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**DOI:**
10.1186/s12884-018-1754-9

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**Document Version**
Publisher's PDF, also known as Version of record

**Citation for published version (Harvard):**
Bell, C, Hughes, L, Akister, T, Ramkhelawon, V, Wilson, A & Lissauer, D 2018, 'What is the result of vaginal cleansing with chlorhexidine during labour on maternal and neonatal infections? A systematic review of randomised trials with meta-analysis', *BMC pregnancy and childbirth*, vol. 18, 139.
https://doi.org/10.1186/s12884-018-1754-9

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What is the result of vaginal cleansing with chlorhexidine during labour on maternal and neonatal infections? A systematic review of randomised trials with meta-analysis

Charlotte Bell, Laura Hughes, Trevor Akister, Vin Ramkhelawon, Amie Wilson and David Lissauer

Abstract

Background: Infection with vaginal microorganisms during labour can lead to maternal and neonatal mortality and morbidity. The objective of this systematic review is to review the effectiveness of intrapartum vaginal chlorhexidine in the reduction of maternal and neonatal colonisation and infectious morbidity.

Methods: Search strategy – Eight databases were searched for articles published in any language from inception to October 2016. Selection criteria – Randomised controlled trials were included. Data Collection and analysis - Publications were assessed for inclusion. Data were extracted and assessed for risk of bias. Relative risks from individual studies were pooled using a random effects model and the heterogeneity of treatment was evaluated using Chi² and I² tests.

Results: Eleven randomised controlled trials (n = 20,101) evaluated intrapartum vaginal chlorhexidine interventions. Meta-analysis found no significant differences between the intervention and control groups for any of the four outcomes: maternal or neonatal colonization or infection. The preferred method for chlorhexidine administration was vaginal irrigation.

Conclusions: Meta-analysis did not demonstrate improved maternal or neonatal outcomes with intrapartum vaginal chlorhexidine cleansing, however this may be due to the limitations of the available studies. A larger, multicentre randomised controlled trial, powered to accurately evaluate the effect of intrapartum vaginal chlorhexidine cleansing on neonatal outcomes may still be informative; the technique of douching may be the most promising.

Keywords: Maternal, Chlorhexidine, Infection, Systematic review, Neonatal, Infection prevention
Background

Maternal and neonatal morbidity and mortality continue to present a serious global problem. In 2015 over 137 million live births were estimated worldwide [1], and 2.7 million neonatal deaths. [1]. A further 303,000 maternal deaths were recorded in 2015 [2].

Between 30 and 40% of neonatal deaths worldwide are caused by infections [3, 4] and 10.7% of maternal deaths (37,285 annually worldwide) are due to sepsis [5]. The greatest burden exists in low-income countries, where 99% of neonatal and maternal deaths occur [6, 7]. Therefore, in order for interventions to have real potential for benefit, it is imperative that they are easily accessible, both financially and in practical application.

During the process of labour, both mother and fetus are susceptible to infection from a range of vaginal microorganisms including Group B streptococcus (GBS), Campylobacter, Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli and Acinetobaumannii [8]. These organisms can lead to maternal and neonatal mortality and morbidities such as sepsicaemia, meningitis and pneumonia in the neonate [9] and chorioamnionitis leading to severe pelvic infection in the mother [10].

The maternal and fetal microbial profile may differ between geographical regions, with GBS having prominence in high-income countries [11]. However, it has been hypothesised that this prominence may be due to the underestimation of GBS prevalence in low income countries; facilities for detection are rarely available and many births take place outside a formal healthcare setting [12]. Thus far, many studies have focused separately on GBS and other vaginal microbes [9, 13–22].

GBS in the neonate is usually acquired through vertical transmission from the mother’s genital tract [23]. A number of strategies have been suggested to reduce vertical transmission of pathogens which colonise the maternal genital tract [13], including the use of intrapartum chemoprophylaxis for GBS-colonised mothers [24] and whole-body washing with chlorhexidine during the last 2 weeks of pregnancy [14]. In particular an important research question has been the use of a chlorhexidine antiseptic to cleanse the vagina during labour to reduce both maternal and neonatal infection [15, 20, 25–30].

