
1	144 (11.5)	757 (13.6)	217 (16.8)	1,279 (22.3)	33 (9.9)	522 (9.4)
2	299 (23.9)	1,314 (23.5)	254 (19.7)	860 (15.0)	34 (10.1)	465 (8.4)
3	218 (17.4)	894 (16.0)	198 (15.3)	598 (10.4)	54 (16.1)	516 (9.3)
4	329 (26.2)	852 (15.3)	331 (25.6)	528 (9.2)	163 (48.7)	645 (11.7)
Missing	3 (0.2)	3 (0.1)	2 (0.2)	4 (0.1)	0	0
Bleeding during pregnancy, *n* (%)						
No	1,249 (99.4)	5,541 (99.2)	1,242 (95.6)	5,601 (97.5)*	320 (95.5)	5,375 (97.1)
Yes	7 (0.6)	44 (0.8)	52 (4.0)	145 (2.5)	15 (4.5)	162 (2.9)
Missing	0	3 (0.1)	0	0	0	0
Delivery period						
Preterm birth, *n* (%)						
Baby born at term	1,201 (95.6)	5,242 (93.9)*	1,268 (98.0)	5,521 (96.1)*	316 (94.3)	5,355 (96.7)*
Baby born after less than 9 months gestation	55 (4.4)	343 (6.1)	26 (2.0)	226 (3.9)	19 (5.7)	182 (3.3)
Season of birth, *n* (%)						
Summer (March–June)	464(36.9)	1,902 (34.1)*	363 (28.1)	1,612 (28.1)	94 (28.1)	1,638 (29.6)
Rainy (July–October)	398 (31.7)	1,826 (32.7)	476 (36.8)	2,163 (37.6)	107 (31.9)	2,061 (37.2)
Winter (November–February)	394 (31.4)	1,857 (33.2)	455 (35.2)	1,972 (34.3)	134 (40.0)	1,838 (33.2)
Baby delivered by skilled birth attendant, *n* (%)[c]						
Yes	171 (13.7)	166 (3.0)*	42 (3.2)	36 (0.6)*	14 (4.2)	10 (0.2)*
No	1,080 (86.3)	5,407 (97.0)	1,252 (96.8)	5711 (99.4)	321 (95.8)	5,527 (99.8)
Missing	5 (0.4)	12 (0.2)	0	0	0	0
Delivery by a TBA, *n* (%)						

Factors Associated with Use of a Clean Delivery Kit	India (*n* = 6,841)		Bangladesh (*n* = 7,041)		Nepal (*n* = 5,872)	
	Used a Kit (*n* = 1,256)	**Did Not Use a Kit (*n* = 5,585)**	**Used a Kit (*n* = 1,294)**	**Did Not Use a Kit (*n* = 5,747)**	**Used a Kit (*n* = 335)**	**Did Not Use a Kit (*n* = 5,537)**
Yes	475 (37.8)	2,135 (38.2)	186 (14.4)	1,693 (29.5)*	241 (72.4)	5,312 (96.7)*
No	781 (62.2)	3,450 (61.8)	1,108 (85.6)	4,054 (70.5)	92 (27.6)	181 (3.3)
Missing	0	0	0	0	2 (0.6)	44 (0.7)
Excessive bleeding during delivery, *n* (%)						
No	1,186 (94.4)	5,296 (94.9)	1,268 (98.0)	5,643 (98.2)	300 (89.6)	5,027 (90.8)
Yes	70 (5.6)	286 (5.1)	26 (2.0)	104 (1.8)	35 (10.4)	510 (9.2)
Missing	0	1 (0.0)	0	2 (0.0)	2 (0.6)	44 (0.8)
Malpresentation at birth						
No	1,239 (99.2)	5,508 (99.0)	1,265 (98.1)	5,611 (97.8)	334 (99.7)	5,468 (99.2)
Yes	10 (0.8)	55 (1.0)	24 (1.9)	126 (2.2)	1 (0.3)	42 (0.8)
Missing	7 (0.6)	22 (0.4)	5 (0.4)	10 (0.2)	0	27 (0.5)
Fever 3 d prior to delivery						
No	1,226 (97.6)	5,388 (96.5)*	1,274 (98.4)	5,617 (97.7)	303 (90.4)	4,776 (86.3)*
Yes	30 (2.4)	197 (3.5)	20 (1.6)	130 (2.3)	32 (9.6)	760 (13.7)
Missing	0	0	0	0	0	1 (0)
Infant appearance 5 min after delivery						
Negative	1,256 (100)	5,571 (99.9)	1,193 (94.2)	5,291 (93.2)	na	na
Positive	0 (0)	7 (0.1)	73 (5.8)	386 (6.8)	na	na
Missing	0	7 (0.1)	28 (2.2)	70 (91.2)	na	na
Umbilical cord wrapped around infant's neck at birth						
No	1,105 (88.0)	4,929 (88.3)	1,266 (97.8)	5,606 (97.6)	na	na
Yes	151 (12.0)	656 (11.7)	28 (2.2)	141 (2.5)	na	na

[*]Differences between clean delivery kit use and non-use tested using chi-square statistic and significant at p<0.05

[a] Not applicable: data were not collected in the study.

[b]Standard terms used in Indian demographic surveys.

[c] Doctor, nurse, or trained midwife.

na, not available.

Table 3. Adjusted odds ratios for the association between clean delivery kit use and clean delivery practices with neonatal mortality.

Practices	All Countries	India (*n* = 6,841)	Bangladesh (*n* = 7,041)	Nepal (*n* = 5,872)
Use of a clean delivery kit[a]	0.52 (0.39–0.68)[b]	0.43 (0.29–0.63)	0.68 (0.44–1.04)	0.51 (0.17–1.51)
Use of a sterilised blade to cut the umbilical cord[c]	0.73 (0.59–0.90)[b]	0.74 (0.51–1.08)	0.67 (0.49–0.92)	0.80 (0.48–1.33)
Washing hands prior to delivery[c]	0.89 (0.73–1.09)[b]	0.69 (0.51–0.94)	0.86 (0.61–1.20)	1.66 (1.06–2.65)
Use of dry cord care[c]	1.51 (1.21–1.88)[b]	1.34 (0.91–1.96)	3.29 (2.27–4.78)	0.48 (0.32–0.73)
Use of antiseptic to clean the cord[c]	0.16 (0.04–0.64)[b]	0.31 (0.04–2.25)	0.12 (0.02–0.84)	na[d]
Use of sterilised thread to tie the cord[e]	0.71 (0.56–0.90)[f]	0.60 (0.39–0.92)	0.77 (0.56–1.05)	na[g]
Use of plastic sheet[e]	0.69 (0.51–0.93)[f]	0.63 (0.31–1.26)	0.68 (0.47–0.97)	na[g]
Use of gloves[e]	0.65 (0.37–1.13)[f]	0.40 (0.16–1.00)	0.94 (0.46–1.91)	na[g]
Use of each additional clean delivery practice[e]	0.84 (0.77–0.92)[f]	0.77 (0.66–0.92)	0.89 (0.79–1.00)	na[g]

[a]Adjusted for clustering, maternal age, maternal education, maternal reading ability, household assets, bleeding in pregnancy, excessive bleeding during delivery, preterm delivery, exclusive breastfeeding for the first 6 weeks of life, season, number of antenatal care visits, malpresentation at delivery, fever 3 d prior to delivery, and, for the pooled analysis, study site.

[b]Data available from India, Bangladesh, and Nepal, *n* = 19,754.

[c]Adjusted for the indicators above and the use of a clean delivery kit.

[d]It was not possible to obtain estimates for this model because of low numbers of cases where antiseptic was used; however, it was possible to include Nepal data in the pooled analysis.

[e]Adjusted for the indicators above, and for delivery by a TBA, cord wrapped around infant's neck at delivery, infant condition at 5 min, parity, delivery by a skilled birth attendant (doctor, nurse, trained midwife).

[f]Data available from India and Bangladesh, *n* = 13,882.

[g]Not applicable: data were not collected in the study.

Appendix 4: Tables from Chapter 4 examining the associations between clean delivery practices and neonatal mortality

Table A4a: Comparison of population characteristics between those deliveries using a clean delivery kit use and those deliveries without kit use

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Neonatal death, *n* (%)												
No	10164 (94.2)	1593 (96.4)	8571 (93.8)	<0.001	24134 (96.9)	3781 (97.7)	20353 (96.8)	0.004	652 (96.3)	155 (97.5)	497 (96.0)	0.475
Yes	629 (5.8)	60 (3.6)	569 (6.2)		768 (3.1)	91 (2.4)	677 (3.2)		25 (3.7)	4 (2.5)	21 (4.1)	
Clean delivery practices												
Hand washing, *n* (%)												
No	7589 (70.1)	849 (51.4)	6740 (73.7)	<0.001	4211 (16.9)	253 (6.5)	3958 (18.8)	<0.001	133 (19.7)	6 (3.8)	127 (24.5)	<0.001
Yes	2607 (24.2)	723 (43.7)	1884 (20.6)		17282 (69.4)	3196 (82.5)	14086 (67.0)		381 (56.3)	135 (84.9)	246 (47.5)	
Missing	597 (5.5)	81 (4.9)	516 (5.7)		3409 (13.7)	423 (10.9)	2986 (14.2)		163 (24.1)	18 (11.3)	145 (28.0)	
Use of sterilised blade to cut the umbilical cord, *n* (%)												
No	8547 (79.2)	1183 (71.6)	7364 (80.6)	<0.001	8584 (34.5)	1132 (29.2)	7452 (35.4)	<0.001	345 (51.0)	31 (19.5)	314 (60.6)	<0.001
Yes	1626 (15.1)	349 (21.1)	1277 (14.0)		14828 (59.6)	2565 (66.2)	12263 (8.3)		329 (48.6)	127 (79.9)	202 (39.0)	
Missing	620 (5.7)	121 (7.3)	499 (5.5)		1490 (6.0)	175 (4.5)	1315 (6.3)		3 (0.4)	1 (0.6)	2 (0.4)	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Use of sterilised thread to tie the cord, *n* (%)												
No	9025 (83.6)	1246 (75.4)	7779 (85.1)	<0.001	9796 (39.3)	1170 (30.2)	8626 (41.0)	<0.001	b	b	b	b
Yes	1314 (12.2)	325 (19.7)	989 (10.8)		13367 (53.7)	2513 (64.9)	10854 (51.6)		b	b	b	
Missing	454 (4.2)	82 (5.0)	372 (4.1)		1739 (7.0)	189 (4.9)	1550 (7.4)		b	b	b	
Use of dry cord care, *n* (%)												
No	2153 (20.0)	266 (16.1)	1887 (20.7)	<0.001	14788 (59.4)	2132 (55.1)	12656 (60.2)	<0.001	197 (29.1)	53 (33.3)	144 (27.8)	0.072
Yes	8640 (80.1)	1387 (83.9)	7253 (79.4)		9999 (40.2)	1720 (44.4)	8279 (39.4)		466 (68.8)	100 (62.9)	366 (70.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		115 (0.5)	20 (0.5)	95 (0.5)		14 (2.1)	6 (3.8)	8 (1.5)	
Use of antiseptic to clean the cord only, *n* (%)												
No	10524 (97.5)	1588 (96.1)	8936 (97.8)	<0.001	22972 (92.3)	3532 (91.2)	19440 (92.4)	0.033	658 (97.2)	149 (93.7)	509 (98.3)	0.003
Yes	269 (2.5)	65 (3.9)	204 (2.2)		1814 (7.3)	320 (8.3)	1494 (7.1)		5 (0.7)	4 (2.5)	1 (0.2)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		116 (0.5)	20 (0.5)	96 (0.5)		14 (2.1)	6 (3.8)	8 (1.5)	

Factors associated with kit use	**India**				**Bangladesh**				**Nepal**			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Use of plastic sheet, *n* (%)												
No	9952 (92.2)	915 (55.4)	9037 (98.9)	<0.001	12663 (50.9)	359 (9.3)	12304 (58.5)	<0.001	b	b	b	b
Yes	841 (7.8)	738 (44.7)	103 (1.1)		12229 (49.1)	3513 (90.7)	8716 (41.5)		b	b	b	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		10 (0.0)	0 (0.0)	10 (0.1)		b	b	b	
Use of gloves to assist delivery, *n* (%)												
No	10409 (96.4)	1373 (83.1)	9036 (98.9)	<0.001	22398 (89.9)	2947 (76.1)	19451 (92.5)	<0.001	b	b	b	b
Yes	384 (3.6)	280 (16.9)	104 (1.1)		2401 (9.6)	895 (23.1)	1506 (7.2)		b	b	b	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		103 (0.4)	30 (0.8)	73 (0.4)		b	b	b	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Maternal characteristics												
Maternal education, *n* (%)												
No education	8066 (74.7)	1104 (66.8)	6962 (76.2)	<0.001	7040 (28.3)	883 (22.8)	6157 (29.3)	<0.001	471 (69.6)	96 (60.4)	375 (72.4)	<0.001
Primary	542 (5.0)	84 (5.1)	458 (5.0)		8926 (35.8)	1277 (33.0)	7649 (36.4)		140 (20.7)	34 (21.4)	106 (20.5)	
Secondary	2185 (20.2)	465 (28.1)	1720 (18.8)		8932 (35.9)	1712 (44.2)	7220 (34.3)		66 (9.8)	29 (18.2)	37 (7.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		4 (0.0)	0 (0.0)	4 (0.02)		0 (0.0)	0 (0.0)	0 (0.0)	
Maternal age in years, *n* (%)												
<20	777 (7.2)	145 (8.8)	632 (6.9)		3735 (15.0)	689 (17.8)	3046 (14.5)	<0.001	51 (7.5)	15 (9.4)	36 (7.0)	0.649
20–29	3996 (37.0)	773 (46.8)	3223 (35.3)		16143 (64.8)	2489 (64.3)	13654 (64.9)		462 (68.2)	104 (65.4)	358 (69.1)	
30–39	1664 (15.4)	277 (16.8)	1387 (15.2)		4751 (19.1)	667 (17.2)	4084 (19.4)		139 (20.5)	35 (22.0)	104 (20.1)	
40+	82 (0.8)	11 (0.7)	71 (0.8)		269 (1.1)	27 (0.7)	242 (1.2)		25 (3.7)	5 (3.1)	20 (3.9)	
Missing	4274 (39.6)	447 (27.0)	3827 (41.9)		4 (0.0)	0 (0.0)	4 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Household assets, *n* (%)												
All	1694(15.7)	275 (16.6)	1419 (15.5)	0.417	9363 (37.6)	1795 (46.4)	7568 (36.0)	<0.001	27 (4.0)	9 (5.7)	18 (3.5)	0.029
Some	6827 (63.3)	1024 (61.9)	5803 (63.5)		6098 (24.5)	879 (22.7)	5219 (24.8)		361 (53.3)	96 (60.4)	265 (51.2)	
None	2272 (21.1)	354 (21.4)	1918 (21.0)		9441 (37.9)	1198 (30.9)	8243 (39.2)		289 (42.7)	54 (34.0)	235 (45.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Parity, *n* (%)												
1	2461 (22.8)	412 (24.9)	2049 (22.4)	0.005	7512 (30.2)	1431 (40.1)	6081 (28.9)	<0.001	81 (12.0)	25 (15.7)	56 (10.8)	0.157
2	2499 (23.2)	403 (24.4)	2096 (22.9)		7221 (29.0)	1140 (29.4)	6081 (28.9)		168 (24.8)	45 (28.3)	123 (23.8)	
3	1963 (18.2)	312 (18.9)	1651 (18.1)		4752 (19.1)	690 (17.8)	4062 (19.3)		171 (25.3)	36 (22.6)	135 (26.1)	
4	3856 (35.7)	525 (31.8)	3331 (36.4)		5414 (21.7)	611 (15.8)	4803 (22.8)		257 (38.0)	53 (33.3)	204 (39.4)	
Missing	14 (0.1)	1 (0.1)	13 (0.1)		3 (0.0)	0 (0.0)	3 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall (*n*=10 793)	Kit use (*n*=1653)	No kit use (*n*=9140)	*p*-value[a]	Overall (*n*=24 902)	Kit use (*n*=3872)	No kit use (*n*=21 030)	*p*-value[a]	Overall (*n*=677)	Kit use (*n*=159)	No kit use (*n*=518)	*p*-value[a]
Antenatal period												
Number of antenatal care visits, *n* (%)												
0	3501 (32.4)	344 (20.8)	3157 (34.5)	<0.001	9032 (36.3)	633 (16.4)	8399 (39.9)	<0.001	300 (44.3)	39 (24.5)	261 (50.4)	<0.001
1	1516 (14.1)	202 (12.2)	1314 (13.4)		5407 (21.7)	650 (16.8)	4757 (22.6)		106 (15.7)	27 (17.0)	79 (15.3)	
2	2471 (22.9)	420 (25.4)	2051 (22.4)		3951 (15.9)	663 (17.1)	3288 (15.6)		87 (12.9)	18 (11.3)	69 (13.3)	
3	1599 (14.8)	286 (17.3)	1313 (14.4)		2904 (11.7)	696 (18.0)	2208 (10.5)		96 (14.2)	29 (18.2)	67 (12.9)	
4	1698 (15.7)	398 (24.1)	1300 (14.2)		3592 (14.4)	1223 (31.6)	2369 (11.3)		88 (13.0)	46 (28.9)	42 (8.1)	
Missing	8 (0.1)	3 (0.2)	5 (0.1)		16 (0.1)	7 (0.2)	9 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Delivery period												
Skilled birth attendant, *n* (%)												
No	10178 (94.3)	1378 (83.4)	8800 (96.3)	<0.001	24370 (97.9)	3703 (95.6)	20667 (98.3)	<0.001	674 (99.6)	156 (98.1)	518 (100.0)	0.013
Yes	553 (5.1)	268 (16.2)	285 (3.1)		521 (2.1)	166 (4.3)	355 (1.7)		3 (0.4)	3 (1.9)	0 (0.0)	
Missing	62 (0.6)	7 (0.4)	55 (0.6)		11 (0.0)	3 (0.1)	8 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

b. Not applicable: data were not collected in the study

Table A4b: Comparison between deliveries with known and missing information on clean delivery kit use