Chlorhexidine is a biguanide antiseptic, which works by disrupting the bacterial cell wall [31]. It is effective against most gram-positive and some gram-negative bacteria, yeasts and many viruses, although variably effective against enveloped viruses [31]. It is ineffective against bacterial spores and mycobacteria [31]. Christensen et al. [13] found that GBS was extremely sensitive to chlorhexidine, with a minimum inhibitory concentration of 0.5-1 mg/l [32]. Chlorhexidine has been shown to have activity against normal vaginal bacteria, which cause puerperal infection, including GBS, E.coli and enterococci [33]. Upon application it is immediately effective, suppressing bacterial growth for up to 24 h [15]. Although not deactivated by alcohol, soaps or lavage fluid, the presence of organic matter such as blood or amniotic fluid may reduce the effectiveness of chlorhexidine [31].

The broad-spectrum antisepsis of the compound makes it particularly suitable for use in the intrapartum environment, where the colonisation of neonates and infectious morbidity of mothers shows an ever-changing pattern [34]. It is effective at a lower pH, which further supports its use in the vagina, which typically has an environment of pH < 4.7 [35]. Chlorhexidine is inexpensive, has no effect on antimicrobial resistance, and is practical and viable to be used in resource-limited settings [36]. It also has a good safety profile [37] and has been studied in the obstetric setting in concentrations ranging from 0.05–4% [11]. The compound is widely available from numerous manufacturers worldwide. Chlorhexidine has thus been proposed as a highly suitable compound for intra-vaginal use to reduce maternal and neonatal sepsis [12, 38].

In 1989, the observation of a reduction of neonatal GBS colonisation led to the recommendation for a larger multicentre trial [16]. More recently, two Cochrane reviews of randomised controlled trials examined aspects of this question [17, 18] both of which were updated in 2014 [9, 19]. Lumbiganon et al. [9] reported data in their Cochrane review which focused on trials comparing chlorhexidine vaginal douching during labour with placebo or other vaginal disinfectant to prevent maternal and neonatal infections, excluding GBS and HIV. The results suggested a trend in the reduction of endometritis through intrapartum vaginal chlorhexidine, but this was not statistically significant. Ohlsson et al. [19] found that a vaginal intrapartum chlorhexidine intervention reduced the GBS colonisation of neonates, but did not reduce early-onset disease, including GBS infection, GBS pneumonia or GBS meningitis. The authors of both reviews concluded that a randomised controlled trial with adequate power and standardised intervention was required, but Ohlsson et al. [19] commented that in developed countries, this may be difficult to justify in the era of antibiotic prophylaxis for GBS infection. However, the scope of these reviews was narrower than this review, and excluded a number studies as they combined the interventions of vaginal cleansing and infant washing. Furthermore the Cochrane reviews separated neonatal infections based on the microorganism responsible, making an overall assessment of the efficacy of this intervention difficult. The following systematic review and meta-analysis of randomised controlled trials focuses on the intrapartum vaginal interventions in vaginal deliveries only, measuring both maternal and neonatal outcomes in terms of infectious morbidity and mortality, irrespective of infectious organisms.
Methods

Types of studies included randomised controlled trials only, comparing the use of intrapartum vaginal chlorhexidine cleansing to no chlorhexidine use or placebo or other vaginal disinfectant, for the reduction of maternal or neonatal infection. Studies that considered HIV-positive participants exclusively were excluded.

Participants considered for inclusion in this review are women undergoing vaginal delivery, in the intrapartum period and having vaginal chlorhexidine cleansing in any setting.

Types of interventions considered were vaginal disinfection with chlorhexidine by any method during labour, compared with placebo or no vaginal disinfection.

Maternal outcomes measured were 1) Colonization during the post-partum period and 2) Clinical infection and / or sepsis during the post-partum period. Neonatal outcomes measured were 1) Colonization during the neonatal period and 2) Clinical infection and / or sepsis during the neonatal period.

Eight electronic databases were searched (PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL, AIM, the Reproductive Health Library, and BioMed Central: from database inception to 10/2016. The following search terms were used ‘Chlorhexidine’, ‘vaginal antiseptic’, ‘vaginal wipe’, ‘vaginal douche’, ‘vaginal cleansing’, ‘bathing’ with ‘pregnancy’, ‘postpartum’, ‘labour’ intrapartum; ‘neonatal’, ‘peripartum’ and ‘mениngitis’, ‘pneumonia’ group B strep, ‘infection’, ‘HIV’, ‘sepsis’, ‘mortality’; ‘omphalitis’, ‘chorioamnionitis’, ‘endometritis’, ‘mature’, ‘infant’, ‘postnatal’. No language restrictions were applied. Databases were searched for papers published until October 2016.

All randomised trials examining the use of vaginal chlorhexidine washing during labour, by any method, which reported maternal or neonatal outcomes were included.

Three authors completed the searches independently (C Bell, L Hughes, T Akister). Two authors independently (C Bell, L Hughes) screened the titles and abstracts to assess for inclusion or exclusion. The two authors then read each paper identified as a result of the search strategy and made a decision on whether it should be included or excluded on the basis of all the defined inclusion criteria. Disagreements were resolved by discussion (T Akister, D Lissauer).

Data was extracted by two authors independently (T Akister, V Ramkhelawon) and tabulated using Microsoft Excel. Any disagreements were resolved by discussion amongst the authorship group and consensus. Data was entered into Review Manager Software Revman 5.0 and checked for accuracy.

Two review authors (T Akister, V Ramkhelawon) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [39]. Any disagreement was resolved by discussion or by involving a third review author.

Specifically, the following aspects of risk bias were assessed in detail: 1) Sequence generation (checking for possible selection bias), 2) Allocation concealment (checking for possible selection bias), 3) Blinding (checking for possible performance bias), 4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations), 5) Selective reporting bias, 6) Other sources of bias.

The overall risk of bias was made using judgements about whether studies were at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions [39]. The likely magnitude and direction of the biases described in points 1 to 6 above was assessed and whether it was likely to impact on the findings.

Data for effect estimates, including 95% confidence intervals, were directly extracted. These results were then included in the meta-analysis, using a random effects model to pool the relative risks from individual studies. The heterogeneity of treatment was evaluated using Chi² and I² tests and presented as forest plots. Analyses were undertaken using Revman 5.0 statistical software and Mantel-Haenszel analysis.

Results

We identified 68 unique papers after searching PubMed, Embase, Medline, The Cochrane Library and Biomed Central. No papers were identified after searching the CINAHL, AIM or RHL databases. Eleven RCTs involving 20,101 women and their infants, were suitable to be included in a systematic review and meta-analysis (Fig. 1). Characteristics of included studies are detailed in Table 1, including potential confounding factors. Only two of the studies [27, 40] were undertaken in low resource settings (Table 1).

There was no significant difference in maternal colonization when using vaginal chlorhexidine intrapartum when compared to the control (Fig. 2). Two studies [21, 27] investigated the effect of chlorhexidine on maternal colonization, including 53 participants in the intervention group and 51 in the control group, which also showed no significant difference on colonization (Relative risk (RR) 0.61, 95% confidence intervals (CI) 0.05-8.08) Heterogeneity – I² = 93%, P < 0.001.

Five studies [28, 30, 40–42] (Fig. 2) containing a total of 12,154 participants (6067 intervention and 6087 control) did not show a statistically significant effect in maternal morbidity (RR 0.91 95% CI 0.69-1.20) with the chlorhexidine intervention. Heterogeneity – I² = 52%, P = 0.08.

The incidence of neonatal colonization was not reduced with any chlorhexidine intervention (Fig. 2). Three studies [22, 42, 43] reported on neonatal colonization on a total of 1948 neonates (949 intervention 999 control) and also
showed no reduction in bacterial transmission (RR 0.75 CI 0.46-1.22). Heterogeneity – $I^2 = 90\%$, $P < 0.001$.