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Neonatal death, *n* (%)												
No	34950 (96.1)	3541 (96.4)	0.387	10164 (94.2)	85 (89.5)	0.052	24134 (96.9)	332 (96.0)	0.305	652 (96.3)	3124 (96.6)	0.676
Yes	1422 (3.9)	133 (3.6)		629 (5.8)	10 (10.5)		768 (3.1)	14 (4.1)		25 (3.7)	109 (3.4)	
Maternal death, *n* (%)												
No	36296 (99.8)	3656 (99.5)	0.001	10750 (99.6)	95 (100.0)	1.000	24870 (99.9)	343 (99.1)	0.012	676 (99.9)	3218 (99.5)	0.335
Yes	76 (0.2)	18 (0.5)		43 (0.4)	0 (0.0)		32 (0.1)	3 (0.9)		1 (0.2)	14 (0.5)	
Clean delivery practices												
Hand washing, *n* (%)												
No	11933 (32.8)	937 (25.5)	<0.001	7589 (70.3)	23 (24.2)	<0.001	4211 (16.9)	13 (3.8)	<0.001	133 (19.7)	901 (27.9)	<0.001
Yes	20270 (55.7)	1065 (29.0)		2607 (24.2)	25 (26.3)		17282 (69.4)	171 (49.4)		381 (56.3)	869 (26.9)	
Missing	4169 (11.5)	1672 (45.5)		597 (5.5)	47 (49.5)		3409 (13.7)	162 (46.8)		163 (24.1)	1463 (45.3)	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Use of sterilised blade to cut the umbilical cord, *n* (%)												
No	17476 (48.1)	2720 (74.0)	<0.001	8547 (79.2)	65 (68.4)	0.015	8584 (34.5)	60 (17.3)	<0.001	345 (51.0)	2595 (80.3)	<0.001
Yes	16783 (46.1)	811 (22.1)		1626 (15.2)	19 (20.0)		14828 (59.55)	174 (50.3)		329 (48.6)	618 (18.1)	
Missing	2113 (5.8)	143 (3.9)		620 (5.7)	11 (11.6)		1490 (6.0)	112 (32.4)		3 (0.4)	20 (0.6)	
Use of sterilised thread to tie the cord, *n* (%)												
No	18821 (52.7)	141 (32.0)	<0.001	9025 (83.6)	72 (75.8)	0.008	9796 (39.3)	69 (19.9)	<0.001	b	b	b
Yes	14681 (41.1)	164 (37.2)		1314 (12.2)	13 (13.7)		13367 (53.7)	151 (43.6)		b	b	
Missing	2193 (6.1)	136 (30.8)		454 (4.2)	10 (10.5)		1739 (7.0)	126 (36.4)		b	b	
Use of dry cord care, *n* (%)												
No	17138 (47.1)	999 (27.2)	<0.001	2153 (20.0)	30 (31.6)	0.005	14788 (59.4)	198 (57.2)	0.697	197 (29.1)	771 (23.9)	0.004
Yes	19105 (52.5)	2631 (71.6)		8640 (80.1)	65 (68.4)		9999 (40.2)	146 (42.2)		466 (68.8)	2420 (74.9)	
Missing	129 (0.4)	44 (1.2)		0 (0.0)	0 (0.0)		115 (0.5)	2 (0.6)		14 (2.1)	42 (1.3)	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Use of antiseptic to clean the cord only, *n* (%)												
No	34154 (93.9)	3568 (97.1)	<0.001	10524 (97.5)	84 (88.4)	<0.001	22972 (92.3)	294 (85.0)	<0.001	658 (97.2)	3190 (98.7)	<0.001
Yes	2088 (5.7)	62 (1.7)		269 (2.5)	11 (11.6)		1814 (7.3)	50 (14.045)		5 (0.7)	1 (0.1)	
Missing	130 (0.4)	44 (1.2)		0 (0.0)	0 (0.0)		116 (0.5)	2 (0.6)		14 (2.1)	42 (1.3)	
Use of plastic sheet, *n* (%)												
No	22615 (63.4)	245 (55.6)	<0.001	9952 (92.2)	89 (93.7)	<0.001	12663 (50.9)	156 (45.1)	0.010	b	b	b
Yes	13070 (36.6)	193 (43.8)		841 (7.8)	4 (4.2)		12229 (49.1)	189 (54.6)		b	b	
Missing	10 (0.0)	3 (0.7)		0 (0.0)	2 (2.1)		10 (0.0)	1 (0.3)		b	b	
Use of gloves to assist delivery, *n* (%)												
No	32087 (91.9)	296 (67.1)	<0.001	10409 (96.4)	82 (86.3)	<0.001	22398 (89.9)	214 (61.9)	<0.001	b	b	b
Yes	2785 (7.8)	137 (31.1)		384 (3.6)	13 (13.7)		2401 (9.6)	124 (35.8)		b	b	
Missing	103 (0.3)	8 (1.8)		0 (0.0)	0 (0.0)		103 (0.4)	8 (2.3)		b	b	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Maternal characteristics												
Maternal education, *n* (%)												
No education	15577 (42.8)	3056 (83.2)	<0.001	8066 (74.7)	62 (65.3)	0.103	7040 (28.3)	71 (20.5)	0.005	471 (69.6)	2923 (90.4)	<0.001
Primary	9608 (26.4)	352 (9.6)		542 (5.0)	6 (6.3)		8926 (35.8)	126 (36.4)		140 (20.7)	220 (6.8)	
Secondary	11183 (30.8)	266 (7.2)		2185 (20.2)	27 (28.4)		8932 (35.9)	149 (43.1)		66 (9.8)	90 (2.8)	
Missing	4 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		4 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Maternal age in years, *n* (%)												
<20	4563 (12.6)	292 (8.0)	<0.001	777 (7.2)	9 (9.5)	<0.001	3735 (15.0)	60 (17.3)	0.619	51 (7.5)	223 (6.9)	<0.001
20–29	20601 (56.6)	2052 (55.9)		3996 (37.0)	19 (20.0)		16143 (64.8)	224 (64.7)		462 (68.2)	1809 (56.0)	
30–39	6554 (18.0)	1036 (28.2)		1664 (15.4)	2 (2.1)		4751 (19.1)	60 (17.3)		139 (20.5)	974 (30.1)	
40+	376 (1.0)	230 (6.3)		82 (0.8)	1 (1.1)		269 (1.1)	2 (0.6)		25 (3.7)	227 (7.0)	
Missing	4278 (11.8)	64 (1.7)		4274 (39.6)	64 (67.4)		4 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Household assets, *n* (%)												
All	11084 (30.5)	252 (6.6)	<0.001	1694 (15.7)	22 (23.2)	0.125	9363 (37.6)	160 (46.2)	0.004	27 (3.0)	60 (1.9)	<0.001
Some	13286 (36.5)	1367 (37.2)		6827 (63.3)	53 (55.8)		6098 (24.5)	73 (21.1)		361 (53.3)	1241 (38.4)	
None	12002 (33.0)	2064 (56.2)		2272 (21.1)	20 (21.1)		9441 (37.9)	113 (32.7)		289 (52.7)	1931 (59.7)	
Missing	0 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	1 (0.0)	
Parity, *n* (%)												
1	10054 (27.6)	502 (13.7)	<0.001	2461 (22.8)	27 (29.4)	0.239	7512 (30.2)	136 (39.3)	0.002	81 (12.0)	339 (10.5)	<0.001
2	9888 (27.2)	707 (19.2)		2499 (23.2)	28 (29.5)		7221 (29.0)	87 (25.1)		168 (24.8)	592 (18.3)	
3	6886 (18.9)	598 (16.3)		1963 (18.2)	13 (13.7)		4752 (19.1)	47 (13.6)		171 (25.3)	538 (16.6)	
4	9527 (26.2)	1867 (50.8)		3856 (35.7)	27 (28.4)		5414 (21.7)	76 (22.0)		257 (38.0)	1764 (54.6)	
Missing	17 (0.1)	0 (0.0)		14 (0.1)	0 (0.0)		3 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Antenatal period												
Number of antenatal care visits, *n* (%)												
0	12833 (35.3)	2561 (69.7)	<0.001	3501 (32.4)	39 (41.1)	0.436	9032 (36.3)	99 (28.1)	0.001	300 (44.3)	2423 (74.9)	<0.001
1	7029 (19.3)	402 (10.9)		1516 (14.1)	12 (12.6)		5407 (21.7)	74 (21.4)		106 (15.6)	316 (9.8)	
2	6509 (17.9)	291 (7.9)		2471 (22.9)	17 (17.9)		3951 (15.9)	67 (19.4)		87 (12.9)	207 (6.4)	
3	4599 (12.6)	200 (5.4)		1599 (14.8)	10 (10.5)		2904 (11.7)	34 (9.8)		96 (1.2)	156 (4.8)	
4	5378 (14.8)	219 (6.0)		1698 (15.7)	17 (17.9)		3592 (14.4)	71 (20.5)		88 (13.0)	131 (4.1)	
Missing	24 (0.1)	1 (0.0)		8 (0.1)	0 (0.0)		16 (0.1)	1 (0.3)		0 (0.0)	0 (0.0)	
Delivery period												
Obstetric Haemorrhage, *n* (%)												
No	31865 (87.6)	3337 (90.8)	<0.001	6641 (61.5)	35 (36.8)	<0.001	249593 (98.8)	334 (96.5)	0.004	631 (93.2)	2968 (91.8)	0.220
Yes	716 (2.0)	280 (7.6)		364 (3.4)	3 (3.2)		306 (1.2)	12 (3.5)		46 (6.8)	265 (8.2)	
Missing	3791 (10.4)	57 (1.6)		3788 (35.1)	57 (60.0)		3 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Factors associated with missing data on kit use	Pooled data			India			Bangladesh			Nepal		
	Data on kit use present (*n*=36 372)	Missing data on kit use (*n*=3674)	*p*-value[a]	Data on kit use present (*n*=10 793)	Missing data on kit use (*n*=95)	*p*-value[a]	Data on kit use present (*n*=24 902)	Missing data kit use (*n*=346)	*p*-value[a]	Data on kit use present (*n*=677)	Missing data on kit use (*n*=3233)	*p*-value[a]
Skilled birth attendant, *n* (%)												
No	35222 (96.8)	3553 (96.7)	0.363	10178 (94.3)	76 (80.0)	<0.001	24370 (97.9)	248 (71.7)	<0.001	674 (99.6)	3229 (99.9)	0.105
Yes	1077 (3.0)	117 (3.2)		553 (5.1)	17 (17.9)		521 (2.1)	96 (27.8)		3 (0.4)	4 (0.1)	
Missing	73 (0.2)	4 (0.1)		62 (0.6)	2 (2.1)		11 (0.0)	2 (0.6)		0 (0.0)	0 (0.0)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

b. Not applicable: data were not collected in the study.

Table A4c: Comparison between deliveries where hand washing was present and where information on hand washing was missing

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	Missing hand washing data (*n*=5841)	*p*-value[a]	Hand washing data present (*n*=10 244)	Missing hand washing data (*n*=644)	*p*-value[a]	Hand washing data present (*n*=21 677)	Missing hand washing data (*n*=3571)	*p*-value[a]	Hand washing data present (*n*=2284)	Missing hand washing data (*n*=1626)	*p*-value[a]
Neonatal death, *n* (%)												
No	32843 (96.0)	5648 (96.7)	0.013	9632 (94.0)	617 (95.81)	0.062	21035 (97.0)	3431(96.1)	0.002	2176 (95.3)	1600 (98.4)	<0.001
Yes	1362 (4.0)	193 (3.3)		612 (6.0)	27 (4.2)		642 (3.0)	140 (3.9)		108 (4.7)	26 (1.6)	
Maternal death, *n* (%)												
No	34130 (99.8)	5822 (99.7)	0.122	10204 (99.6)	641 (99.5)	0.767	21651 (99.9)	3562 (99.8)	0.049	2275 (99.6)	1619 (99.6)	0.860
Yes	75 (0.2)	19 (0.3)		40 (0.39)	3 (0.47)		26 (0.1)	9 (0.3)		9 (0.4)	7 (0.4)	
Clean delivery practices												
Use of clean delivery kit, *n* (%)												
No	27041 (79.1)	3647 (62.4)	<0.001	8624 (84.2)	516 (80.1)	<0.001	18044 (83.2)	2986 (83.6)	<0.001	373 (16.3)	145 (8.9)	<0.001
Yes	5162 (15.1)	522 (8.9)		1572 (15.4)	81 (12.6)		3449 (15.9)	423 (11.9)		141 (6.2)	18 (1.1)	
Missing	2002 (5.9)	1672 (28.6)		48 (0.5)	47 (7.3)		184 (0.9)	162 (4.5)		1770(77.5)	1463 (90.0)	

Factors associated with missing data on hand washing	Pooled data		India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	Missing hand washing data (*n*=5841)	*p*-value[a]	Hand washing data present (*n*=10 244)	Missing hand washing data (*n*=644)	*p*-value[a]	Hand washing data present (*n*=21 677)	Missing hand washing data (*n*=3571)	*p*-value[a]	Hand washing data present (*n*=2284)	Missing hand washing data (*n*=1626)	*p*-value[a]
Use of sterilised blade to cut the umbilical cord, *n* (%)												
No	16950 (49.6)	3246 (55.6)	<0.001	8182 (79.9)	430 (66.8)	<0.001	7180 (33.1)	1464 (41.0)	<0.001	1588 (69.9)	1352 (83.7)	<0.001
Yes	15735 (46.0)	1859 (31.8)		1519 (14.8)	126 (19.6)		13533 (62.4)	1469 (41.1)		683 (30.1)	264 (16.3)	
Missing	1520 (4.4)	736 (12.6)		543 (5.3)	88 (13.7)		964 (4.5)	638 (17.9)		13 (0.6)	10 (0.6)	
Use of sterilised thread to tie the cord, *n* (%)												
No	16825 (52.7)	2137 (50.7)	<0.001	8592 (83.9)	505 (78.4)	<0.001	8233 (37.9)	1632 (45.7)	<0.001	b	b	b
Yes	13552 (42.5)	1293 (30.7)		1264 (12.3)	63 (9.8)		12288 (56.7)	1230 (34.4)		b	b	
Missing	1544 (4.8)	785 (18.6)		388 (3.8)	76 (11.8)		1156 (5.3)	709 (19.9)		b	b	

Factors associated with missing data on hand washing	**Pooled data**			**India**			**Bangladesh**			**Nepal**		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Use of dry cord care, *n* (%)												
No	15174 (44.4)	2963 (50.7)	<0.001	2056 (20.1)	127 (19.7)	0.830	12594 (58.1)	2392 (67.0)	<0.001	524 (22.9)	444 (27.3)	0.0003
Yes	18886 (55.2)	2850 (48.8)		8188 (79.9)	517 (80.3)		8977 (41.4)	1168 (32.7)		1721 (75.4)	1165 (71.7)	
Missing	145 (0.4)	28 (0.5)		0 (0.0)	0 (0.0)		106 (0.5)	11 (0.3)		39 (1.7)	17 (1.1)	
Use of antiseptic to clean the cord only, *n* (%)												
No	32230 (94.2)	5492 (94.0)	0.762	9987 (97.5)	621 (96.4)	0.098	20004 (92.3)	3262 (91.4)	0.021	2239 (98.0)	1609 (99.0)	0.027
Yes	1829 (5.4)	321 (5.5)		257 (2.5)	23 (3.6)		1566 (7.2)	298 (0.4)		6 (0.3)	0 (0.0)	
Missing	146 (0.4)	28 (0.5)		0 (0.0)	0 (0.0)		107 (0.5)	11 (0.3)		39 (1.7)	17 (1.1)	
Use of plastic sheet, *n* (%)												
No	20446 (64.1)	2414 (57.3)	<0.001	9448 (92.2)	593 (92.1)	<0.001	10998 (50.7)	1821 (51.0)	0.101	b	b	b
Yes	11468 (35.9)	1795 (42.6)		796 (7.8)	49 (7.6)		10672 (49.2)	1746 (48.9)		b	b	
Missing	7 (0.0)	6 (0.1)		0 (0.0)	2 (0.3)		7 (0.0)	4 (0.1)		b	b	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Use of gloves to assist delivery, *n* (%)												
No	29325 (91.9)	3778 (89.6)	<0.001	9898 (96.6)	593 (92.1)	<0.001	19427 (89.6)	3185 (89.2)	<0.001	b	b	b
Yes	2515 (7.9)	407 (9.7)		346 (3.4)	51 (7.9)		2169 (10.0)	356 (10.0)		b	b	
Missing	81 (0.3)	30 (0.7)		0 (0.0)	0 (0.0)		81 (0.4)	30 (0.8)		b	b	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Maternal characteristics												
Maternal education, *n* (%)												
No education	15777 (45.5)	2787 (46.9)	0.171	7682 (75.0)	446 (69.3)	0.005	6228 (28.7)	883 (24.7)	<0.001	1947 (82.3)	1447 (89.0)	0.003
Primary	8732 (25,2)	1507 (25.4)		507 (5.0)	41 (6.4)		7757 (35.8)	1295 (36.3)		235 (10.3)	125 (7.7)	
Secondary	10147 (29.3)	1647 (27.7)		2055 (20.1)	157 (24.4)		7689 (35.5)	1392 (39.0)		102 (4.5)	54 (3.3)	
Missing	4 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)		3 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)	
Maternal age in years, *n* (%)												
<20	3952 (11.6)	873 (15.0)	<0.001	719 (7.0)	67 (10.4)	<0.001	3093 (14.3)	702 (19.7)	<0.001	170 (7.4)	104 (6.4)	0.013
20–29	19292 (56.4)	3361 (57.5)		3830 (37.4)	185 (28.7)		14098 (65.0)	2269 (63.5)		1364 (59.7)	907 (55.8)	
30–39	6473 (18.9)	1117 (19.1)		1623 (15.8)	43 (6.7)		4237 (19.6)	574 (16.1)		613 (26.8)	500 (30.8)	
40+	462 (1.4)	144 (2.5)		79 (0.8)	4 (0.6)		246 (1.1)	25 (0.7)		137 (6.0)	115 (7.1)	
Missing	3996 (11.7)	346 (5.9)		3993 (39.0)	345 (53.6)		3 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Household assets, *n* (%)												
All	9803 (28.7)	1523 (26.1)	<0.001	1600 (15.6)	116 (18.0)	0.098	8147 (37.6)	1376 (38.5)	0.002	56 (2.5)	31 (1.9)	<0.001
Some	12711 (37.2)	1942 (33.3)		6470 (63.2)	410 (63.7)		5238 (24.2)	933 (26.1)		1003 (43.9)	599 (36.8)	
None	11690 (34.2)	2376 (40.7)		2174 (21.2)	118 (18.3)		8292 (38.3)	1262 (35.3)		1224 (53.6)	996 (61.3)	
Missing	1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.0)	0 (0.0)	
Parity, *n* (%)												
1	8940 (26.1)	1616 (27.7)	<0.001	2279 (22.3)	209 (32.5)	<0.001	6399 (29.5)	1249 (35.0)	<0.001	262 (11.5)	158 (9.7)	<0.001
2	9112 (26.6)	1483 (25.4)		2396 (23.4)	131 (20.3)		6245 (28.8)	1063 (29.8)		471 (20.6)	289 (17.8)	
3	6487 (19.0)	997 (17.1)		1852 (18.1)	124 (19.3)		4195 (19.4)	604 (16.9)		440 (19.3)	269 (16.5)	
4	9650 (28.2)	1744 (29.9)		3704 (36.2)	179 (27.8)		4835 (22.3)	655 (18.3)		1111 (49.6)	910 (56.0)	
Missing	16 (0.1)	0 (0.0)		13 (0.1)	1 (0.2)		3 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Factors associated with missing data on hand washing	Pooled data		India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Antenatal period												
Number of antenatal care visits, *n* (%)												
0	12728 (37.2)	2666 (45.6)	<0.001	3352 (32.7)	188 (29.2)	0.001	7869 (36.3)	1262 (35.3)	0.075	1507 (66.0)	1216 (74.8)	<0.001
1	6380 (18.7)	1051 (18.0)		1437 (14.0)	91 (14.1)		4683 (21.6)	798 (22.4)		260 (11.4)	162 (10.0)	
2	5949 (17.4)	851 (14.6)		2357 (23.0)	131 (20.3)		3402 (15.7)	616 (17.3)		190 (8.3)	104 (6.4)	
3	4225 (12.4)	574 (9.8)		1516 (14.8)	93 (14.4)		2549 (11.8)	389 (10.9)		160 (7.0)	92 (5.7)	
4	4903 (14.3)	694 (11.9)		1575 (15.4)	140 (21.7)		3161 (14.6)	502 (14.1)		167 (7.3)	52 (3.2)	
Missing	20 (0.1)	5 (0.1)		7 (0.1)	1 (0.2)		13 (0.1)	4 (0.1)		0 (0.0)	0 (0.0)	
Delivery period												
Obstetric Haemorrhage, *n* (%)												
No	29843 (87.3)	5359 (91.8)	<0.001	6330 (61.8)	346 (53.7)	<0.001	21420 (98.8)	3507 (98.2)	0.001	2093 (91.6)	1506 (92.6)	0.263
Yes	797 (2.3)	199 (3.4)		350 (3.4)	17 (2.6)		256 (1.2)	62 (1.7)		191 (8.4)	120 (7.4)	
Missing	3565 (10.4)	283 (4.9)		3564 (34.8)	281 (43.6)		1 (0.0)	2 (0.1)		0 (0.0)	0 (0.0)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 205)	**Missing hand washing data (*n*=5841)**	***p*-value[a]**	**Hand washing data present (*n*=10 244)**	**Missing hand washing data (*n*=644)**	***p*-value[a]**	**Hand washing data present (*n*=21 677)**	**Missing hand washing data (*n*=3571)**	***p*-value[a]**	**Hand washing data present (*n*=2284)**	**Missing hand washing data (*n*=1626)**	***p*-value[a]**
Skilled birth attendant, *n* (%)												
No	33178 (97.0)	5597 (95.5)	<0.001	9677 (94.5)	577 (89.6)	<0.001	21224 (97.9)	3394 (95.0)	<0.001	2277 (99.7)	1626 (100.0)	0.025
Yes	959 (2.8)	235 (4.0)		505 (4.9)	65 (10.1)		447 (2.1)	170 (4.8)		7 (0.3)	0 (0.0)	
Missing	68 (0.2)	9 (0.2)		62 (0.6)	2 (0.3)		6 (0.0)	7 (0.2)		0 (0.0)	0(0.0)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

b. Not applicable: data were not collected in the study.

Table A4d: Missing data patterns for models testing for the association between kit use or handwashing and neonatal mortality where “1” indicates a variable is present in the missing data pattern, and “0" indicates a variable is absent in the missing data pattern

	Missing data pattern							
Percent	Household assets	Education	Parity	Number of antenatal care visits	Skilled birth attendant	Maternal age	Kit use	Hand washing
76	1	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1	0
5	1	1	1	1	1	1	0	1
4	1	1	1	1	1	1	0	0
4	1	1	1	1	1	0	1	1
<1	1	1	1	1	1	0	1	0
<1	1	1	1	1	0	1	1	1
<1	1	1	1	1	0	0	1	1
<1	1	1	1	0	1	1	1	1
<1	1	1	0	1	1	0	1	1
<1	1	1	1	1	1	0	0	0
<1	1	1	1	1	1	0	0	1
<1	1	1	1	1	0	1	1	0
<1	1	0	1	1	1	1	1	1
<1	1	1	0	1	1	1	1	1
<1	1	1	1	0	1	1	1	0
<1	1	1	1	1	0	1	0	1
<1	0	1	1	1	1	1	0	1
<1	1	0	1	1	1	1	1	0
<1	1	1	0	1	1	0	1	1
<1	1	1	1	0	0	1	1	0
<1	1	1	1	0	1	0	1	1
<1	1	1	1	0	1	0	0	0
<1	1	1	1	0	1	1	0	1
<1	1	1	1	1	0	0	1	0
<1	1	1	1	1	0	0	0	0
<1	1	1	1	1	0	1	1	1

Appendix 5: Copy of a manuscript submitted to *PLoS ONE* Entitled: Using observational data to estimate the effect of handwashing by birth attendants on maternal deaths after home deliveries in rural Bangladesh, India and Nepal

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Abstract

Background

Globally, puerperal sepsis accounts for an estimated 8-12% of maternal deaths, but evidence is lacking on the extent to which clean delivery practices could improve maternal survival. We used data from the control arms of four cluster-randomised controlled trials conducted in rural India, Bangladesh and Nepal, to examine associations between clean delivery kit use and handwashing by the birth attendant with maternal mortality among home deliveries.

Methods

We tested associations between clean delivery practices and maternal deaths, using a pooled dataset for 40,602 home births across sites in the three countries. Cross-sectional data were analysed by fitting logistic regression models with and without multiple imputation, and confounders were selected a priori using causal directed acyclic graphs. The robustness of estimates was investigated through sensitivity analyses.

Results

Handwashing was associated with a 49% reduction in the odds of maternal mortality after adjusting for confounding factors (AOR 0.51, 95% CI 0.28 – 0.93). Assuming handwashing data were more likely to be missing if handwashing was not used by the delivery attendant, the association between handwashing and maternal death was over estimated in the multiple imputation analysis where data were assumed to be missing at random. Sensitivity analyses, accounting for possible differential misclassification bias in the instance of a maternal death, also indicated that the association between handwashing and maternal death had been over estimated.

Conclusions

Although our evidence suggests that handwashing in delivery is critical for maternal survival among home deliveries in rural South Asia, the exact magnitude of this effect is uncertain due to inherent biases associated with observational data.

Background

Reducing maternal deaths during pregnancy, childbirth and the first 42 days after delivery is a major global health challenge addressed by the fifth Millennium Development Goal (MDG). The MDG target is to reduce the Maternal Mortality Ratio (MMR) by three-quarters between 1990 and 2015.[1] Ninety percent of such maternal deaths occur in Sub-Saharan Africa and South Asia. In South Asia, MMR declined 4% per year between 1990 and 2011.[2,3] In 2011, Bangladesh's MMR was estimated at 247 per 100 000 live births (Uncertainty interval (UI) 197 - 309), India's at 187 (UI 142 - 238), and Nepal's at 316 (UI 241 - 407).[3]

Puerperal sepsis is an infection arising from the genital tract that can occur between rupture of membranes and 42 days after birth.[4] It is responsible for approximately 10% of maternal deaths in Africa and 12% in Asia.[5] Morbidity due to puerperal sepsis is estimated to affect between 5% and 10% of pregnant women.[6] However, obtaining cause-specific maternal morbidity and mortality data for low- and middle-income countries is difficult, as many estimates come from hospital-based studies that are not representative of the substantial proportion of deliveries that still occur in the home.[7,8] Adding to this uncertainty, a hospital-based study in Mozambique showed sensitivities of less than 50% for a clinical diagnosis of infection-related maternal death when compared to the gold standard of diagnosis through autopsy.[9] Sepsis-related maternal deaths and morbidity are under-diagnosed and sepsis exacerbates risk from other causes of death such as haemorrhage and abortion.[10]

To prevent sepsis, the World Health Organization (WHO) promotes the observance of "six cleans" at the time of delivery: clean hands, clean perineum, clean delivery surface, clean cord and tying instruments, and clean cutting surfaces.[11] Clean delivery kits usually include soap for washing the birth attendant's hands and mother's perineum, a plastic sheet to provide a clean delivery surface, a clean thread for tying the umbilical cord, a new blade for cutting the cord, and pictorial instructions to illustrate the sequence of events during a delivery.[11]

Two recent systematic reviews examined the effects of clean delivery kits on maternal and neonatal health.[12,13] One review found three studies specifically testing the impact of complex intervention packages, including clean delivery kits, on maternal outcomes.[12,14-16] Two of these studies indicate that clean delivery practices, especially the use of clean kits, improve maternal outcomes, particularly puerperal sepsis.[14,16] The review concluded that providing kits to facilitate clean delivery practices seemed commonsense, but that there was no evidence of independent effects of kits separable from those achieved by broader intervention packages.[12]

Observational studies are prone to bias, depending on maternal and newborn outcomes and on the recall period. A classic study highlighted the dangers of maternal recall bias by demonstrating that mothers of infants with sudden infant death syndrome (SIDS) experienced higher sensitivities in the ability to recall antibiotic use than mothers of surviving infants, resulting in an estimated odds ratio biased away from the null hypothesis.[18, 19]

Given the known importance of clean delivery practices for maternal health, conducting cluster randomized control trials (cRCTs) testing their promotion either as a package (through clean delivery kits, for example) or individually would be unethical. However, examining the associations of clean delivery practices with maternal deaths using observational data allows estimating the potential impact that their successful promotion might have on maternal mortality at population level. Obtaining unbiased estimates for these associations using observational data requires adjustment for potential sources of bias such as confounding, missing data, and misclassification. To date, there has been a lack of high quality studies with sufficient power to examine the effects of clean delivery practices on maternal mortality whilst accounting for such biases using appropriate sensitivity analyses.

In this paper we use a large observational dataset from the control arms of four previously conducted cRCTs to examine the associations between maternal mortality and the use of a clean delivery kit and handwashing with soap by the birth attendant in rural South Asian communities.[20-23]

Methods

Study populations

We used data from 40,602 home deliveries in the control arms of four community-based cRCTs carried out between 2000 and 2011 in India, Bangladesh and Nepal.[20-24] In India, baseline data collected prior to the cRCT using the same data collection methods were also included. In Nepal, data collection continued after the completion of the cRCT and before the intervention was implemented in control clusters, allowing for the use of additional data from control clusters.

The study areas included three rural districts in eastern India, three in Bangladesh and one in Nepal; Figure 1 shows their locations. In India and Nepal, clean delivery practices including kits were promoted and distributed through the health system as part of government initiatives to improve birth outcomes. In Bangladesh, BRAC, a developmental organisation, makes and distributes kits at a low cost. A previous publication reports detail of kit manufacturing and distribution.[25] Data on kit use and handwashing were collected in each of the studies. Our analysis was limited to mothers of either live-born or stillborn infants delivered at home.

Ethics statement

Research ethics approval for the trials during which data for the study came from in-country Ethical Review Committees (ERC): the ERC of the Diabetic Association of Bangladesh (BADAS); an independent ERC in Jamshedpur, India, steered by the Indian Council of Medical Research (ICMR) Guidelines of 2006 (Ekjut trial); and the Nepal Health Research Council. Approval was also obtained from the Institute of Child Health and Great Ormond Street Hospital for Children (UK) Research Ethics Committee (ERC).

Participants in the trials were all women of reproductive age (defined as aged 15-49) who had recently experienced a pregnancy and delivery. Although some of these participants would have been minors (defined as under 18), we did not use different consent procedures for them because the vast majority were married and starting their own families, which made seeking consent from guardians redundant. Consent for minors was therefore the same as for older participants. All trials were conducted in disadvantaged areas with low levels of female literacy and all participants gave consent in writing or by thumbprint.

Surveillance systems: data collection and management

Data were collected on paper, checked by auditors, entered by data entry operators and cross-checked by data managers. Databases were created and managed in Microsoft Access or SQL Server. Separate datasets for each study and a pooled dataset consisting of information common to the three sites were prepared for statistical analysis in Stata, release 12.0 (Stata Corp, College Station, Tx).[26] All sites gathered information about maternal socio-demographic characteristics and events during the antenatal, delivery and postnatal periods through a structured questionnaire administered to mothers around six weeks after delivery. Details of the individual surveillance systems can be found elsewhere.[20-24] All data included in this analysis can be found in Supporting Information 1 (S1).

Exposures and outcome

Table 1 describes the data collected by vital events surveillance systems that were similar in all three sites. Maternal death was defined by ICD-10 as death of a woman during pregnancy or up to 42 days after delivery or termination of pregnancy.[4] We were interested in the effect of hygiene during delivery, and therefore selected the main outcome as postpartum maternal death (after delivery and within 42 days). The exposures of interest were two intrapartum practices that could potentially reduce puerperal sepsis: use of clean delivery kit and handwashing with soap by birth attendant.

Confounders

Based on existing literature, the following potential confounders were considered: maternal age (15 – 49), maternal education (none, primary, and secondary and above), number of antenatal care visits (0 – 4+), delivery assisted by a skilled birth attendant (country-specific definitions defined by Demographic Health Survey data, most recent version for country in question: India and Nepal: doctor, nurse or trained midwife; Bangladesh: doctor, nurse, trained midwife, family welfare visitor, community skilled birth attendant)[27-29], household assets (all included households with any of the following items; television, fridge, electricity; some assets referred to households having any one of the following; a bicycle, radio, fan or phone, and no assets referred to a household not having any of the above mentioned assets), parity (0 – 4+), and study site.[7,30] The use of a clean delivery kit was considered a potential confounder in analyses exploring the effects of handwashing on maternal death. Initially, univariable analyses were performed to assess whether potential confounders, clean delivery practices and maternal mortality differed between deliveries with and without handwashing by birth attendant, separately for each study site (Table 2).

After univariable analyses, directed acyclic graphs (DAGs) were used to inform the statistical modelling of the relationships between each of the separate clean delivery practices, maternal mortality and potential confounders to ensure that the confounders selected were appropriate.[31] The DAGs supported the appropriateness of all selected confounders for inclusion in the models. Details of confounder selection can be found in S2.

Statistical methods

Analyses were performed as follows: first, logistic regression models were fitted to the pooled data to examine the association of individual clean delivery practices with maternal death, controlling for confounders available at all sites to ensure comparability of results. To determine the appropriateness of using a pooled dataset, an interaction term was introduced between each individual clean delivery practice and study site, with results confirming similar associations in the three study sites. Secondly, these analyses were repeated separately for the three study sites. Finally, for all models, possible modifying effects of the confounders on the association between clean delivery practices and maternal mortality were tested by including a two-way interaction term where it was decided *a priori* that there was a plausible explanation for this effect.

Due to the small number of mothers who died after delivery, low uptake of skilled delivery attendants, and large numbers of missing data on clean delivery kit use in Nepal, convergence problems were encountered when iteratively fitting the models to calculate adjusted estimates for the effect of handwashing on postpartum maternal mortality. As a result, skilled attendant and clean delivery kit were not included in the adjusted analysis. To provide some information on how excluding these confounders could have affected our estimates, a sensitivity analysis was performed whereby results were compared both with and without skilled attendant and clean delivery kit, separately and simultaneously, using data from India and Bangladesh. Results indicated no differences, when comparing adjusted models with skilled attendant and kit use (AOR, 0.45, 95% CI: 0.24 – 0.87) to adjusted models without skilled attendant and kit use (0.43, 0.22 – 0.84). Due to large numbers of missing data on kit use, there were also convergence issues in calculating adjusted estimates for the effect of kit use on postpartum maternal mortality and hence it was not possible to include Nepal in this part of the analysis.

As data were collected from 18 geographic clusters in India, nine in Bangladesh, and 12 in Nepal, maternal mortality could be correlated within clusters. The estimated intra-cluster correlation coefficient (ICC) was <0.0001 using the pooled dataset, as well as for the individual study sites, indicating that such correlation was minimal. We therefore fitted logistic regression models with fixed effect terms only. Variance inflation factors (VIF) showed no evidence of multicollinearity in any model.

Sensitivity analyses

Missing data

We compared demographic, antenatal, and delivery characteristics, including clean delivery practices, maternal and neonatal outcomes, between respondents with recorded data on handwashing and those with missing data, using chi-squared and Fisher's exact tests where appropriate. In India, data on handwashing were missing in 6% (*n*=664), in Bangladesh 14% (*n*=3639) and in Nepal 42% (*n*=1639) of all deliveries. To reduce bias and loss of information due to missing data, we used multiple imputation by chained equations (MICE) as implemented in the MI command in Stata, under the assumption that data were missing at random (MAR).[32] Variables used in the MICE models consisted of the key outcome maternal death, previously mentioned confounders, and covariates found to be predictors of missingness that were not already considered, including obstetric haemorrhage.[33,34] Although it was not possible to include skilled birth attendant and kit use as confounders in the adjusted model, it was possible to include them as predictors of missingness in the MICE models.

To test modest departures from MAR, a weighted sensitivity analysis using the Selection Model Approach was applied to our findings after multiple imputation.[35-37] The estimates of the odds ratio of maternal death following handwashing compared to without handwashing from each imputation were weighted and their average then calculated. The weights were determined by the assumed value of the log odds ratio of the probability of handwashing being observed when handwashing occurred, compared to when handwashing did not occur, which is denoted by δ.[35-37] If $\delta=0$ then handwashing is MAR. Given the social desirability bias in reporting clean deliveries, we hypothesize that handwashing data were more likely to be missing in cases in which the delivery attendant did not wash her hands and so $\delta>0$. Details of this analysis can be found in S3.

Exposure misclassification bias

The accuracy of recall of the main exposures of clean delivery practices may depend on factors such as neonatal or maternal survival, as well as on different morbidity patterns experienced by mother and infant. Based on this assumption, we used maternal death as a proxy measure for which we gauged the differential sensitivities and specificities for the observed handwashing variable. We followed the methods developed by Lyles and Lin, in which estimated odds ratios accounting for misclassification rates of the main exposure, handwashing, were obtained fitting adjusted logistic regression models with appropriate weights based on assumed sensitivities and specificities; standard errors for these estimates were calculated using a jackknife procedure.[38] Due to complexities in assigning different weights to each level of the models' parameters, only those confounders with the greatest effect on estimates evaluating for effects of handwashing on maternal mortality were used that included maternal age and study site. Analysis for misclassification bias was carried out in SAS version 9.3.[39] Details are in S3.

Results

Study population

We analysed data from 40,602 mothers who gave birth at home between 2005 and 2011 in India (*n*=11,063), Bangladesh (*n*=25,591) and Nepal *(n*=3948). In total, there were 73 maternal deaths just after delivery and up to 42 days postpartum across all study sites; 18 deaths in India (0.16% of deliveries), 43 deaths in Bangladesh (0.17%), and 12 deaths in Nepal (0.30%). Median maternal age was 25 years in India, 24 in Bangladesh and 26 in Nepal. In India, 5% (590/11063) of mothers had a home delivery assisted by a skilled birth attendant, compared with 3% (900/25591) in Bangladesh, and 0.2% (7/3948) in Nepal. Clean delivery kits were used in 15% of deliveries in India (1684/11 063) and Bangladesh (3901/25 591), but in only 4% of deliveries in Nepal (157/3948). There was substantial variation in the proportion of birth attendants washing their hands before delivery: in India it was 24% (2677/11 063), compared with 69% (17639/25 591) in Bangladesh, and 32% (1258/3948) in Nepal.

Table 2 compares deliveries with and without handwashing by the birth attendant. There was evidence that handwashing improved maternal survival in India and Bangladesh (p=0.050 and p=0.048, respectively), but not in Nepal (p=0.799); however, in Nepal only eight maternal deaths with data on handwashing were reported and four maternal deaths had no information on handwashing. Clean delivery kit use was associated with birth attendant handwashing in all three study sites (p<0.001).

Clean delivery practices and maternal mortality

Table 3 shows estimates from the unadjusted analysis, and Table 4 results from adjusted analyses before and after multiple imputations, exploring the associations between clean delivery practices and maternal mortality. The unadjusted pooled analysis showed that handwashing was associated with a 54% reduction in the odds of a postpartum maternal death (OR 0.46, 95% CI: 0.26 - 0.36) and adjusted analysis a 49% reduction in maternal deaths (AOR 0.51, 0.28 – 0.93). Multiple imputation had little effect on this estimate (0.48, 0.26 – 0.90). Use of clean delivery kit was not associated with reductions in postpartum maternal mortality.

Sensitivity analysis

Missing data: Table S4 shows the differences in characteristics of mothers with complete data and those with missing data. Overall, 19% (*n*=14) of the 73 postpartum maternal deaths had no data on handwashing. Results from MICE models accounting for missing data under the MAR assumption can be found in Table 4, and show that imputed estimates and estimates from the observed data were similar.

In analyses assuming that the probability of handwashing being reported when it occurred was greater than the probability of handwashing being reported when it did not, the strength of association between handwashing and maternal mortality was reduced compared to analysis assuming data were MAR. The AORs ranged from 0.554 (95% CI: 0.321 – 0.958) to 0.574 (0.338 – 0.975). Details of these results can be found in Table 5.

Exposure misclassification bias: The sensitivity analysis to assess whether the estimates from the complete-case analysis were subject to differential misclassification bias revealed that the strength of the association between handwashing and postpartum maternal death weakened. Table 6, provides a range of estimates for different combinations of proposed sensitivities and specificities for the ability to accurately recall handwashing. For example, assuming differential misclassification with sensitivities and specificities of 0.73 and 0.93 in the instance of maternal death, and 0.86 and 0.89 in the instance of survival, yielded AOR=0.68 (0.21 – 2.25); for respective sensitivities and specificities of (0.90, 0.94) and (0.93, 0.89) we had

AOR=0.54 (0.27 – 1.15). Results indicated that adjusted estimates depended more on sensitivities than on specificities.