Five studies [20, 29, 30, 41, 42] (Fig. 2) looked at neonatal infection and sepsis. This included 4297 infants in the intervention arm and 4342 in the control group. There was also no reduction with vaginal chlorhexidine (RR 0.74 CI 0.52-1.06). There was significant heterogeneity in the meta-analysis of neonatal colonization ($p < 0.001$, $I^2 = 90\%$), but no evidence of significant heterogeneity in the meta-analysis of neonatal sepsis/infection as their outcome ($p < 0.26$, $I^2 = 24\%$). Further analysis of this outcome was undertaken, discriminating between douching and wipes/gel/cream (Fig. 2). The results favoured the douching method, for which the result for neonatal colonization was significant ($p < 0.001$) (Fig. 2). Unfortunately, this particular analysis only contained one study [42].

**Discussion**

The meta-analysis did not demonstrate a reduction in maternal colonization or in maternal sepsis/infection when using intrapartum vaginal chlorhexidine cleansing. The incidences of neonatal colonization and neonatal infection/sepsis were also not significantly reduced by this intervention. However, although these results did not show a statistically significant reduction in outcomes, there appeared to be a trend towards a reduction in maternal infection and neonatal colonisation and infection with the douching method, which suggest this subject may warrant further study.

All of the 11 studies reviewed were randomised trials, but seven were assessed to be at high risk of bias in one or more categories. For example, two studies [23, 27] did not perform an intention to treat analysis, which can lead to a failure to preserve randomisation of the groups.