Discussion

Our pooled, complete-case analysis for study sites in India, Bangladesh, and Nepal indicated that handwashing by the birth attendant was associated with a 49% reduction in the odds of postpartum maternal death after adjustment for potential confounders. Use of a clean delivery kit was not associated with a reduction in maternal mortality at individual sites or in the pooled analysis.

Our findings need to be interpreted with caution due to limitations imposed by the use of observational data that require the following criteria to be met: the exposure variable should not contain any measurement error, the assignment of confounders should occur randomly in exposed and unexposed groups, and the exposed and unexposed groups should have equal probability of having missing data.[40] The analyses testing the sensitivity to the MAR assumption indicated that the association between handwashing and maternal death was an over-estimation of the true effect, providing that data were more likely to be missing in the absence of handwashing.

The sensitivity analyses taking into account differential misclassification for reporting of handwashing by the birth attendant demonstrated that even modest reductions in sensitivity and specificity weakened the estimates obtained from the complete-case analysis. Although there were clear reductions in maternal mortality, confidence intervals based on a jackknife procedure were relatively wide due to the uncertainty associated with the variability in the observed data, and the fact there were very few maternal deaths. However, as no data were available on the accuracy with which clean delivery practices were recalled, we do not feel that this sensitivity analysis invalidates our main study findings; rather, it suggests that they are likely to be biased.

Although the difficulties in studying maternal mortality have been well documented, and include factors such as a large sample size with the associated costs, these obstacles should not act as a deterrent.[41] The availability of observational data alongside the recent advances in robust statistical techniques, removes the excessive costs associated with recruiting required sample sizes, making this approach feasible. As an example, in our study, it was not possible to conduct an analysis using data on cause of death, and physician-led verbal autopsy reports from the India cRCT indicate that only 19 (17%) of the 109 maternal deaths were due to sepsis, and in the Nepal cRCT similar verbal autopsy reports suggested that two (14%) of the 13 maternal deaths were due to sepsis. Physician-led verbal autopsy reports were not available from Bangladesh. If the above findings on cause of death were similar to our data, we would expect approximately 11 of the 73 maternal deaths to be sepsis-related. In our study, it was possible to demonstrate through sensitivity analyses, that given these verbal autopsy findings, it is unlikely that the reduction in the odds of postpartum maternal death was as large as was estimated by the complete case analysis. Besides findings from the sensitivity analysis, it is also possible that this large reduction may be partly the result of handwashing serving as a proxy for other health-promoting behaviours or social support networks.

If the reductions in the odds of a maternal death were entirely due to handwashing acting as a proxy measure for unobserved confounders, misclassification bias, and missing data, one might have expected similar findings with the use of a clean delivery kit, which was not the case. A previous analysis of the associations between clean delivery practices, clean delivery kit use and neonatal mortality found that not all components of the clean delivery kit were being used, suggesting that the delivery attendant was not washing her hands with soap in all instances.[25] These findings may explain why clean delivery kit use was not as effective in reducing maternal mortality as was the case with handwashing by the birth attendant. Our results were similar to those of previous studies demonstrating that, although kits improved rates of puerperal sepsis, no clear effects on maternal mortality were found.[13,14]

Other evidence suggests that improved maternal survival due to handwashing by the birth attendant is irrefutable. In the 1840s, the Hungarian clinician Ignaz Semmelweis promoted handwashing with a chlorine solution, leading to a subsequent decline in puerperal sepsis mortality rates from more than 900 to 300 per 1000 births.[42] Handwashing campaigns have also been shown to improve child health overall.[43] A systematic review found that handwashing with soap has the potential to reduce diarrhoeal disease by 42-47%, with the possibility of saving millions of lives if implemented and scaled up appropriately.[43] Another recent systematic review found that water, sanitation and hygiene (WASH) interventions, including handwashing promotion, have benefits for the growth of children under five.[44] Hygiene campaigns aimed at improving clean delivery practices may have similar benefits.

Previously, we found that kit use was associated with a reduction in neonatal mortality and that a combination of clean delivery practices was essential to this improvement.[25] Given the potential for kits to not only improve neonatal survival but also reduce maternal mortality and morbidity, careful consideration needs to be given to their contents and appropriate clean delivery practices. Kits may also be used as a vehicle for components to reduce other causes of maternal mortality, such as misoprostol, a drug known to be effective in reducing the incidence of postpartum haemorrhage.[45] However, it is essential not to discourage women from delivering in institutions while promoting the use of clean delivery kits.

Given the evidence base for hygiene in improving maternal mortality and morbidity associated with puerperal sepsis, the question of how to promote beneficial practices in underserved rural populations in South Asia is an important one. A recent meta-analysis involving seven cRCTs suggested beneficial effects on neonatal and maternal survival of an intervention involving community mobilisation through participatory women's groups.[46] In the three trials where the intervention was most successful and data were available, clean delivery practices, including clean delivery kit use and handwashing by the birth attendant were more common in intervention than control clusters.[19,21,22] Working with community-based women's groups may therefore have substantial benefits for maternal survival, partly by improving clean delivery practices during home births in settings where they are common.

Our study has several strengths: it draws on a large, population-based dataset with a shorter recall period than Demographic Health Surveys (i.e. six weeks vs. up to five years), features an additional indicator unavailable elsewhere for home births (handwashing), and gives careful consideration to potential sources of bias. Our findings demonstrate that improving hygiene through handwashing is likely to improve maternal survival following home births in rural settings in South Asia where there is minimal access to skilled birth attendants. However, the true effect if all forms of bias were removed is difficult to gauge, and is most likely weaker than the estimate from the complete case analysis.

Acknowledgments

We would like to thank our colleagues at MIRA (Nepal) in particular Aman Sen Gupta, Kirti Man Tumbahangphe, and Ekjut (India) and the Perinatal Care Project (BADAS, Bangladesh) including Sanjit Kumer, members of the partner communities, and the mothers and relatives who agreed to be interviewed. We are grateful to Jonathan Bartlett from the London School of Hygiene and Tropical Medicine for important insights on the sensitivity analysis on missing data and misclassification bias.

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<u>Figures:</u>

Figure 1: Location of sites included in the study (located in main thesis, Figure 3.1)

Tables: (located at end of manuscript)

Table 1: Characteristics of study populations included in the analysis

Table 2: Comparison of deliveries with and without handwashing

Table 3: Unadjusted odds ratios (95% CI) for the association between clean delivery kit use, and handwashing, with maternal mortality

Table 4: Adjusted odds ratios (95% CI) for the association between clean delivery kit use, and handwashing, with maternal mortality obtained from logistic regression models with and without multiple imputation

Table 5: Adjusted odds ratios (95% CI) for different departures from the missing at random assumption, for the exposure variable of handwashing assuming greater probability of handwashing data being missing when handwashing did not occur

Table 6: Adjusted odds ratios (95% CI) for different combinations sensitivity (SE) and specificity (SP) values, assuming differential misclassification in the instance of maternal death and maternal survival of the exposure variable of handwashing

Supporting Information:

Data S1: Dataset for analysis of clean delivery practices and maternal mortality **(not included in manuscript)**

Text S2: Use of directed acyclic graphs to select confounders

Text S3: Sensitivity analysis for missing data bias and misclassification bias

Table S4: Comparison of deliveries with missing and complete data on handwashing by the birth attendant

Abbreviations

AOR: Adjusted odds ratio

cRCT: Cluster-randomised controlled trial

DAG: Directed acyclic graph

ICD-10: International Classification of Disease, 10th edition

MDG: Millennium Development Goals

MMR: Maternal mortality ratio

OR: Odds ratio

WHO: World Health Organization

Table 1: Characteristics of study populations included in the analysis

Country	India	Bangladesh	Nepal
Location	Three districts of Jharkhand and Orissa (eastern India):	Three rural districts:	Makwanpur district
	Keonjhar, West Singhbhum and Saraikela	Bogra, Maulvibazaar and Faridpur	
Study period	1. Baseline surveillance: Nov 21, 2004 - July 30, 2005	1. 1st cRCT: Feb 1, 2005 to Dec 31, 2007	1. cRCT: Nov 1, 2001 to Oct 31, 2003
	2. cRCT: July 31, 2005, to July 30, 2008	2. 2nd cRCT: Jan 1 2009 to June 20111	2. Surveillance data: Nov 1, 2003 - March 2005
Study design	1. Baseline surveillance, not a cRCT	1. Factorial design, cluster randomised controlled trial, open cohort.	Cluster randomised controlled trial, matched design and closed cohort.
	2. Cluster randomised controlled trial, open cohort.	2. Cluster randomised controlled trial, open cohort	Post cRCT, roll-out of intervention into control clusters.
Cluster characteristics	8-10 villages with residents classified as tribal or OBC	Villages making up a union	Village Development Committees
Clusters analysed, n	18	9	12
Participants	Women aged between 15 and 49 who had given birth in study period, and their infants	Women aged between 15 and 49 who had given birth in study period, and their infants.	Women aged between 15 and 49, married and with potential to become pregnant in study period, and their infants
Deliveries analysed, n	11,063	25,591	3948
Maternal mortality rate prior to initial intervention (per 1000 00 live births)	51021	38046	53947
Contents of clean delivery kits	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Instructions available in government kits only.	Soap, razor, plastic sheet, string, gauze. Plastic coin to use as surface to cut the cord. Instructions available in government kits only.
Individual clean delivery practices recorded separately from kit use	Hand washing, use of boiled blade to cut cord, type of cord care (dry or other), use of boiled thread to tie the cord, use of plastic sheet and use of gloves.	Hand washing, use of boiled blade to cut cord, type of cord care (dry or other), use of boiled thread to tie the cord, use of plastic sheet and use of gloves.	Handwashing, use of boiled blade to cut cord, type of cord care (dry or other)

Country	India	Bangladesh	Nepal
Concurrent activities to promote clean delivery practices and kit use	In both intervention and control areas, strengthening the activities of village health and sanitation committees.	Training was provided to nurses, doctors and paramedical staff in essential newborn care, including the six cleans.	Health service strengthening across intervention and control areas included training of all health workers on the six cleans.

Table 2: Comparison of deliveries with and without handwashing

Factors associated with handwashing	India				Bangladesh				Nepal			
	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a
	(n=10,399)	(*n* = 2677)	(*n* = 7722)		*(n=21,952)*	(*n* = 17,639)	(*n* = 4313)		(*n*=2309)	(*n* = 1258)	(*n* =1051)	
Postpartum maternal death, *n* (%)												
No	10381 (99.83)	2676 (99.96)	7705 (99.78)	0.05	21919 (99.85)	17617 (99.88)	4302 (99.74)	0.048	2301 (99.65)	1254 (99.68)	1047 (99.62)	0.799
Yes	18 (0.17)	1 (0.04)	17 (0.22)		33 (0.15)	22 (0.12)	11 (0.26)		8 (0.35)	4 (0.32)	4 (0.38)	
Use of clean delivery kit, *n* (%)												
No	8750 (84.14)	1907 (71.24)	6843 (88.62)	<0.001	18283 (83.29)	14230 (80.67)	4053 (93.97)	<0.001	387 (16.76)	253 (20.11)	134 (12.75)	<0.001
Yes	856 (11.09)	743 (25.75)	856 (11.09)		3472 (15.82)	3225 (18.28)	247 (5.73)		139 (6.02)	133 (10.57)	6 (0.57)	
Missing	23 (0.23)	27 (1.01)	23 (0.30)		197 (0.90)	184 (1.04)	13 (0.30)		1783 (77.22)	872 (69.32)	911 (86.68)	
Maternal characteristics												

Factors associated with handwashing	**India**				**Bangladesh**				**Nepal**			
	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a
	(n=10,399)	(*n* = 2677)	(*n* = 7722)		*(n=21,952)*	(*n* = 17,639)	(*n* = 4313)		(*n*=2309)	(*n* = 1258)	(*n* =1051)	
Maternal education, *n* (%)												
No education	7797 (74.98)	1783 (66.60)	6014 (77.88)	<0.001	6013 (27.39)	4467 (25.32)	1546 (35.85)	<0.001	1967 (85.19)	1007 (80.05)	960 (91.34)	<0.001
Primary	525 (5.05)	101 (7.13)	334 (4.33)		7967 (36.29)	6302 (35.73)	1665 (38.60)		240 (10.39)	165 (12.12)	75 (7.14)	
Secondary	2077 (17.79)	703 (26.26)	1374 (17.79)		7968 (36.29)	6867 (38.93)	1101 (25.53)		102 (4.42)	86 (6.84)	16 (1.52)	
Missing	0 (0.00)	0 (0.00)	0 (0.00)		4 (0.02)	3 (0.02)	1 (0.02)		0 (0.00)	0 (0.00)	0 (0.00)	
Maternal age in years, *n* (%)												
<20	1021 (9.82)	307 (11.47)	714 (9.25)	<0.001	3156 (14.38)	2596 (14.72)	560 (12.98)	<0.001	172 (7.45)	102 (8.11)	70 (6.66)	<0.001
20–29	5488 (52.77)	1538 (57.48)	3950 (51.15)		14238 (64.86)	11518 (65.30)	2720 (63.07)		1384 (59.94)	803 (63.83)	581 (55.28)	
30–39	2155 (20.72)	414 (15.47)	1741 (22.55)		4287 (19.53)	3314 (18.79)	973 (22.56)		612 (26.50)	293 (23.29)	319 (30.35)	

Factors associated with handwashing	**India**				**Bangladesh**				**Nepal**			
	Overall	Handwashing	No handwashing	*p*[a]	Overall	Handwashing	No handwashing	*p*[a]	Overall	Handwashing	No handwashing	*p*[a]
	(n=10,399)	(*n* = 2677)	(*n* = 7722)		*(n=21,952)*	(*n* = 17,639)	(*n* = 4313)		(*n*=2309)	(*n* = 1258)	(*n* =1051)	
40+	109 (1.07)	25 (0.93)	84 (1.09)		267 (1.22)	207 (1.17)	60 (1.39)		141 (6.11)	60 (4.77)	81 (7.71)	
Missing	1626 (15.54)	393 (14.68)	1233 (15.97)		4 (0.02)	4 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	
Household assets, *n* (%)[c]												
All	1630 (15.67)	506 (18.90)	1124 (14.56)	<0.001	8275 (37.70)	7038 (39.90)	1237 (28.68)	<0.001	56 (2.43)	48 (3.82)	8 (0.76)	<0.001
Some	6557 (63.05)	1634 (61.04)	4923 (63.75)		5417 (24.68)	4355 (24.69)	1062 (24.62)		1009 (43.70)	582 (46.26)	427 (40.63)	
None	2212 (21.27)	537 (20.06)	1675 (21.69)		8260 (37.63)	6246 (35.41)	2014 (46.70)		1243 (53.83)	627 (49.84)	616 (58.61)	
Missing	0	0	0		0 (0.00)	0 (0.00)	0 (0.00)		1 (0.04)	1 (0.08)	0 (0.00)	
Parity, *n* (%)												
1	2340 (22.50)	684 (25.55)	1656 (21.45)	<0.001	6507 (29.64)	5504 (31.20)	1003 (23.26)	<0.001	266 (11.52)	159 (12.64)	107 (10.18)	<0.001

Factors associated with handwashing	India				Bangladesh				Nepal			
	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a
	(n=10,399)	(*n* = 2677)	(*n* = 7722)		*(n=21,952)*	(*n* = 17,639)	(*n* = 4313)		(*n*=2309)	(*n* = 1258)	(*n* =1051)	
2	2410 (23.18)	654 (24.43)	1756 (22.74)		6318 (28.68)	5171 (29.32)	1147 (26.59)		481 (20.83)	291 (22.13)	190 (18.08)	
3	1878 (18.06)	519 (19.39)	1359 (17.60)		4201 (19.14)	3278 (18.58)	923 (21.40)		446 (19.32)	263 (20.91)	183 (17.41)	
4	3757 (36.13)	816(30.48)	2941 (38.09)		4923 (22.43)	3683 (20.88)	1240 (28.75)		1163 (48.33)	545 (43.32)	571 (54.33)	
Missing	14 (0.13)	4 (0.15)	10 (0.13)		3 (0.01)	3 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	
Antenatal period												
Number of antenatal care visits, *n* (%)												
0	3413 (32.82)	755 (28.20)	2658 (34.42)	<0.001	7931 (36.13)	5973 (33.86)	1958 (45.40)	<0.001	1533 (66.39)	755 (60.02)	778 (74.02)	<0.001
1	1471 (14.15)	386 (14.42)	1085 (14.05)		4768 (21.72)	3805 (21.57)	963 (22.33)		257 (11.13)	138 (10.97)	119 (11.32)	
2	2375 (22.84)	560 (20.92)	1815 (23.50)		3423 (15.59)	2844 (16.12)	579 (13.42)		189 (8.19)	116 (9.22)	73 (6.95)	

Factors associated with handwashing	**India**				**Bangladesh**				**Nepal**			
	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a	Overall	Handwashing	No handwashing	p^a
	(n=10,399)	(*n* = 2677)	(*n* = 7722)		*(n=21,952)*	(*n* = 17,639)	(*n* = 4313)		(*n*=2309)	(*n* = 1258)	(*n* =1051)	
3	1528 (14.69)	452 (16.88)	1076 (13.93)		2584 (11.77)	2157 (12..23)	427 (9.90)		162 (7.02)	111 (8.82)	51 (4.85)	
4	1606 (15.44)	522 (19.50)	1084 (14.04)		3232 (14.72)	2850 (16.16)	382 (8.82)		168 (7.28)	138 (10.97)	30 (2.85)	
Missing	6 (0.06)	2 (0.07)	4 (0.06)		14 (0.06)	10 (0.06)	4 (0.09)		0 (0.00)	0 (0.00)	0 (0.00)	
Skilled birth attendant												
No	9816 (94.39)	2259 (84.39)	7557 (97.86)	<0.001	21276 (96.92)	16987 (96.30)	4289 (99.44)	<0.001	2302 (99.70)	1253 (99.60)	1049 (99.81)	0.466
Yes	523 (5.03)	410 (15.32)	113 (1.46)		666 (3.03)	642 (3.64)	24 (0.56)		7 (0.30)	5 (0.40)	2 (0.19)	
Missing	60 (0.58)	8 (0.30)	52 (0.67)		10 (0.05)	10 (0.06)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	

a. *p*-value obtained through chi square statistic or Fisher's exact test where appropriate
b. Data were not collected in the study
c. Household assets include the following definition for the different categories: all assets include those households containing any one of the following items; television, fridge, electricity; some assets refer households having any one of the following; a bicycle, radio, fan or phone, and no assets refer to a household not having any of the above mentioned assets.