There is significant clinical heterogeneity in the studies analysed (Table 1). In particular, different methods of vaginal cleansing with chlorhexidine were used. In eight studies [20, 21, 27, 30, 41, 42, 44] an irrigation or ‘douching’ method was used, whilst others used gel [23], wipes [40] or cream [22]. In the analysis of these treatment differences, douching was suggested to be more effective, but this may not be a reliable conclusion as only one study [42] with neonatal colonization as an outcome employed irrigation and only one study with maternal sepsis/infection as an outcome [40] used wipes. It is however conceivable that the act of mechanically flushing the vaginal walls could play a part in the physical removal of pathogenic and commensal
| Study, Country       | Details                                                                 | Population                                                                 | Criteria for exclusion from study | Characteristics of mothers | Characteristics of neonates | Potential confounders | Intervention | Control      | Number of participants | Outcomes                                                                 |
|---------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|----------------------------|---------------------------|------------------------|--------------|--------------|-----------------------|--------------------------------------------------------------------------|
| Adriaanse et al 1995, Holland | At onset of labour, the attending obstetrician applied 10 ml chlorhexidine (CHX) gel around the portio vaginalis and into the fornices. This procedure was repeated after 10 h in case delivery had not yet occurred. | Pregnant women from two hospitals with obstetric services in the city of Nijmegen, the Netherlands. | Known GBS carrier, use of antibiotics during the 4 weeks before admission, planned caesarean section, antepartum foetal death, suspected congenital abnormalities and premature labour. | No significant difference between groups | No significant differences between the three groups, except for the % of neonates admitted to the (special) neonatal care unit (P = 0.012) in the CHX and control group. | No special training given to doctors giving intervention, no protocol given for intervention e.g. timing of washing. | 10ml 0.3% CHX gel | Standard care | 1020     | Participating women, 522 were enrolled in one hospital and 498 in the other. Of the 981 analysed mother-infant pairs, 327 were assigned to the chlorhexidine group, 328 to the placebo group and 326 to the control group. | Primary outcomes were vertical GBS transmission to the neonate. Secondary goals were to study the vertical transmission rates of E. coli, S. aureus and C. albicans, and to establish neonatal and maternal morbidity. Neonatal septicemia, meningitis and pneumonia diagnosed from the positive cultures of blood or CSF or tracheal aspirate. |
| Burman 1992, Sweden | 60mls of solution (CHX or sterile water) was used to flush the anterior fornix, vaginal walls and urethral orifice in a spiral outward motion by a midwife. This was repeated every 6 hours until delivery. Flush was counted if birth occurred > 1 hour after flush and no more than 6 hours lapsed between flushes. | Pregnant women who were urogenital carriers of GBS from 10 Swedish hospitals. | Pre term infants (<37 weeks) planned caesarean section, pregnancy complications after the 30th week of gestation requiring hospital admission, twin or multiple pregnancies, suspected congenital abnormality of the infant, known or suspected allergy to CHX, previous invasive GBS infection, antibiotics during the 2 weeks before admission, and antepartum foetal death. | Not analysed | No significant differences seen | No rigorous set procedure for flushing e.g. time taken to flush, no specialist training given to midwives, multiparity pregnancies excluded, group sizes not even, maternal characteristics not determined. | 60 ml 2g/l CHX given as 2 30ml ampules via catheter | 60 ml sterile saline | 4483 women 2238 CHX group and 2245 saline placebo group | Rate of admission of babies to special-care neonatal units within 48 h of delivery. Admissions for sepsis/meningitis, pneumonia, skin infection, meconium aspiration, surveillance, maladaptation and non-specific problems were included. |
| Study, Country | Details | Population | Criteria for exclusion from study | Characteristics of mothers | Characteristics of neonates | Potential confounders | Intervention | Control | Number of participants | Outcomes |
|---------------|---------|------------|-----------------------------------|-----------------------------|-----------------------------|-----------------------|--------------|---------|------------------------|----------|
| Cutland et al 2009 South Africa | pads soaked in water or CHX around gloved fingers. Fingers were rotated circumferentially over the cervix and vaginal walls, and the external genitalia wiped | 15-51) and their neonates born to South African women at Chris Hani-Barraganthe hospital, Soweto, South Africa | caesarean section, antepartum haemorrhage, known severe congenital malformation, intrauterine death, allergy to CHX, face presentation, genital warts or ulcers, full cervical dilatation, and age younger than 15 years. | No volumes or times of washing stated | All participants had CHX wash including controls, no exclusion criteria e.g. for prior antibiotic use. | 2g/l CHX | Standard care | 78 patients in total 31 in chx and 47 in the control group. | Maternal urogenital colonization GBS at 4 days post-partum. |
| Dykes et al 1987, Sweden | Midwives used a compress steeped in the 2g/L CHX solution. Compress turned three times around the cervix then over the vaginal walls using spiral movements outwards. Procedure was repeated twice with new compresses. Fourth compress was pressed against the cervical orifice and then used for washing of labia minora and the introitus. All pregnant women attending the antenatal clinics in the region served by the Department of Obstetrics, University Hospital, Lund, who were GBS positive (urogenital tract) at weeks 32 and 36 and at onset of labour. | Not stated | Not analysed | Not analysed | | | | | | transmission GBS within 1st 3 days of life. Neonatal sepsis defined as clinical diagnosis or culture positive. Maternal sepsis defined as admission within 14 days of delivery for endometritis (at least two of uterine tenderness, fever, foul-smelling or purulent lochia, or vaginal discharge), culture confirmed infection of sterile site, or perineal wound infection among vaginal parturients. |