Table 3: Unadjusted odds ratios for association between clean delivery kit use and handwashing, with maternal mortality

Clean delivery practices	**Pooled data [a]**		**India**		**Bangladesh**		**Nepal**	
	Unadjusted OR (95% CI)	*p*[b]	Unadjusted OR (95% CI)	*p*[b]	Unadjusted OR (95% CI)	*p*[b]	Unadjusted OR (95% CI)	*p*[b]
Use of clean delivery kit [d]	1.19 (0.60 - 2.36)	0.616	0.69 (0.16 - 2.30)	0.619	1.46 (0.67 - 3.18)	0.344	[c]	
Washing hands prior to delivery	0.46 (0.26 - 0.36)	0.010	0.17 (0.02 - 1.27)	0.084	0.49 (0.24 - 1.01)	0.053	0.83 (0.21 - 3.35)	0.799

a. Pooled analysis adjusted for study site.
b. Wald test.
c. Unknown due to all mothers who died having MIssing data on clean delivery kit use
d. Excludes Nepal data due to convergence issues

Table 4: Adjusted odds ratios (95% CI) for the association between clean delivery kit use and handwashing, with maternal mortality obtained from logistic regression models with and without multiple imputation

Clean delivery practices	Model type	Pooled data		India		Bangladesh		Nepal	
		AOR (95% CI)	*p*[a]	AOR (95% CI)	*p* [a]	AOR (95% CI)	*p* [a]	AOR (95% CI)	*p* [a]
Use of clean delivery kit	Logistic regression [b, e]	1.26 (0.62 - 2.56)	0.519	0.66 (0.15 - 2.93)	0.587	1.61 (0.71 - 3.68)	0.256	[f]	
	Multiple imputation [c]	1.18 (0.62 - 2.24)	0.612	0.68 (0.15 - 2.99)	0.605	1.45 (0.63 - 3.30)	0.381	[f]	
Washing hands prior to delivery	Logistic regression [b]	0.51 (0.28 - 0.93)	0.028	0.15 (0.02 - 1.11)	0.063	0.57 (0.27 - 1.23)	0.154	0.83 (0.19 – 3.56)	0.800
	Multiple imputation [c, d]	0.48 (0.26 - 0.90)	0.022	0.15 (0.02 - 1.13)	0.066	0.58 (0.27 - 1.25)	0.162	0.91 (0.23 - 3.65)	0.898

a. Wald test.
b. Adjusted for maternal age, maternal education, parity, number of antenatal care visits, household assets, and for the pooled analysis, study site.
c. Multiple imputation models taking into account variables describe in b, as well as predictors of MIssingness including obstetric haemorrhage, and skilled birth attendant
d. Multiple imputation models also included clean delivery kit use as predictor of MIssingness.
e. It was not possible to include Nepal in the pooled analysis of kit use due to convergence issues caused by large numbers of MIssing/unknown data.
f. Model would not converge due large number of deliveries with MIssing/unknown data on kit use

Table 5: Adjusted odds ratios (95% CI) for different departures from the missing at random assumption (δ*), for the exposure variable of handwashing assuming greater probability of handwashing data being missing when handwashing did not occur

δ	AOR (95% CI)
0.40	0.574 (0.338 – 0.975)
0.30	0.573 (0.337 – 0.975)
0.20	0.572 (0.336 – 0.974)
0.15	0.568 (0.332 – 0.970)
0.10	0.554 (0.321 – 0.958)

* δ is the log odds ratio of the probability of handwashing data being observed when handwashing occurred compared to when handwashing did not occur

** Models have been adjusted to similar confounders and predictors of missingness as multiple imputation models found in Table 4.

Table 6: Adjusted odds ratios (95% CI) for different combinations sensitivity (SE) and specificity (SP) values, assuming differential misclassification in the instance of maternal death and maternal survival of the exposure variable of handwashing

Assumed SE	**Assumed SP** (maternal death, maternal survival)		
(maternal death, maternal survival)	0.89, 0.85	0.93, 0.89	0.97, 0.93
0.73, 0.86	0.67 (0.18 – 2.51)	0.68 (0.21 – 2.25)	0.69 (0.23 – 2.06)
0.90, 0.94	0.53 (0.24 – 1.20)	0.54 (0.27 – 1.15)	0.55(0.27 – 1.11)

* 95% CI calculated using jackknife standard error
** Analysis was based on complete cases only, and adjusted for maternal age and country

Supplementary information 2: Confounder selection

Directed acyclic graphs (DAGs) were used to model the associations between selected confounders with each other, with the individual clean delivery practices (exposures), and with the outcome of post-natal maternal death. These DAGs then informed the statistical modelling of the relationship between each of the separate clean delivery practices and maternal mortality, taking confounders into account.[1] In order to better approximate the causal relationships, the DAGs were modelled in relation to the pregnancy timeline from the pre-conception period to the post-natal period. Figure 1 shows the relationship between handwashing and post-partum maternal death and shows the appropriateness of all confounders. Figure 2 shows the relationship between using a clean delivery kit and post-partum maternal death and, contrary to Figure 1 that illustrates the inappropriateness of including individual clean delivery practices as potential confounders.

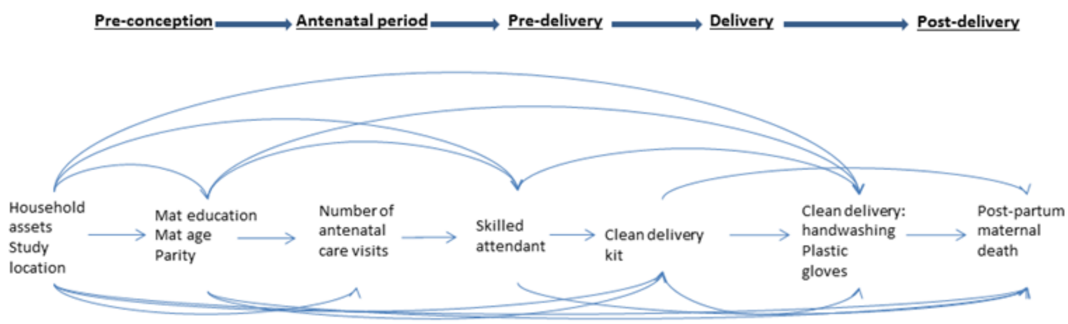

Figure 1. DAG showing possible causal relationships between handwashing, maternal mortality, and potential confounders in relation to the pregnancy time-line

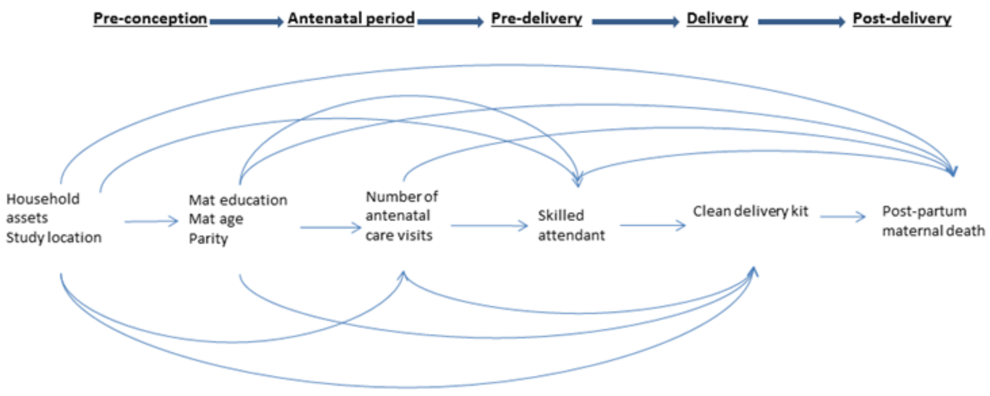

Figure 2. DAG showing possible causal relationships between use of a clean delivery kit, maternal mortality, and potential confounders in relation to the pregnancy time-line

References:

1. Textor J, Hardt J, Knuppel S (2011) DAGitty: A graphical tool for analyzing causal diagrams. Epidemiology 22: 745.

Supplementary information 3: Sensitivity analysis

Missing data

As previously described, multiple imputation by chained equations (MICE) models were used to impute the data, assuming data were missing at random (MAR). Due to differences between sites in the way data were collected, predictors of missing data, and the amount of missing data, the missing data mechanism might have differed between study sites; data were therefore imputed separately. Rubin's rules were used to summarize estimates and their standard errors from analyses of 15 separate imputed datasets.[1]

It is difficult to ascertain the missingness mechanism for the handwashing variable, especially given that our data comes from three separate study sites. Indeed, even in circumstances where the mechanism is not as ambiguous as is the case with this dataset, it is impossible to determine whether data is MAR or missing not at random (MNAR) from the data alone.[2] When performing multiple imputation assuming the data is MAR estimates for handwashing are subject to bias if data is MNAR whether or not the missingness mechanism is dependent on the maternal death outcome.[3]

To assess the sensitivity of our findings against modest departures from the MAR assumption, a weighted sensitivity analysis using the Selection Model Approach was applied.[4-6] Briefly, once data had been imputed under MAR, parameter estimates from each imputed dataset were reweighted to allow for the data to be missing not at random (MNAR). The chosen weights, used to reweight the data to account for MNAR, are dependent on the assumed degree of departure from MAR. The parameter used to re-weight the data, denoted by δ, is the log odds ratio of the probability of handwashing data being observed when handwashing occurred compared to when handwashing did not occur.[4-6] If $\delta=0$, handwashing could be considered to be MAR, $\delta>0$ indicates that the probability of observing handwashing when handwashing occurred was greater than when it did not, and $\delta<0$ indicates that the probability of observing handwashing when handwashing occurred was less. As δ decreases from zero, the probability of handwashing data being observed when handwashing occurred is less than the probability of handwashing data being observed when handwashing did not occur (i.e. greater probability of missing handwashing variable when handwashing occurred). We hypothesize that due to the social desirability bias in reporting clean delivery practices, it is more likely that handwashing was missing in instances where handwashing was not used, compared to when handwashing was used (i.e. $\delta>0$).

To gain insight into the missingness mechanism, logistic regression models were fitted to explore the relationship with missing handwashing, and potential predictors of missingness including maternal death. A multivariate model was fitted with the outcome of missing handwashing, and imputed values of potential predictors of missingness including the study outcome.[6] Results indicated that the missingness mechanism depends on a neonatal death, clean delivery kit use, maternal age, and skilled delivery attendant. There was some evidence that the outcome of a maternal death was associated with missing handwashing data.

To test the stability of our model, we considered different degrees of departure from the MAR assumption by considering plausible values of δ ranging from 0.10 to 0.40. This range corresponds to odds ratios for the data being observed when handwashing occurred compared to when it did not, ranging from 1.11 to 1.50 (i.e. exponential of 0.10 and 0.40).

Exposure misclassification bias:

Maternal death was used as a proxy for which we determined how accurately handwashing by the delivery attendant was reported. In the event of a maternal death, there is likely to be reduced sensitivity and increased specificity in the ability to accurately report handwashing. As an example, in the event of a maternal death it is expected that a close relative will be searching for explanations as to why the death occurred, and that by under-reporting behaviours that improve survival they may partially explain why the death occurred, which will in turn decrease the sensitivity. Using the same reasoning, it is likely that specificity will be higher than when a woman survived, as most relatives are unlikely to classify handwashing as occurring, when in fact it did not occur, as they are searching for an explanation of why the woman did not survive.

In most cases, the mother will survive childbirth. The sensitivity of reporting handwashing in these cases is likely to be higher than in the event of a maternal death as mothers are going to be more likely to report desirable behaviours. Using the same reasoning, it is likely that the specificity will be lower than in the instance of a maternal death, as women are most likely to misclassify not washing their hands as washing their hands in order to report socially desirable behaviours.

Methods based on a weighted logistic regression model recently developed by Lyles and Lin allow estimating odds ratios accounting for misclassification rates of the main exposure.[7] The required weights are obtained from the positive and negative predictive values, which are computed using pre-specified sensitivities and specificities, the outcome of interest, the observed exposure of interest and other important covariates.

The weights are then used to fit the model of interest to an expanded dataset and a jackknife approach is used to compute standard errors for the estimated odds ratios.[7]

For our analyses, we used a similar approach, assuming differential misclassification using complete-case analysis only. Our model included: the main exposure of handwashing, the outcome of maternal death, the confounders of study site and maternal age and the weights. Due to complexities in assigning different weights to each level of the models' parameters, only those confounders with the greatest effect on estimates evaluating for effects of handwashing on maternal mortality were included.

Differential misclassification assumes that sensitivities and specificities would differ depending on whether the mother lived or died. Based on this assumption, we tried several combinations of sensitivities and specificities to test the robustness of our findings, as shown in the Table 2. The restrictions imposed on the choice of different sensitivities and specificities were as follows:

Probability of handwashing < sensitivity of handwashing

Probability of handwashing > 1- specificity of handwashing

It was observed that 62% of delivery attendants were reported to have washed their hands, and this limited the extent to which we could evaluate different sensitivities and specificities.

Table 2: Combinations of sensitivities and specificities used to evaluate misclassification bias

	Sensitivity	Specificity	Sensitivity	Specificity
Maternal outcome	**Maternal survival**		**Post-partum maternal death**	
Combination 1	0.73	0.89	0.86	0.85
Combination 2	0.73	0.93	0.86	0.89
Combination 3	0.73	0.97	0.96	0.93
Combination 4	0.90	0.89	0.84	0.85
Combination 5	0.90	0.93	0.94	0.89
Combination 6	0.90	0.97	0.94	0.93

References:

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Supplementary information 4: Comparison between deliveries with complete information on handwashing and deliveries with missing information on handwashing

Factors Associated with Handwashing	India			Bangladesh			Nepal		
	Handwashing present (*n*=10 399)	**Handwashing missing (*n*=664)**	***p*-value [a]**	**Handwashing present (*n*=21 952)**	**Handwashing missing (*n*=3639)**	***p*-value [a]**	**Handwashing present (*n*=2309)**	**Handwashing missing (*n*=1639)**	***p*-value [a]**
Maternal death *n* (%)									
No	10381 (99.83)	664 (100.00)	0.623	21919 (99.85)	3629 (99.73)	0.090	2301 (99.65)	1635 (99.76)	0.771
Yes	18 (0.17)	0 (0.00)		33 (0.15)	10 (0.27)		8 (0.35)	4 (0.24)	
Missing	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Neonatal health									
Neonatal survival									
Alive at 28 days	9540 (94.38)	611 (95.77)	0.137	20796 (97.19)	3420 (96.39)	0.009	2157 (95.57)	1591 (98.45)	<0.001
Neonatal death	568 (5.62)	27 (4.23)		602 (2.81)	128 (3.61)		100 (4.43)	25 (1.55)	
Stillbirth									
No	10108 (97.20)	638 (96.08)	0.094	21398 (97.48)	3548 (97.50)	0.935	2257 (97.75)	1616 (98.60)	0.054
Yes	291 (2.80)	26 (3.92)		554 (2.52)	91 (2.50)		52 (2.25)	23 (1.40)	
Clean delivery practices	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Use of clean delivery kit, *n* (%)									
No	8750 (84.14)	528 (79.52)	<0.001	18283 (83.29)	3033 (83.35)	<0.001	387 (16.76)	146 (8.91)	<0.001
Yes	1599 (15.38)	85 (12.80)		3472 (15.82)	429 (11.78)		139 (6.02)	18 (1.10)	
Missing	50 (0.48)	51 (7.68)		197 (0.90)	177 (4.86)		1783 (77.22)	1475 (89.99)	

Factors Associated with Handwashing	India			Bangladesh			Nepal		
	Handwashing present (*n*=10 399)	**Handwashing missing (*n*=664)**	***p*-value [a]**	**Handwashing present (*n*=21 952)**	**Handwashing missing (*n*=3639)**	***p*-value [a]**	**Handwashing present (*n*=2309)**	**Handwashing missing (*n*=1639)**	***p*-value [a]**
Use of plastic sheet, *n* (%)									
No	9580 (92.12)	611 (92.02)	0.005	10888 (49.60)	1821 (50.04)	0.011	[b]	[b]	[b]
Yes	819 (7.88)	51 (7.68)		11058 (50.38)	1813 (49.82)		[b]	[b]	
Missing	0 (0.00)	2 (0.30)		6 (0.03)	5 (0.16)		[b]	[b]	
Use of gloves to assist delivery, *n* (%)									
No	10036 (96.51)	610 (91.87)	<0.001	19679 (89.65)	3234 (88.87)	<0.001	[b]	[b]	[b]
Yes	363 (3.49)	54 (8.13)		2198 (10.01)	375 (10.31)		[b]	[b]	
Missing	0 (0.00)	0 (0.00)		75 (0.34)	31 (0.82)		[b]	[b]	
Maternal characteristics									
Maternal education, *n* (%)									
No education	7797 (74.98)	463 (69.73)	0.009	6013 (27.39)	863 (23.72)	<0.001	1967 (85.19)	1461 (89.14)	0.001
Primary	525 (5.05)	44 (6.63)		7967 (36.29)	1339 (36.80)		240 (10.39)	124 (7.57)	
Secondary	2077 (19.77)	157 (23.64)		7968 (36.30)	1436 (39.46)		102 (4.42)	54 (3.29)	
Missing	0 (0.00)	0 (0.00)		4 (0.02)	1 (0.03)		0 (0.00)	0 (0.00)	

Factors Associated with Handwashing	India			Bangladesh			Nepal		
	Handwashing present (*n*=10 399)	**Handwashing missing (*n*=664)**	***p*-value [a]**	**Handwashing present (*n*=21 952)**	**Handwashing missing (*n*=3639)**	***p*-value [a]**	**Handwashing present (*n*=2309)**	**Handwashing missing (*n*=1639)**	***p*-value [a]**
Maternal age in years, *n* (%)									
<20	1021 (9.82)	92 (13.86)	<0.001	3156 (14.38)	714 (19.62)	<0.001	172 (7.75)	107 (6.53)	0.008
20–29	5488 (52.77)	317 (47.74)		14238 (64.86)	2315 (63.62)		1384 (59.94)	912 (55.64)	
30–39	2155)20.72)	100 (15.06)		4287 (19.53)	582 (15.99)		612 (26.50)	503 (30.69)	
40+	109 (1.05)	5 (0.75)		267 (1.22)	27 (0.74)		141 (6.11)	117 (7.14)	
Missing	1626 (15.64)	150 (22.59)		4 (0.02)	1 (0.03)		0 (0.00)	0 (0.00)	
Household assets, *n* (%)									
All	1630 (15.67)	117 (17.62)	0.193	8275 (37.70)	1406 (38.64)	0.001	56 (2.43)	31 (1.89)	<0.001
Some	6557 (63.05)	422 (63.55)		5417 (24.68)	974 (26.77)		1009 (43.70)	600 (36.61)	
None	2212 (21.27)	125 (18.83)		8260 (37.63)	1259 (34.63)		1243 (53.83)	1008 (61.50)	
Missing	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		1 (0.04)	0 (0.00)	
Parity, n (%)									
1	2340 (22.50)	215 (32.38)	<0.001	6507 (29.64)	1280 (35.17)	<0.001	266 (11.52	163 (9.95)	<0.001
2	2410 (23.18)	139 (20.93)		6318 (28.78)	1065 (29.27)		481 (20.83)	290 (17.69)	
3	1878 (18.06)	128 (19.28)		4201 (19.14)	620 (17.04)		446 (19.32)	268 (16.35)	
4	3757 (36.13)	181 (27.26)		4823 (22.43)	674 (18.52)		1116 (48.33)	918 (56.1)	
missing	14 (0.13)	1 (0.15)		3 (0.01)	0 (0.00)		0 (0.00)	0 (0.00)	