| Study, Country | Details | Population | Criteria for exclusion from study | Characteristics of mothers | Characteristics of neonates | Potential confounders | Intervention | Control | Number of participants | Outcomes |
|---------------|---------|------------|-----------------------------------|---------------------------|---------------------------|-----------------------|--------------|---------|------------------------|----------|
| Eriksen et al 1997, USA | 20 cc of a 0.4% CHX solution was placed around the portio vaginallis and fornices using a syringe. Women in the control group were irrigated with 20 cc of sterile water. | Women admitted to the Lyndon Baines Johnson Hospital, Texas, USA labour and delivery room | Preterm labour, foetal distress, malpresentation, intrapartum infection, cervical dilatation >6 cm, and known allergy to CHX. | Not reported | Not reported | Patients with prior use of antibiotics not excluded, no protocol for washing procedure | 20cc 0.4% CHX | 20cc sterile water | 947 patients were randomized to CHX (481) or of sterile water (466) | Incidence of neonatal pneumonia, culture proven neonatal sepsis, and use of the antibiotics in the neonate. The diagnosis of neonatal pneumonia was made by the attending physician if the neonate was febrile and had chest radiograph findings consistent with the diagnosis. Neonatal sepsis was diagnosed if the infant had a positive blood or CSF culture, along with a clinical course consistent with sepsis. |
| Hennequin 1995, Denmark | Vaginal examinations of the treated group were systematically performed with gloves lubricated with 5 ml CHX digluconate 1% cream; the control group was examined with uncoated gloves. | Pregnant antenatally screened GBS positive pregnant women attending the labour ward | Not stated | Not reported | Not reported | No exclusion criteria e.g. abx use ruptured membranes etc, no protocol for vaginal examination, no training given | 5 ml CHX digluconate 1% cream | Standard care | 59 women in total 28 CHX cream 31 control | Mother Infant GBS transmission. |
| Pereira et al 2011, Zimbabwe | Vulva cleansing with a 4x4 cotton wool ball soaked in 15-20ml 1% CHX solution followed by vaginal cleansing with another cotton wool ball as described above. The process was repeated from onset every 2 hours. | Pregnant women attending Harare central hospital who had no allergy to CHX, lived in close proximity to the hospital and planned to have a vaginal birth. | None stated | No significant difference between groups | Apgar scores were significantly higher in CHX group. However neonatal outcomes not included as had full body washing. | No exclusion criteria, no training given, | 15-20ml 1% CHX | Standard care | 502 women in total 2:1 randomisation 334 to chx and 168 to UC. However only 37 women were swabbed for cultures. 5 in UC 32 in chx. | Safety, acceptability and antimicrobial effect of 1% CHX. Maternal vaginal colonisation (any species) was primary antimicrobial effect measured. |
| Rouse et al 1997, USA | Irrigations were performed either during active labour or before planned caesarean | Pregnant women at 24 weeks gestation or more at Cooper Green | Contraindication to digital cervical examination (e.g., placenta previa), active | Significant differences seen in maternal age, nulliporous, meconium and | Not analysed | Prophylactic antibiotics given for early onset neonatal group B | 0.2% CHX | 200ml sterile water vaginal wash out pre delivery | A total of 1024 patients were enrolled: 508 in the CHX group | Primary outcomes: Maternal chorioamnionitis and endometritis Other outcomes: UTI and wound infection. |
| Study, Country | Details | Population | Criteria for exclusion from study | Characteristics of mothers | Characteristics of neonates | Potential confounders | Intervention | Control | Number of participants | Outcomes |
|---------------|---------|------------|----------------------------------|----------------------------|---------------------------|-----------------------|--------------|---------|-----------------------|----------|
| Rouse et al 2003, USA | See Rouse 1997 performed every 6 hours (maximum 4 irrigations) | Hospital, hospital in Birmingham, Alabama, serving publicly funded patients | See Rouse 1997 No significant difference between groups seen. | Not analysed | Prophylactic antibiotics given See Rouse 1997 | See Rouse 1997 | See Rouse 1997 | 1041 participants 525 in chx; 516 in control | and 516 in the placebo group. | hyperbilirubinaemia, Death, necrotizing enterocolitis, supplemental oxygen, APGAR and intraventricular haemorrhage. |
| Stray-Pedersen et al 1999, Norway | Douching started by intravaginal insertion of catheter towards the cervix. The bottle was squeezed while the catheter was retracted slowly. Patient remained supine for 5 min. Process repeated every 6 hours. | Over 9 Months pregnant women were consecutively selected from the Aker University Hospital, Norway. The first 4 months was a reference period and the next five months the intervention period. | None given | No significant difference between groups | No significant difference between groups | Ampicillin was given to women with prolonged delivery > 24 hours | Reference phase standard care. Intervention phase vaginal douche with sterile saline | 120 ml 0.2% CHX douche | 548 in chx douche 583 control (saline douche) 858 reference group (nothing) | GBS transmission, Maternal outcomes (postpartum UTI and fever) Fever was recorded when temperature exceeded 38.5°C during the first 24 h after delivery, or if the temperature thereafter exceeded 38°C on two occasions at least 4 h apart, provided that other obvious explanations were absent. Neonatal outcomes (Septicaemia, Strep. agalactiae sepsis Respiratory problems and Superficial infections) |
| Sweeten et al 1997, USA | Women randomized to the study arm | Women admitted to Lyndon Baines | No significant difference | No training given, no set | No significant difference | No significant difference | No training given, no set | CHX group 481 Placebo 466 | Maternal outcomes were intraamniotic infection and endometritis. Diagnosis of... |
Table 1 Characteristics of studies included in meta-analysis (Continued)

| Study, Country | Details | Population Details | Criteria for exclusion from study | Characteristics of mothers | Characteristics of neonates | Potential confounders | Intervention | Control | Number of participants | Outcomes |
|----------------|---------|---------------------|-----------------------------------|---------------------------|---------------------------|------------------------|-------------|---------|-----------------------|----------|
|                |         | Johnson General Hospital, USA labour and delivery suite at or greater than 36 weeks' gestation | received 20 ml of a 0.4% CHX solution. The solution was placed around the portio vaginalis and fornices with a syringe. Women in the control group were irrigated with 20 ml of sterile water. | intraamniotic infection, cervical dilatation >6 cm and known allergy to CHX. | between groups | protocol e.g. timing | intraamniotic infection was made if temperature >100°F with two of the following criteria: maternal tachycardia, uterine tenderness, foul-smelling amniotic fluid, maternal leukocytosis, or foetal tachycardia. Diagnosis of endometritis was defined as a postpartum oral temperature >101 °F, uterine tenderness, and no other source of infection. Patients with a diagnosis of intraamniotic infection could not also be included in the endometritis group. |
bacteria. This would oppose the theory that a prolonged contact time found with the use of gel or cream would enhance the bactericidal effects of chlorhexidine.

The use of a control also varied between studies, with three [20, 41, 42] using sterile saline, three [28, 30, 44] using sterile water, one [23] using another placebo and four [21, 22, 27, 40] using no intervention as controls. Aside from the lack of blinding in the non-treatment controls, confounding may have occurred in the use of saline or water. The effect of these controls on vaginal bacteria, whether chemical or mechanical, should be determined.

Some studies included in their analysis the outcomes of mothers who underwent emergency caesarean section [20, 23, 30, 41]. Studies that exclusively focused on women undergoing caesarean section were excluded from our review, but a proportion of women in labour will inevitably require surgical intervention. The intention-to-treat analysis employed may have preserved randomisation, but may also have had an impact on the outcome, as the contamination of the neonate with vaginal bacteria may be less likely if that neonate has not passed through the vagina. Notably, the studies by Rouse et al. [30, 41] also administered one dose of a second-generation cephalosporin to these mothers, which also risks masking the effects of vaginal washing on maternal infection. The same studies also gave prophylactic antibiotics to any mother at risk of early onset GBS infections, which may also have masked both maternal and neonatal complications. In contrast, Burman et al. [20] had ‘GBS carrier status’ as an inclusion criterion (Table 1). In addition, some of the studies did not take account of the duration of labour or prolonged rupture of membranes, which may have led to bias, whilst the Rouse studies [30, 41] administered prophylactic antibiotics to these participants (Table 1).

The studies reviewed also differ in terms of the level of care provider carrying out the intervention, with four [20, 21, 40, 42] using midwives and five [23, 28, 30, 41, 44] using doctors and/or medical students, two unknown [22, 27]. However, the person(s) within each study responsible for performing the intervention (or control, where applicable) varied within the study itself, which may also have influenced outcomes.