Factors Associated with Handwashing	India			Bangladesh			Nepal		
	Handwashing present (*n*=10 399)	**Handwashing missing (*n*=664)**	***p*-value [a]**	**Handwashing present (*n*=21 952)**	**Handwashing missing (*n*=3639)**	***p*-value [a]**	**Handwashing present (*n*=2309)**	**Handwashing missing (*n*=1639)**	***p*-value [a]**
Antenatal period									
Number of antenatal care visits, *n* (%)									
0	3413 (32.82)	198 (29.82)	0.005	7931 (36.13)	1274 (35.01)	0.089	1533 (66.39)	1228 (74.92)	<0.001
1	1471 (14.15)	94 (14.16)		4768 (21.72)	813 (22.34)		257 (11.13)	163 (9.95)	
2	2375 (22.84)	137 (20.63)		3423 (15.59)	626 (17.20)		189 (8.19)	104 (6.35)	
3	1582 (14.69)	94 (14.16)		2584 (11.77)	401 (11.02)		162 (7.02)	92 (5.61)	
4	1606 (15.44)	140 (21.08)		3232 (14.72)	521 (14.32)		168 (7.28)	52 (3.17)	
Missing	6 (0.06)	1 (0.15)		14 (0.06)	4 (0.11)		0 (0.00)	0 (0.00)	
Delivery period									
Delivery by a skilled birth attendant									
No	9816 (94.39)	595 (89.61)	<0.001	21276 (96.92)	3397 (93.35)	<0.001	2302 (99.70)	1639 (100.00)	0.046
Yes	523 (5.03)	67 (10.09)		466 (2.12)	234 (6.43)		7 (0.30)	0 (0.00)	
Missing	60 (0.58)	2 (0.30)		10 (0.05)	8 (0.22)		0 (0.00)	0 (0.00)	
Obstetric haemorrhage									
No	6392 (61.47)	357 (53.77)		14500 (66.05)	2166 (59.52)	<0.001	2105 (91.17)	1517 (92.56)	0.118
Yes	352 (3.38)	17 (2.56)		7450 (33.94)	1471 (40.42)		204 (8.83)	122 (7.44)	
Missing	3655 (35.15)	290 (43.46)		2 (0.01)	3 (0.05)		0 (0.00)	0 (0.00)	

a. *p*-value obtain with a Wald test
b. b Data were not collected in the study
c. Country specific definitions defined by Demographic Health Survey data (most recent version in question). India and Nepal: Doctor, Nurse or trained midwife; Bangladesh: doctor, nurse, midwife, paramedic, family welfare visitor, community skilled birth attendant

Appendix 6: Tables from Chapter 5 examining the associations between clean delivery practices and maternal mortality

Table A6a: Comparison of deliveries with and without hand washing

Factors associated with hand washing	India				Bangladesh				Nepal			
	Overall (*n*=10 399)	**Hand washing (*n*=2677)**	**No hand washing (*n*=7722)**	***p*-value[a]**	**Overall (*n*=21 952)**	**Hand washing (*n*=17 639)**	**No hand washing (*n*=4313)**	***p*-value[a]**	**Overall (*n*=2309)**	**Hand washing (*n*=1258)**	**No hand washing (*n*=1051)**	***p*-value[a]**
Postpartum maternal death, *n* (%)												
No	10381 (99.83)	2676 (99.96)	7705 (99.78)	0.057	21919 (99.85)	17617 (99.88)	4302 (99.74)	0.048	2301 (99.65)	1254 (99.68)	1047 (99.62)	0.799
Yes	18 (0.17)	1 (0.04)	17 (0.22)		33 (0.15)	22 (0.12)	11 (0.26)		8 (0.35)	4 (0.32)	4 (0.38)	
Use of clean delivery kit, *n* (%)												
No	8750 (84.14)	1907 (71.24)	6843 (88.62)	<0.001	18283 (83.29)	14230 (80.67)	4053 (93.97)	<0.001	387 (16.76)	253 (20.11)	134 (12.75)	<0.001
Yes	856 (11.09)	743 (25.75)	856 (11.09)		3472 (15.82)	3225 (18.28)	247 (5.73)		139 (6.02)	133 (10.57)	6 (0.57)	
Missing	23 (0.23)	27 (1.01)	23 (0.30)		197 (0.90)	184 (1.04)	13 (0.30)		1783 (77.22)	872 (69.32)	911 (86.68)	

Factors associated with hand washing	India				Bangladesh				Nepal			
	Overall (*n*=10 399)	**Hand washing (*n*=2677)**	**No hand washing (*n*=7722)**	***p*-value[a]**	**Overall (*n*=21 952)**	**Hand washing (*n*=17 639)**	**No hand washing (*n*=4313)**	***p*-value[a]**	**Overall (*n*=2309)**	**Hand washing (*n*=1258)**	**No hand washing (*n*=1051)**	***p*-value[a]**
Maternal education, *n* (%)												
No education	7797 (74.98)	1783 (66.60)	6014 (77.88)	<0.001	6013 (27.39)	4467 (25.32)	1546 (35.85)	<0.001	1967 (85.19)	1007 (80.05)	960 (91.34)	<0.001
Primary	525 (5.05)	191 (7.13)	334 (4.33)		7967 (36.29)	6302 (35.73)	1665 (38.60)		240 (10.39)	165 (12.12)	75 (7.14)	
Secondary	2077 (17.79)	703 (26.26)	1374 (17.79)		7968 (36.29)	6867 (38.93)	1101 (25.53)		102 (4.42)	86 (6.84)	16 (1.52)	
Missing	0 (0.00)	0 (0.00)	0 (0.00)		4 (0.02)	3 (0.02)	1 (0.02)		0 (0.00)	0 (0.00)	0 (0.00)	
Maternal age in years, *n* (%)												
<20	1021 (9.82)	307 (11.47)	714 (9.25)	<0.001	3156 (14.38)	2596 (14.72)	560 (12.98)	<0.001	172 (7.45)	102 (8.11)	70 (6.66)	<0.001
20–29	5488 (52.77)	1538 (57.48)	3950 (51.15)		14238 (64.86)	11518 (65.30)	2720 (63.07)		1384 (59.94)	803 (63.83)	581 (55.28)	
30–39	2155 (20.72)	414 (15.47)	1741 (22.55)		4287 (19.53)	3314 (18.79)	973 (22.56)		612 (26.50)	293 (23.29)	319 (30.35)	
40+	109 (1.07)	25 (0.93)	84 (1.09)		267 (1.22)	207 (1.17)	60 (1.39)		141 (6.11)	60 (4.77)	81 (7.71)	
Missing	1626 (15.54)	393 (14.68)	1233 (15.97)		4 (0.02)	4 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	

Factors associated with hand washing	India				Bangladesh				Nepal			
	Overall (*n*=10 399)	**Hand washing (*n*=2677)**	**No hand washing (*n*=7722)**	***p*-value[a]**	**Overall (*n*=21 952)**	**Hand washing (*n*=17 639)**	**No hand washing (*n*=4313)**	***p*-value[a]**	**Overall (*n*=2309)**	**Hand washing (*n*=1258)**	**No hand washing (*n*=1051)**	***p*-value[a]**
Household assets, *n* (%)												
All	1630 (15.67)	506 (18.90)	1124 (14.56)	<0.001	8275 (37.70)	7038 (39.90)	1237 (28.68)	<0.001	56 (2.43)	48 (3.82)	8 (0.76)	<0.001
Some	6557 (63.05)	1634 (61.04)	4923 (63.75)		5417 (24.68)	4355 (24.69)	1062 (24.62)		1009 (43.70)	582 (46.26)	427 (40.63)	
None	2212 (21.27)	537 (20.06)	1675 (21.69)		8260 (37.63)	6246 (35.41)	2014 (46.70)		1243 (53.83)	627 (49.84)	616 (58.61)	
Missing	0.00	0.00	0.00		0 (0.00)	0 (0.00)	0 (0.00)		1 (0.04)	1 (0.08)	0 (0.00)	
Parity, *n* (%)												
1	2340 (22.50)	684 (25.55)	1656 (21.45)	<0.001	6507 (29.64)	5504 (31.20)	1003 (23.26)	<0.001	266 (11.52)	159 (12.64)	107 (10.18)	<0.001
2	2410 (23.18)	654 (24.43)	1756 (22.74)		6318 (28.68)	5171 (29.32)	1147 (26.59)		481 (20.83)	291 (22.13)	190 (18.08)	
3	1878 (18.06)	519 (19.39)	1359 (17.60)		4201 (19.14)	3278 (18.58)	923 (21.40)		446 (19.32)	263 (20.91)	183 (17.41)	
4	3757 (36.13)	816(30.48)	2941 (38.09)		4923 (22.43)	3683 (20.88)	1240 (28.75)		1163 (48.33)	545 (43.32)	571 (54.33)	
Missing	14 (0.13)	4 (0.15)	10 (0.13)		3 (0.01)	3 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	

Factors associated with hand washing	India				Bangladesh				Nepal			
	Overall (*n*=10 399)	Hand washing (*n*=2677)	No hand washing (*n*=7722)	*p*-value[a]	Overall (*n*=21 952)	Hand washing (*n*=17 639)	No hand washing (*n*=4313)	*p*-value[a]	Overall (*n*=2309)	Hand washing (*n*=1258)	No hand washing (*n*=1051)	*p*-value[a]
Number of antenatal care visits, *n* (%)												
0	3413 (32.82)	755 (28.20)	2658 (34.42)	<0.001	7931 (36.13)	5973 (33.86)	1958 (45.40)	<0.001	1533 (66.39)	755 (60.02)	778 (74.02)	<0.001
1	1471 (14.15)	386 (14.42)	1085 (14.05)		4768 (21.72)	3805 (21.57)	963 (22.33)		257 (11.13)	138 (10.97)	119 (11.32)	
2	2375 (22.84)	560 (20.92)	1815 (23.50)		3423 (15.59)	2844 (16.12)	579 (13.42)		189 (8.19)	116 (9.22)	73 (6.95)	
3	1528 (14.69)	452 (16.88)	1076 (13.93)		2584 (11.77)	2157 (12..23)	427 (9.90)		162 (7.02)	111 (8.82)	51 (4.85)	
4	1606 (15.44)	522 (19.50)	1084 (14.04)		3232 (14.72)	2850 (16.16)	382 (8.82)		168 (7.28)	138 (10.97)	30 (2.85)	
Missing	6 (0.06)	2 (0.07)	4 (0.06)		14 (0.06)	10 (0.06)	4 (0.09)		0 (0.00)	0 (0.00)	0 (0.00)	
Skilled birth attendant, *n* (%)												
No	9816 (94.39)	2259 (84.39)	7557 (97.86)	<0.001	21276 (96.92)	16987 (96.30)	4289 (99.44)	<0.001	2302 (99.70)	1253 (99.60)	1049 (99.81)	0.466
Yes	523 (5.03)	410 (15.32)	113 (1.46)		666 (3.03)	642 (3.64)	24 (0.56)		7 (0.30)	5 (0.40)	2 (0.19)	
Missing	60 (0.58)	8 (0.30)	52 (0.67)		10 (0.05)	10 (0.06)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

Table A6b: Comparison of deliveries with and without clean delivery kit use

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall	**Kit use**	**No kit use**	***p*-value[a]**	**Overall**	**Kit use**	**No Kit use**	***p*-value[a]**	**Overall**	**Kit use**	**No Kit use**	***p*-value[a]**
	(*n*=10 962)	**(*n*=1684)**	**(*n*=9278)**		**(*n*=25 217)**	**(*n*=3901)**	**(*n*=21 316)**		**(*n*=690)**	**(*n*=157)**	**(*n*=533)**	
Postpartum maternal death, *n* (%)												
No	10944 (99.84)	1682 (99.88)	9262 (99.88)	1.00	25179 (99.85)	3893 (99.79)	21286 (99.86)	0.341	690 (100.00)	157 (100.00)	533 (100.00)	b
Yes	18 (0.16)	2 (0.12)	16 (0.17)		38 (0.15)	8 (0.21)	30 (0.14)		0 (0.00)	0 (0.00)	0 (0.00)	
Missing	0 (0.00)	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	
Hand washing, *n* (%)												
No	7699 (70.23)	856 (50.83)	6843 (73.76)	<0.001	4300 (17.05)	247 (6.33)	4053 (19.01)	<0.001	140 (20.29)	6 (3.82)	134 (25.14)	<0.001
Yes	2650 (24.17)	743 (44.12)	1907 (20.55)		17455 (69.22)	3225 (82.67)	14230 (66.76)		386 (55.94)	133 (84.71)	253 (47.47)	
Missing	613 (5.59)	85 (5.05)	528 (5.69)		3462 (13.73)	429 (11.00)	3033 (14.23)		164 (23.77)	18 (11.46)	146 (27.39)	
Maternal education, *n* (%)												
No education	8193 (74.74)	1128 (66.98)	7065 (76.15)	<0.001	6800 (26.97)	852 (21.84)	5948 (27.90)	<0.001	479 (69.42)	94 (59.87)	385 (72.23)	<0.001
Primary	562 (5.13)	88 (5.23)	474 (5.11)		9170 (36.36)	1301 (33.35)	7869 (36.92)		144 (20.87)	34 (21.66)	110 (20.64)	
Secondary	2207 (20.13)	468 (27.79)	1739 (18.74)		9242 (36.65)	1748 (44.81)	7494 (35.16)		67 (9.71)	29 (18.47)	38 (7.13)	
Missing	0 (0.00)	0 (0.00)	0 (0.00)		5 (0.02	0 (0.00)	5 (0.02)		0 (0.00)	0 (0.00)	0 (0.00)	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall	Kit use	No kit use	*p*-value[a]	Overall	Kit use	No Kit use	*p*-value[a]	Overall	Kit use	No Kit use	*p*-value[a]
	(*n*=10 962)	(*n*=1684)	(*n*=9278)		(*n*=25 217)	(*n*=3901)	(*n*=21 316)		(*n*=690)	(*n*=157)	(*n*=533)	
Maternal age in years, *n* (%)												
<20	1098 (10.02)	182 (10.81)	916 (9.87)	0.002	3808 (15.01)	701 (17.97)	3107 (14.58)	<0.001	54 (7.83)	15 (9.55)	39 (7.32)	0.701
20–29	5759 (52.54)	941 (55.88)	4818 (51.93)		16311 (64.68)	2500 (64.09)	13811 (64.79)		471 (68.26)	104 (66.24)	367 (68.86)	
30–39	2242 (20.45)	320 (19.00)	1922 (20.72)		4802 (19.04)	673 (17.25)	4129 (19.37)		137 (19.86)	33 (21.02)	104 (19.51)	
40+	113 (1.03)	12 (0.71)	101 (1.09)		291 (1.15)	27 (0.69)	264 (1.24)		28 (4.06)	5 (3.18)	23 (4.32)	
Missing	1750 (15.96)	220 (13.60)	1521 (16.39)		5 (0.02)	0 (0.00)	5 (0.02)		0 (0.00)	0 (0.00)	0 (0.00)	
Household assets, *n* (%)												
All	1724 (15.73)	279 (16.57)	1445 (15.57)	0.527	9498 (37.67)	1809 (46.37)	7689 (36.07)	<0.001	27 (3.91)	9 (5.73)	18 (3.38)	0.015
Some	6924 (63.16)	1046 (62.11)	5878 (63.35)		6315 (25.04)	901 (23.10)	5414 (25.40)		364 (52.75)	95 (60.51)	269 (50.47)	
None	2314 (21.11)	359 (21.32)	1955 (21.07)		9404 (37.29)	1191 (30.53)	8213 (38.53)		299 (43.33)	53 (33.76)	246 (46.15)	
Missing	0 (0.00)	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	0 (0.00)	

Factors associated with kit use	India				Bangladesh				Nepal			
	Overall	**Kit use**	**No kit use**	***p*-value**[a]	**Overall**	**Kit use**	**No Kit use**	***p*-value**[a]	**Overall**	**Kit use**	**No Kit use**	***p*-value**[a]
	(*n*=10 962)	**(*n*=1684)**	**(*n*=9278)**		**(*n*=25 217)**	**(*n*=3901)**	**(*n*=21 316)**		**(*n*=690)**	**(*n*=157)**	**(*n*=533)**	
Parity, *n* (%)												
1	2527 (23.05)	424 (25.18)	2103 (22.67)	0.002	7645 (30.32)	1447 (37.09)	6198 (29.08)	<0.001	84 (12.17)	25 (15.92)	59 (11.07)	0.136
2	2521 (23.00)	412 (24.47)	2109 (22.73)		7291 (28.91)	1148 (29.43)	6143 (28.82)		171 (24.78)	45 (28.66)	126 (34.64)	
3	1990 (18.15)	316 (18.76)	1674 (18.04)		4766 (18.90)	695 (17.82)	4071 (19.10)		174 (25.22)	36 (22.93)	138 (25.89)	
4	3909 (35.66)	531 (31.53)	3378 (36.41)		5512 (21.86(	611 (15.66)	4901 (22.99)		261 (37.83)	51 (32.48)	210 (39.40)	
Missing	15 (0.14)	1 (0.06)	14 (0.15)		3 (0.01)	0 (0.00)	3 (0.01)		0 (0.00)	0 (0/00)	0 (0.00)	
Number of antenatal care visits, *n* (%)												
0	3571 (32.58)	349 (20.72)	3222 (34.73)	<0.001	9101 (36.09)	635 (16.28)	8466 (39.72)	<0.001	309 (44.78)	39 (24.84)	270 (50.66)	<0.001
1	1552 (14.16)	211 (12.53)	1341 (14.45)		5502 (21.82)	651 (16.69)	4851 (22.76)		107 (15.51)	26 (16.56)	81 (15.20)	
2	2492 (22.73)	424 (25.18)	2068 (22.29)		3975 (15.76)	662 (16.97)	3313 (15.54)		87 (12.61)	17 (10.83)	70 (13.13)	
3	1612 (14.71)	292 (17.34)	1320 (14.23)		2943 (11.67)	702 (18.00)	2241 (10.51)		98 (14.20)	29 (18.47)	69 (12.95)	
4	1728 (15.76)	405 (24.05)	1323 (14.26)		3679 (14.59)	1243 (31.86)	2436 (11.43)		89 (12.90)	46 (29.30)	43 (8.07)	
Missing	7 (0.06)	3 (0.18)	4 (0.04)		17 (0.07)	8 (0.21)	9 (0.04)		0 (0.00)	0 (0.00)	0 (0.00)	

Factors associated with kit use	**India**				**Bangladesh**				**Nepal**			
	Overall	**Kit use**	**No kit use**	***p*-value[a]**	**Overall**	**Kit use**	**No Kit use**	***p*-value[a]**	**Overall**	**Kit use**	**No Kit use**	***p*-value[a]**
	(*n*=10 962)	**(*n*=1684)**	**(*n*=9278)**		**(*n*=25 217)**	**(*n*=3901)**	**(*n*=21 316)**		**(*n*=690)**	**(*n*=157)**	**(*n*=533)**	
Skilled birth attendant, *n* (%)												
No	10332 (94.25)	1404 (83.37)	8928 (96.23)	<0.001	24421 (96.84)	3680 (94.33)	20741 (97.30)	<0.001	687 (99.57)	154 (98.09)	533 (100.00)	0.001
Yes	569 (5.19)	273 (16.21)	296 (3.19)		781 (3.10)	218 (5.59)	563 (2.64)		3 (0.43)	3 (1.91)	0 (0.00)	
Missing	61 (0.56)	7 (0.42)	54 (0.58)		15 (0.06)	3 (0.08)	12 (0.06)		0 (0.00)	0 (0.00)	0 (0.00)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate
b. Not possible to obtain *p*-value for this association.

Table A6c: Comparison between deliveries with complete information on hand washing and deliveries with missing information on hand washing

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**
	(*n*=34 660)	**(*n*=5942)**		**(*n*=10 399)**	**(*n*=664)**		**(*n*=21 952)**	**(*n*=3639)**		**(*n*=2309)**	**(*n*=1639)**	
Postpartum maternal death, *n* (%)												
No	34601 (99.83)	5928 (99.76)	0.272	10381 (99.83)	664 (100.00)	0.623	21919 (99.85)	3629 (99.73)	0.090	2301 (99.65)	1635 (99.76)	0.771
Yes	59 (0.17)	14 (0.24)		18 (0.17)	0 (0.00)		33 (0.15)	10 (0.27)		8 (0.35)	4 (0.24)	
Neonatal death, *n* (%)												
Alive at 28 days	32493 (93.75)	5622 (94.6)	0.014	9540 (94.38)	611 (95.77)	0.137	20796 (97.19)	3420 (96.39)	0.009	2157 (95.57)	1591 (98.45)	<0.001
Neonatal death,	1270 (3.66)	180 (3.03)		568 (5.62)	27 (4.23)		602 (2.81)	128 (3.61)		100 (4.43)	25 (1.55)	
Stillbirth, *n* (%)												
No	33763 (97.41)	5802 (97.64)	0.295	10108 (97.20)	638 (96.08)	0.094	21398 (97.48)	3548 (97.50)	0.935	2257 (97.75)	1616 (98.60)	0.054
Yes	897 (2.59)	140 (2.36)		291 (2.80)	26 (3.92)		554 (2.52)	91 (2.50)		52 (2.25)	23 (1.40)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**
	(*n*=34 660)	**(*n*=5942)**		**(*n*=10 399)**	**(*n*=664)**		**(*n*=21 952)**	**(*n*=3639)**		**(*n*=2309)**	**(*n*=1639)**	
Use of clean delivery kit, *n* (%)												
No	27420 (79.11)	3707 (62.39)	<0.001	8750 (84.14)	528 (79.52)	<0.001	18283 (83.29)	3033 (83.35)	<0.001	387 (16.76)	146 (8.91)	<0.001
Yes	5210 (15.03)	532 (8.95)		1599 (15.38)	85 (12.80)		3472 (15.82)	429 (11.78)		139 (6.02)	18 (1.10)	
Missing	2030 (5.86)	1703 (28.66)		50 (0.48)	51 (7.68)		197 (0.90)	177 (4.86)		1783 (77.22)	1475 (89.99)	
Maternal education, *n* (%)												
No education	15777 (45.52)	2787 (46.90)	0.088	7797 (74.98)	463 (69.73)	0.009	6013 (27.39)	863 (23.72)	<0.001	1967 (85.19)	1461 (89.14)	0.001
Primary	8732 (25.19)	1507 (25.36)		525 (5.05)	44 (6.63)		7967 (36.29)	1339 (36.80)		240 (10.39)	124 (7.57)	
Secondary	10147 (29.28)	1647 (27.72)		2077 (19.77)	157 (23.64)		7968 (36.30)	1436 (39.46)		102 (4.42)	54 (3.29)	
Missing	4 (0.01)	1 (0.02)		0 (0.00)	0 (0.00)		4 (0.02)	1 (0.03)		0 (0.00)	0 (0.00)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**
	(*n*=34 660)	**(*n*=5942)**		**(*n*=10 399)**	**(*n*=664)**		**(*n*=21 952)**	**(*n*=3639)**		**(*n*=2309)**	**(*n*=1639)**	
Maternal age, *n* (%)												
<20	4349 (12.55)	913 (15.37)	<0.001	1021 (9.82)	92 (13.86)	<0.001	3156 (14.38)	714 (19.62)	<0.001	172 (7.75)	107 (6.53)	0.008
20–29	21110 (60.91)	3544 (59.64)		5488 (52.77)	317 (47.74)		14238 (64.86)	2315 (63.62)		1384 (59.94)	912 (55.64)	
30–39	7054 (20.35)	1185 (19.94)		2155)20.72)	100 (15.06)		4287 (19.53)	582 (15.99)		612 (26.50)	503 (30.69)	
40+	517 (1.49)	149 (2.51)		109 (1.05)	5 (0.75)		267 (1.22)	27 (0.74)		141 (6.11)	117 (7.14)	
Missing	1630 (4.70)	151 (2.54)		1626 (15.64)	150 (22.59)		4 (0.02)	1 (0.03)		0 (0.00)	0 (0.00)	
Household assets, *n* (%)												
All	9961 (28.74)	1554 (26.15)	<0.001	1630 (15.67)	117 (17.62)	0.193	8275 (37.70)	1406 (38.64)	0.001	56 (2.43)	31 (1.89)	<0.001
Some	12983 (37.46)	1996 (33.59)		6557 (63.05)	422 (63.55)		5417 (24.68)	974 (26.77)		1009 (43.70)	600 (36.61)	
None	11715 (33.80)	2392 (40.26)		2212 (21.27)	125 (18.83)		8260 (37.63)	1259 (34.63)		1243 (53.83)	1008 (61.50)	
Missing	1 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		1 (0.04)	0 (0.00)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**	**Hand washing data present**	**Hand washing data missing**	***p*-value [a]**
	(*n*=34 660)	**(*n*=5942)**		**(*n*=10 399)**	**(*n*=664)**		**(*n*=21 952)**	**(*n*=3639)**		**(*n*=2309)**	**(*n*=1639)**	
Parity, n (%)												
1	9113 (26.29)	1658 (27.90)	<0.001	2340 (22.50)	215 (32.38)	<0.001	6507 (29.64)	1280 (35.17)	<0.001	266 (11.52	163 (9.95)	<0.001
2	9209 (26.57)	1494 (25.14)		2410 (23.18)	139 (20.93)		6318 (28.78)	1065 (29.27)		481 (20.83)	290 (17.69)	
3	6525 (18.83)	1016 (17.10)		1878 (18.06)	128 (19.28)		4201 (19.14)	620 (17.04)		446 (19.32)	268 (16.35)	
4	9796 (28.26)	1773 (29.84)		3757 (36.13)	181 (27.26)		4823 (22.43)	674 (18.52)		1116 (48.33)	918 (56.1)	
Missing	17 (0.05)	1 (0.02)		14 (0.13)	1 (0.15)		3 (0.01)	0 (0.00)		0 (0.00)	0 (0.00)	
Number of antenatal care visits, *n* (%)												
0	12877 (37.15)	2700 (45.44)	<0.001	3413 (32.82)	198 (29.82)	0.005	7931 (36.13)	1274 (35.01)	0.089	1533 (66.39)	1228 (74.92)	<0.001
1	6496 (18.74)	1070 (18.01)		1471 (14.15)	94 (14.16)		4768 (21.72)	813 (22.34)		257 (11.13)	163 (9.95)	
2	5987 (17.27)	867 (14.59)		2375 (22.84)	137 (20.63)		3423 (15.59)	626 (17.20)		189 (8.19)	104 (6.35)	
3	4274 (12.33)	587 (9.88)		1582 (14.69)	94 (14.16)		2584 (11.77)	401 (11.02)		162 (7.02)	92 (5.61)	
4	5006 (14.44)	713 (12.00)		1606 (15.44)	140 (21.08)		3232 (14.72)	521 (14.32)		168 (7.28)	52 (3.17)	
Missing	20 (0.06)	5 (0.08)		6 (0.06)	1 (0.15)		14 (0.06)	4 (0.11)		0 (0.00)	0 (0.00)	

Factors associated with missing data on hand washing	Pooled data			India			Bangladesh			Nepal		
	Hand washing data present (*n*=34 660)	**Hand washing data missing (*n*=5942)**	***p*-value [a]**	**Hand washing data present (*n*=10 399)**	**Hand washing data missing (*n*=664)**	***p*-value [a]**	**Hand washing data present (*n*=21 952)**	**Hand washing data missing (*n*=3639)**	***p*-value [a]**	**Hand washing data present (*n*=2309)**	**Hand washing data missing (*n*=1639)**	***p*-value [a]**
Delivery by a skilled birth attendant, *n* (%)												
No	33394 (96.35)	5631 (94.77)	<0.001	9816 (94.39)	595 (89.61)	<0.001	21276 (96.92)	3397 (93.35)	<0.001	2302 (99.70)	1639 (100.00)	0.046
Yes	1196 (3.45)	301 (5.87)		523 (5.03)	67 (10.09)		666 (2.12)	234 (6.43)		7 (0.30)	0 (0.00)	
Missing	70 (0.20)	10 (0.17)		60 (0.58)	2 (0.30)		10 (0.05)	8 (0.22)		0 (0.00)	0 (0.00)	
Obstetric haemorrhage, *n* (%)												
No	22997 (66.35)	4040 (67.99)	<0.001	6392 (61.47)	357 (53.77)		14500 (66.05)	2166 (59.52)	<0.001	2105 (91.17)	1517 (92.56)	0.118
Yes	8006 (23.10)	1610 (27.10)		352 (3.38)	17 (2.56)		7450 (33.94)	1471 (40.42)		204 (8.83)	122 (7.44)	
Missing	3657 (10.55)	292 (4.91)		3655 (35.15)	290 (43.46)		2 (0.01)	3 (0.05)		0 (0.00)	0 (0.00)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

Table A6d: Comparison between deliveries with complete information on clean delivery kit use and deliveries with missing information on kit use

Factors associated with missing data on clean delivery kit use	Pooled data			India			Bangladesh			Nepal		
	Data for kit use present (*n*=36 869)	Data for kit use missing (*n*=3733)	*p*-value [a]	Data for kit use present (*n*=10 962)	Data for kit use missing (*n*=101)	*p*-value [a]	Data for kit use present (*n*=25 217)	Data for kit use missing (*n*=374)	*p*-value [a]	Data for kit use present (*n*=690)	Data for kit use missing (*n*=3258)	*p*-value [a]
Postpartum maternal death, *n* (%)												
No	36813 (99.85)	3716 (99.54)	<0.001	10944 (99.84)	101 (100.00)	1.00	25179 (99.85)	369 (98.66)	<0.001	690 (100.00)	3246 (99.63)	0.242
Yes	56 (0.15)	17 (0.46)		18 (0.16)	0 (0.00)		38 (0.15)	5 (1.34)		0 (0.00)	12 (0.37)	
Neonatal death, *n* (%)												
Alive at 28 days	34591 (96.31)	3524 (94.40)	0.473	10067 (94.51)	84 (89.36)	0.030	23877 (97.07)	339 (96.03)	0.243	647 (96.57)	3101 (96.82)	0.741
Neonatal death	1324 (3.69)	126 (3.45)		585 (5.49)	10 (10.64)		716 (2.91)	14 (3.97)		23 (3.43)	102 (3.18)	
Stillbirth, *n* (%)												
No	35015 (97.41)	3650 (97.78)	0.179	10652 (97.17)	94 (93.07)	0.014	24593 (97.53)	353 (94.39)	<0.001	670 (97.10)	3203 (98.31)	0.034
Yes	954 (2.59)	83 (2.22)		310 (2.83)	7 (6.93)		624 (2.47)	21 (5.61)		20 (2.90)	55 (1.69)	

Factors associated with missing data on clean delivery kit use	Pooled data			India			Bangladesh			Nepal		
	Data for kit use present	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**
	(*n*=36 869)	**(*n*=3733)**		**(*n*=10 962)**	**(*n*=101)**		**(*n*=25 217)**	**(*n*=374)**		**(*n*=690)**	**(*n*=3258)**	
Hand washing, *n* (%)												
No	12139 (32.92)	947 (25.37)	<0.001	7699 (70.23)	23 (22.77)	<0.001	4300 (17.05)	13 (3.48)	<0.001	140 (20.29)	911 (27.96)	<0.001
Yes	20491 (55.58)	1083 (29.01)		2650 (24.17)	27 (26.73)		17455 (69.22)	184 (49.20)		386 (55.94)	872 (26.76)	
Missing	4239 (11.50)	1703 (45.62)		613 (5.59)	51 (50.50		3462 (13.73)	177 (47.33)		164 (23.77)	1475 (45.27)	
Maternal education, *n* (%)												
No education	15472 (41.96)	3092 (82.83)	<0.001	8193 (74.14)	67 (66.34)	0.154	6800 (26.97)	76 (20.32)	0.014	479 (69.42)	2949 (90.52)	<0.001
Primary	9876 (26.79)	363 (9.72)		562 (5.13)	7 (6.93)		9170 (36.36)	136 (36.36)		144 (20.87)	220 (6.75)	
Secondary	11516 (31.23)	278 (7.45)		2207 (20.13)	27 (26.73)		9242 (36.65)	162 (43.32)		67 (9.71)	89 (2.73)	
Missing	5 (0.01)	0 (0.00)		0 (0.00)	0 (0.00)		5 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	

Factors associated with missing data on clean delivery kit use	Pooled data			India			Bangladesh			Nepal		
	Data for kit use present	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**
	(*n*=36 869)	**(*n*=3733)**		**(*n*=10 962)**	**(*n*=101)**		**(*n*=25 217)**	**(*n*=374)**		**(*n*=690)**	**(*n*=3258)**	
Maternal age in years, *n* (%)												
<20	4960 (13.45)	302 (8.09)	<0.001	1098 (10.02)	15 (13.85)	0.017	3808 (15.10)	62 (16.58)	0.87	54 (7.83)	225 (6.91)	<0.001
20–29	22541 (61.14)	2113 (56.60)		5759 (52.54)	46 (45.54)		16311 (64.68)	242 (64.71)		471 (68.26)	1825 (56.02)	
30–39	7181 (19.48)	1058 (28.34)		2242 (20.45)	13 (12.87		4802 (19.04)	67 (17.91)		137 (19.86)	978 (30.02)	
40+	432 (1.17)	234 (6.27)		113 (1.03)	1 (0.99)		291 (1.15)	3 (0.80)		28 (4.06)	230 (7.06)	
Missing	1755 (4.76)	26 (0.70)		1750 (15.96)	26 (25.74)		5 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	
Household assets, *n* (%)												
All	11249 (30.51)	266 (7.13)	<0.001	1724 (15.73)	23 (22.77)	0.106	9498 (37.67)	183 (48.93)	<0.001	27 (3.91)	60 (1.84)	<0.001
Some	13603 (36.90)	1376 (36.86)		6924 (63.16)	55 (54.46)		6315 (25.04)	76 (20.32)		364 (52.75)	1245 (38.21)	
None	12017 (32.59)	2090 (55.99)		2314 (21.11)	23 (22.77)		9404 (37.29)	115 (30.75)		299 (43.33)	1952 (59.91)	
Missing	0 (0.00)	1 (0.03)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	

Factors associated with missing data on clean delivery kit use	Pooled data			India			Bangladesh			Nepal		
	Data for kit use present	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**
	(*n*=36 869)	**(*n*=3733)**		**(*n*=10 962)**	**(*n*=101)**		**(*n*=25 217)**	**(*n*=374)**		**(*n*=690)**	**(*n*=3258)**	
Parity, n (%)												
1	10256 (27.82)	515 (13.80)	<0.001	2527 (23.05)	28 (27.72)	0.447	7645 (30.32)	142 (37.97)	0.011	84 (12.17)	345 (10.59)	<0.001
2	9983 (27.08)	720 (19.29)		2521 (23.00)	28 (27.72)		7291 (28.91)	92 (24.60)		171 (24.78)	600 (18.42)	
3	6930 (18.80)	611 (16.37)		1990 (18.15)	16 (15.84)		4766 (18.90)	55 (14.71)		174 (25.22)	540 (16.57)	
4	9682 (26.26)	1887 (50.55)		3909 (35.06)	29 (28.71)		5512 (21.86)	85 (22.73)		261 (37.83)	1773 (54.42)	
Missing	18 (0.05)	0 (0.00)		15 (0.14)	0 (0.00)		3 (0.01)	0 (0.00)		0 (0.00)	0 (0.00)	
Number of antenatal care visits, *n* (%)												
0	12981 (35.21)	2596 (69.54)	<0.001	3571 (32.58)	40 (39.60)	0.561	9101 (36.09)	104 (27.81)	0.001	309 (44.78)	2452 (75.26)	<0.001
1	7161 (19.42)	405 (10.85)		1552 (14.16)	13 (12.87)		5502 (21.82)	79 (21.12)		107 (15.51)	313 (9.61)	
2	6554 (17.78)	30 (8.04)		2492 (22.73)	20 (19.80)		3975 (15.76)	74 (19.79)		87 (12.61)	206 (6.32)	
3	4653 (12.62)	208 (5.57)		1612 (14.71)	10 (9.90)		2943 (11.67)	42 (11.23)		98 (14.20)	156 (4.79)	
4	5496 (14.91)	223 (5.97)		1728 (15.76)	18 (17.82)		3679 (14.59)	74 (19.79)		89 (12.90)	131 (4.02)	
Missing	24 (0.07)	1 (0.03)		7 (0.06)	0 (0.00)		17 (0.07)	1 (0.27)		0 (0.00)	0 (0.00)	

Factors associated with missing data on clean delivery kit use	**Pooled data**			**India**			**Bangladesh**			**Nepal**		
	Data for kit use present	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**	**Data for kit use present**	**Data for kit use missing**	***p*-value [a]**
	(*n*=36 869)	**(*n*=3733)**		**(*n*=10 962)**	**(*n*=101)**		**(*n*=25 217)**	**(*n*=374)**		**(*n*=690)**	**(*n*=3258)**	
Delivery by a skilled birth attendant, *n* (%)												
No	35440 (96.12)	3585 (96.03)	0.366	10332 (94.25)	79 (78.22)	<0.001	24421 (96.84)	252 (67.38)	<0.001	687 (99.57)	3254 (99.88)	0.077
Yes	1353 (3.67)	144 (3.86)		569 (5.19)	21 (20.79)		781 (3.10)	119 (31.82)		3 (0.43)	4 (0.12)	
Missing	76 (0.21)	4 (0.11)		61 (0.56)	1 (0.99)		15 (0.06)	3 (0.80)		0 (0.00)	0 (0.00)	
Obstetric haemorrhage, *n* (%)												
No	23816 (64.60)	3221 (86.82)	<0.001	6711 (61.22)	38 (37.62)	<0.001	16467 (65.30)	199 (53.21)	<0.001	638 (92.46)	2984 (91.59)	0.449
Yes	9164 (24.86)	452 (12.11)		366 (3.34)	3 (2.97)		8746 (34.68)	175 (46.79)		52 (7.54)	274 (8.41)	
Missing	3889 (10.55)	60 (1.61)		3885 (35.44)	60 (59.41)		4 (0.02)	0 (0.00)		0 (0.00)	0 (0.00)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate

Table A6e: Missing data patterns for models estimating the effect of kit use or hand washing on maternal mortality where "1" indicates a variable is present in the missing data pattern, and "0" indicates a variable is absent in the missing data pattern

	Missing data pattern							
Percent	Household assets	Education	Parity	Antenatal care visits	Skilled birth attendant	Maternal age	Kit use	Hand wash
76	1	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1	0
5	1	1	1	1	1	1	0	1
4	1	1	1	1	1	1	0	0
4	1	1	1	1	1	0	1	1
<1	1	1	1	1	1	0	1	0
<1	1	1	1	1	0	1	1	1
<1	1	1	1	1	0	0	1	1
<1	1	1	1	0	1	1	1	1
<1	1	1	0	1	1	1	1	1
<1	1	1	1	1	1	0	0	0
<1	1	1	1	1	1	0	0	0
<1	1	1	1	1	0	1	1	0
<1	1	0	1	1	1	1	1	1
<1	1	1	0	1	1	1	1	1
<1	1	1	1	0	1	1	1	0
<1	1	1	1	1	0	1	0	1
<1	0	1	1	1	1	1	0	1
<1	1	0	1	1	1	0	1	0
<1	1	1	0	1	1	0	1	0
<1	1	1	1	0	0	1	1	1
<1	1	1	1	0	1	0	1	0
<1	1	1	1	0	1	1	1	1
<1	1	1	1	0	1	1	0	0
<1	1	1	1	1	0	0	0	0

Appendix 7: Tables from Chapter 7 examining the influence of women's groups on the use clean delivery practices in rural South Asia

Table A7a: Comparison of maternal and delivery characteristics between intervention and control arms using data collected for the first six months for each of the four cRCTs

Potential source of bias	Pooled data			India			Bangladesh 1			Bangladesh 2			Nepal		
	Control	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**
Attended a women's group meeting in intervention clusters, *n* (%)															
No	c	23307 (79.7)	c	c	5155 (62.2)	c	c	13008 (96.7)	c	c	3391 (70.7)	c	c	1753 (64.2)	c
Yes	c	5933 (20.3)		c	3131 (37.8)		c	419 (3.1)		c	1407 (29.3)		c	976 (35.8)	
Number of antenatal care visits, *n* (%)															
0	2258 (44.2)	2256 (42.9)	<0.001	383 (32.8)	511 (40.3)	<0.001	818 (48.8)	977 (58.7)	<0.001	448 (31.6)	418 (26.6)	0.004	609 (72.4)	350 (46.5)	<0.001
1	923 (18.1)	859 (16.3)		182 (15.6)	202 (15.9)		346 (20.6)	240 (14.4)		309 (21.8)	327 (20.8)		86 (10.2)	90 (12.0)	
2	752 (14.7)	865 (16.5)		233 (20.0)	261 (20.6)		246 (14.7)	204 (12.3)		213 (15.0)	303 (19.3)		60 (7.1)	97 (12.9)	
3	576 (11.3)	565 (10.7)		198 (17.0)	136 (10.7)		143 (8.5)	114 (6.9)		181 (12,8)	220 (14.0)		54 (6.4)	95 (12.6)	
4	595 (11.7)	714 (13.6)		172 (14.7)	158 (12.5)		123 (7.3)	129 (7.8)		268 (18.9)	306 (19.4)		32 (3.8)	121 (16.1)	

Potential source of bias	Pooled data			India			Bangladesh 1			Bangladesh 2			Nepal		
	Control	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]
Type of birth attendant, *n* (%)															
Skilled	182 (3.6)	110 (2.1)	<0.001	55 (4.7)	29 (2.3)	<0.001	50 (3.0)	21 (1.3)	<0.001	75 (5.3)	54 (3.4)	<0.001	2 (0.24)	6 (0.8)	0.017
Unskilled but trained	2866 (56.0)	3322 (63.0)		546 (46.67)	501 (39.2)		1037 (61.6)	1304 (78.0)		1234 (87.0)	1450 (92.1)		49 (5.8)	67 (8.9)	
Unskilled and untrained	2060 (40.3)	1835 (34.8)		563 (48.1)	740 (58.1)		597 (35.5)	346 (20.7)		110 (7.8)	70 (4.5)		790 (93.9)	680 (90.3)	
Clean delivery practices															
Use of clean delivery kit, *n* (%)															
No	3695 (85.6)	3679 (77.9)	<0.001	1040 (89.8)	1137 (89.5)	0.819	1378 (85.2)	1050 (64.7)	<0.001	1183 (84.0)	1302 (84.8)	0.572	95 (70.9)	190 (65.3)	0.253
Yes	621 (14.4)	1041 (22.1)		118 (10.2)	133 (10.5)		239 (14.8)	573 (35.3)		225 (16.0)	234 (15.2)		39 (29.1)	101 (34.7)	
Birth attendant washed hands prior to delivery, *n* (%)															
No	1544 (36.3)	1930 (29.5)	<0.001	750 (69.0)	833 (70.4)	0.482	406 (27.0)	290 (19.1)	<0.001	172 (14.8)	131 (9.4)	<0.001	216 (43.4)	136 (22.3)	<0.001
Yes	2708 (63.7)	3327 (70.5)		337 (31.0)	351 (29.7)		1096 (73.0)	1231 (80.9)		993 (85.2)	1270 (90.7)		282 (56.6)	475 (77.7)	

Potential source of bias	Pooled data			India			Bangladesh 1			Bangladesh 2			Nepal		
	Control	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**
Used of sterilised blade to cut the cord [b], *n* (%)															
No	2339 (49.4)	2070 (42.3)	<0.001	883 (82.8)	945 (79.7)	0.062	345 (21.8)	400 (25.6)	0.012	492 (38.9)	392 (27.8)	<0.001	619 (75.9)	333 (45.4)	<0.001
Yes	2392 (50.6)	2822 (57.7)		184 (17.2)	241 (20.3)		1239 (78.2)	1164 (74.4)		772 (61.1)	1017 (72.2)		197 (24.1)	400 (54.6)	
Use of sterilised thread to tie the cord[b], *n* (%)															
No	1961 (50.4)	1865 (44.9)	<0.001	964 (89.1)	1028 (85.5)	0.011	439 (28.0)	420 (26.9)	0.501	558 (44.9)	417 (29.9)	<0.001	d	d	d
Yes	1932 (49.6)	2292 (55.1)		118 (10.9)	174 (14.5)		1128 (72.0)	1139 (73.1)		686 (55.1)	979 (70.1)		d	d	
Use of plastic sheet, *n* (%)															
No	2862 (67.0)	2261 (50.1)	<0.001	1116 (95.5)	672 (52.8)	<0.001	1171 (69.5)	1078 (64.5)	0.002	575 (40.6)	511 (32.6)	<0.001	d	d	d
Yes	1409 (33.0)	2249 (49.9)		53 (4.5)	601 (47.2)		513 (30.5)	593 (35.5)		843 (59.5)	1055 (67.4)		d	d	
Missing															
Use of gloves to assist delivery, *n* (%)															
No	3908 (92.1)	4265 (94.8)	<0.001	1123 (96.0)	1251 (98.2)	0.001	1561 (92.7)	1596 (95.5)	0.001	1224 (88.0)	1418 (91.2)	0.004	d	d	d
Yes	337 (7.9)	235 (5.2)		47 (4.0)	23 (1.8)		123 (7.3)	75 (4.5)		167 (12.1)	137 (8.8)		d	d	

Potential source of bias	Pooled data			India			Bangladesh 1			Bangladesh 2			Nepal		
	Control	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]	**Control**	**Intervention**	***p*-value**[a]
Practiced dry cord care [b], n (%)															
No	1875 (38.1)	1916 (37.7)	0.715	174 (15.3)	411 (33.1)	<0.001	302 (18.9)	169 (10.7)	<0.001	1182 (85.4)	1189 (77.7)	<0.001	217 (26.9)	147 (20.3)	0.002
Yes	3052 (61.9)	3166 (62.3)		963 (84.7)	832 (66.9)		1298 (81.1)	1415 (89.3)		202 (14.6)	341 (22.3)		589 (73.1)	578 (79.7)	
Application of antiseptic to the cord [c], n (%)															
No	4791 (97.2)	4895 (96.3)	0.009	1120(98.5)	1226 (98.6)	0.793	1583 (98.9)	1578 (99.6)	0.023	1284 (92.8)	1374 (89.8)	0.005	804 (99.8)	717 (98.9)	0.038
Yes	136 (2.8)	187 (3.7)		17 (1.5)	17 (1.4)		17 (1.1)	6 (0.4)		100 (7.2)	156 (10.2)		2 (0.3)	8 (1.1)	
Maternal characteristics															
Maternal education, *n* (%)															
Secondary	1240 (24.3)	1193 (22.6)	0.150	227 (19.4)	227 (17.8)	0.516	412 (24.5)	369 (22.1)	<0.001	566 (39.9)	543 (34.5)	0.010	35 (4.2)	54 (7.2)	<0.001
Primary	1296 (25.3)	1362 (25.8)		54 (4.6)	54 (4.2)		640 (38.0)	557 (33.3)		526 (37.1)	637 (40.5)		76 (9.0)	114 (15.1)	
No education	2578 (50.4)	2717 (51.5)		889 (76.0)	993 (77.9)		632 (37.5)	745 (44.6)		327 (23.0)	394 (25.0)		730 (86.8)	585 (77.7)	
Mean maternal age in years (SD)	25.4 (0.08)	25.1 (0.1)	0.011	25.3 (0.18)	25.0 (0.16)	0.283	25.0 (0.13)	24.9 (0.1)	0.61	24.8 (0.1)	24.7 (0.1)	0.649	27.3 (0.2)	26.4 (0.2)	0.013

Potential source of bias	Pooled data			India			Bangladesh 1			Bangladesh 2			Nepal		
	Control	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**	**Control**	**Intervention**	***p*-value[a]**
Household assets, *n* (%)															
All	2020 (39.5)	2089 (39.6)	0.057	227 (19.4)	307 (24.1)	0.016	921 (64.7)	917 (54.9)	<0.001	396 (27.9)	449 (28.5)	0.382	476 (56.6)	416 (55.3)	<0.001
Some	1864 (36.5)	2011 (38.1)		777 (66.4)	807 (63.3)		249 (14.8)	355 (21.2)		487 (34.3)	568 (36.1)		351 (41.7)	281 (37.3)	
None	1230 (24.1)	1172 (22.2)		166 (14.2)	160 (12.6)		514 (30.5)	399 (23.9)		536 (37.8)	557 (35.4)		14 (1.7)	56 (7.4)	
Parity, *n* (%)															
1	1313 (25.7)	1419 (26.9)	0.402	270 (23.1)	315 (24.8)	0.317	507 (30.1)	528 (31.6)	0.594	431 (30.4)	478 (30.4)	0.743	105 (12.5)	98 (13.0)	<0.001
2	1336 (26.1)	1382 (26.2)		260 (22.2)	291 (22.9)		488 (29.0)	452 (27.1)		422 (29.7)	462 (29.4)		166 (19.7)	177 (23.5)	
3	941 (18.4)	961 (18.2)		217 (18.6)	201 (15.8)		313 (18.6)	307 (18.4)		282 (19.9)	296 (18.8)		129 (15.3)	157 (20.9)	
4	1524 (29.8)	1506 (25.6)		423 (36.2)	463 (36.5)		376 (22.3)	384 (23.0)		284 (20.0)	338 (21.5)		441 (52.4)	321 (42.6)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate.
b. Excludes stillbirths.
c. Not applicable (women only attendant women's groups in the intervention arm).
d. Variables not collected for the Nepal cRCT.

Table A7b: Differences in missing data of factors associated with hand washing between intervention and control arms for the pooled dataset as well as the individual cRCTs

	Pooled data			India			Bangladesh			Bangladesh 2nd Trial			Nepal		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Clean delivery practices															
Clean delivery kit use, *n* (%)															
Present	24613 (89.2)	27379 (93.6)	<0.001	7194 (99.4)	8260 (99.7)	0.006	12376 (98.2)	13199 (98.3)	0.526	4500 (98.9)	4736 (98.7)	0.509	543 (16.9)	1184 (43.4)	<0.001
missing	2986 (10.8)	1861 (6.4)		44 (0.6)	26 (0.3)		227 (1.8)	228 (1.7)		52 (1.1)	62 (1.3)		2663 (83.1)	1545 (56.6)	
Hand washing, *n* (%)															
Present	23360 (84.6)	26065 (89.1)	<0.001	6857 (94.7)	7889 (95.2)	0.178	10840 (86.0)	11674 (86.9)	0.028	3800 (83.5)	4309 (89.8)	<0.001	1863 (58.1)	2193 (80.4)	<0.001
missing	4239 (15.4)	3175 (10.9)		381 (5.3)	397 (4.8)		1763 (14.0)	1753 (13.1)		752 (16.5)	489 (10.2)		1343 (41.9)	536 (19.6)	

	Pooled data			India			Bangladesh			Bangladesh 2nd Trial			Nepal		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Use of sterilised blade to cut the umbilical cord, *n* (%)															
Present	25544 (92.6)	27244 (93.2)	0.004	6758 (93.4)	7826 (94.5)	0.005	11569 (91.8)	12410 (92.4)	0.059	4092 (89.9)	4344 (90.5)	0.295	3125 (97.5)	2664 (97.6)	0.720
missing	2055 (7.5)	1996 (6.8)		480 (6.6)	460 (5.6)		1034 (8.2)	1017 (7.6)		460 (10.1)	454 (9.5)		81 (2.5)	65 (2.4)	
Use of sterilised thread to tie the cord, *n* (%)															
Present	22305 (91.4)	24531 (92.5)	<0.001	6823 (94.3)	7873 (95.0)	0.038	11441 (90.8)	12338 (91.9)	0.001	4041 (88.8)	4320 (90.0)	0.047	b	b	b
Missing	2088 (8.6)	1980 (7.5)		415 (5.7)	413 (5.0)		1162 (9.2)	1089 (8.1)		511 (11.2)	478 (10.0)		b	b	
Use of dry cord care, *n* (%)															
Present	9916 (35.9)	9609 (32.9)	<0.001	7048 (97.4)	8053 (97.2)	0.475	12151 (96.4)	12934 (96.3)	0.713	4552 (100.0)	4798 (100.0)	c	3099 (96.7)	2634 (96.5)	0.761
Missing	749 (2.7)	821 (2.8)		190 (2.6)	233 (2.8)		452 (3.6)	493 (3.7)		0 (0.0)	0 (0.0)		107 (3.3)	95 (3.5)	

	Pooled data			**India**			**Bangladesh**			**Bangladesh 2nd Trial**			**Nepal**		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Use of antiseptic to clean the cord only, *n* (%)															
Present	25869 (93.7)	27318 (93.4)	0.314	7048 (97.4)	8053 (97.2)	0.475	12151 (96.4)	12934 (96.3)	0.713	4552 (100.0)	4798 (100.0)	c	3099 (96.7)	2634 (96.5)	0.761
Missing	749 (2.7)	821 (2.8)		190 (2.6)	233 (2.8)		452 (3.6)	493 (3.7)		0 (0.0)	0 (0.0)		107 (3.3)	95 (3.5)	
Use of plastic sheet, *n* (%)															
Present	24384 (100.0)	26488 (99.9)	0.025	7236 (100.0)	8284 (100.0)	c	12603 (100.0)	13427 (100.0)	c	4545 (99.9)	4777 (99.6)	0.012	b	b	b
Missing	9 (0.0)	23 (0.1)		2 (0.0)	2 (0.0)		0 (0.0)	0 (0.0)		7 (0.1)	21 (0.4)		b	b	
Use of gloves to assist delivery, *n* (%)															
Present	24304 (99.6)	26477 (99.9)	<0.001	7238 (100.0)	8286 (100.0)	c	12603 (100.0)	13427 (100.0)	c	4463 (98.0)	4764 (99.3)	<0.001	b	b	b
Missing	89 (0.4)	34 (0.1)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		89 (2.0)	34 (0.7)		b	b	

	Pooled data			India			Bangladesh			Bangladesh 2nd Trial			Nepal		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Maternal characteristics															
Maternal education, *n* (%)															
Present	27595 (100.0)	29240 (100.0)	0.056	7238 (100.0)	8286 (100.0)	c	12603 (100.0)	13427 (100.0)	c	4548 (99.9)	4798 (100.0)	0.056	3206 (100.0)	2729 (100.0)	c
Missing	4 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		4 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Maternal age in years, *n* (%)															
Present	27091 (98.2)	28626 (97.9)	0.026	6733 (93.0)	7690 (92.8)	0.601	12600 (100.0)	13409 (99.9)	0.002	4552 (100.0)	4798 (100.0)	c	3206 (100.0)	2729 (100.0)	c
Missing	508 (1.8)	614 (2.1)		505 (7.0)	596 (7.2)		3 (0.0)	18 (0.1)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Household assets, *n* (%)															
Present	27599 (100.0)	29240 (100.0)	c	7238 (100.0)	8286 (100.0)	c	12603 (100.0)	13427 (100.0)	c	4552 (100.0)	4798 (100.0)	c	3206 (100.0)	2729 (100.0)	c
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

	Pooled data			India			Bangladesh			Bangladesh 2nd Trial			Nepal		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Parity, *n* (%)															
Present	27597 (100.0)	29233 (100.0)	0.114	7237 (100.0)	8279 (99.9)	0.075	12603 (100.0)	13427 (100.0)	c	4551 (100.0)	4798 (100.0)	0.487	3206 (100.0)	2729 (100.0)	c
Missing	2 (0.0)	7 (0.0)		1 (0.0)	7 (0.1)		0 (0.0)	0 (0.0)		1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Antenatal period															
Number of antenatal care visits, *n* (%)															
Present	27576 (99.9)	29197 (99.8)	0.026	7232 (99.9)	8258 (99.7)	0.001	12586 (99.9)	13413 (99.9)	0.474	4552 (100.0)	4797 (100.0)	1.000	3206 (100.0)	2729 (100.0)	c
Missing	23 (0.1)	43 (0.2)		6 (0.1)	28 (0.3)		17 (0.1)	14 (0.1)		0 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)	
Delivery period															
Obstetric Haemorrhage, *n* (%)															
Present	27591 (100.0)	29233 (100.0)	0.711	7233 (99.9)	99.9)	0.742	12603 (100.0)	13427 (100.0)	c	4549 (99.9)	4795 (99.9)	1.000	3206 (100.0)	2729 (100.0)	c
Missing	8 (0.0)	7 (0.0)		5 (0.1)	4 (0.1)		0 (0.0)	0 (0.0)		3 (0.1)	3 (0.1)		0 (0.0)	0 (0.0)	

	Pooled data			India			Bangladesh			Bangladesh 2nd Trial			Nepal		
	Intervention (*n*=27 599)	**Control (*n*=29 240)**	***p*-value[a]**	**Intervention (*n*=7238)**	**Control (*n*=8284)**	***p*-value[a]**	**Intervention (*n*=12 603)**	**Control (*n*=14 427)**	***p*-value[a]**	**Intervention (*n*=4552)**	**Control (*n*=4798)**	***p*-value[a]**	**Intervention (*n*=3206)**	**Control (*n*=2729)**	***p*-value[a]**
Skilled birth attendant, *n* (%)															
Present	27592 (99.9)	29227 (100.0)	0.016	7221 (99.8)	8273 (99.8)	0.270	12603 (100.0)	13427 (100.0)	c	4542 (99.8)	4798 (100.0)	0.001	3206 (100.0)	2729 (100.0)	c
Missing	27 (0.1)	13 (0.0)		17 (0.2)	13 (0.2)		0 (0.0)	0 (0.0)		10 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	

a. *p*-value obtained through chi-squared statistic or Fisher's exact test where appropriate.

b. Not collected for the Nepal cRCT.

c. Not possible to calculate.

Table A7c: Missing data patterns for clean delivery kit use where "1" indicates a variable is present in the missing data pattern, and "0" indicates a variable is absent in the missing data pattern

	Missing data pattern						
Percent	Women's group attendance	Education	Parity	Type of birth attendant	Number of antenatal care visits	Maternal age	Clean delivery kit use
89	1	1	1	1	1	1	1
8`	1	1	1	1	1	1	0
2	1	1	1	1	1	0	1
1	1	1	1	1	0	1	1
1	1	1	1	0	1	1	1
1	1	1	1	1	1	0	0
1	1	1	0	1	1	0	1
1	1	0	1	1	1	1	1
1	1	1	1	1	0	0	1
1	1	1	0	1	1	1	1
1	1	1	1	1	0	1	0
1	1	1	1	0	1	0	1
1	0	1	1	1	1	1	0
1	1	1	0	1	0	0	1

Table A7d: Missing data patterns for hand washing by the birth attendant where "1" indicates a variable is present in the missing data pattern, and "0" indicates a variable is absent in the missing data pattern

	Missing data pattern							
Percent	Women's group attendance	Education	Parity	Type of birth attendant	Number of antenatal care visits	Maternal age	Kit use	Hand wash
80	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	0
5	1	1	1	1	1	1	0	1
3	1	1	1	1	1	1	0	0
2	1	1	1	1	1	0	1	1
1	1	1	1	0	1	0	1	0
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	0	1	0	1
1	1	1	1	1	1	0	1	1
1	1	1	0	1	0	0	1	0
1	1	1	1	1	1	0	0	1
1	1	0	1	1	1	1	1	0
1	1	1	0	1	0	1	0	1
1	1	1	1	1	1	0	1	0
1	1	1	1	0	1	0	1	1
1	1	1	1	1	1	1	1	1
1	0	1	1	1	0	1	0	1
1	1	0	1	1	1	1	1	1
1	1	1	0	1	0	0	1	0
1	1	1	1	0	1	1	0	1
1	1	1	1	1	1	0	1	0
1	1	1	1	1	0	1	1	1