The studies reviewed showed heterogeneity for their location. Nine studies were conducted in high-income countries (4 USA, 5 Scandinavia) and only two in developing countries (1 South Africa, 1 Zimbabwe). The Zimbabwean study [27] showed a highly statistically significant result favouring the use of chlorhexidine for the prevention of maternal colonisation. The South African study failed to show a favourable result for the outcome of maternal infection/sepsis. Notably, this study also used vaginal wiping instead of irrigation as the method of intervention, which may be a less effective technique. However, despite such notable heterogeneity between studies, the authors feel that the studies showed sufficient homogeneity in their populations, interventions and outcomes to warrant meta-analysis. It was also felt that the efficacy of the intervention, that is vaginal, intrapartum chlorhexidine, should not be directly affected by the geographical location of the study. Nonetheless, the intervention itself may be economically and technically viable for a low-income setting.

Cochrane reviews [9, 17–19] have previously focused on GBS and other infections separately, concluding that intravaginal/intrapartum chlorhexidine was effective in significantly reducing neonatal colonization with GBS. But they stated that this alone was not sufficient to support the use of the intervention. Our review has also found that, when assessing maternal and neonatal colonization and infectious morbidity of all organisms (excluding HIV) there is no statistical significance to the results, but there is a suggestion that intervention may lead to a reduction in neonatal infection/sepsis.

Goldenberg et al. [38] analysed studies using vaginal chlorhexidine, with or without a neonatal wash, with particular reference to the low income countries. Their analysis of two large, non-randomised studies suggested that one or both of these interventions was successful in improving both maternal and neonatal outcomes. However we believe that it is still useful to separate the two interventions as in our review, to determine the individual effect of each. This is particularly important when considering potential implementation in the low-income countries, where cost-effectiveness and cost-benefit analyses would be of paramount importance, as well as the simplicity of the intervention.

McClure et al. [11] reviewed studies using any chlorhexidine interventions including vaginal, neonatal wipes and umbilical cord cleansing. The group suggested that although several studies reviewed showed promising results, the lack of truly randomized trial evidence stood as a major barrier to implementing the use of chlorhexidine interventions in low-resource settings. Again, we feel that it is advantageous to separate the interventions in order to assess their individual efficacy as exclusive interventions, before combining the outcomes in such a review. Mullany et al. [12] used similar inclusion criteria to McClure et al. [11] for their review, which concluded that although the various chlorhexidine interventions showed promise in reducing neonatal morbidity and mortality, their individual efficacy should be determined before implementation in low-resource settings. We have begun this process in our review, in order to ascertain whether a larger scale randomised controlled trial would be justifiable for the separate intervention of vaginal chlorhexidine washing.

The two Cochrane reviews did this in relation to vaginal, intrapartum chlorhexidine, but may have limited
Fig. 2 Forest plot comparing the following outcomes and interventions: 1) maternal colonisation; 2) maternal sepsis/infection; 3) neonatal colonisation; 4) neonatal sepsis/infection; 5) maternal sepsis/infection – douching; 6) maternal sepsis/infection – wipes; 7) neonatal colonisation – douching; 8) neonatal colonisation – gel/cream
interpretation by separating the causative organisms. As it has been hypothesized that the apparent low prevalence of GBS in low-resource settings may be attributable to under-diagnosis [12], we felt that it was important to conduct our review to include all causative agents.

The Dykes [21], Adriaanse [23], Burman [20] and Stray-Pedersen [42] studies all supported the use of vaginal intrapartum chlorhexidine. All of these studies were conducted in Scandinavian hospitals; therefore the results may not be generalisable to the populations of less developed countries, where a majority of the maternal and neonatal burden of disease exists. Furthermore it is in this setting that the lack of resources and high number of community births make an effective, safe, cheap and low-skill intervention particularly beneficial. In this setting non-randomised studies such as Mushangwe [45] and Taha [46] show promising results.

Conclusions
Our review shows that intrapartum, vaginal chlorhexidine may lead to a reduction in neonatal infection/sepsis. It is still unclear whether chlorhexidine concentration and method of administration will have a significant impact on outcome, due to the heterogeneity of existing studies. It is therefore our belief that a larger, multicentre, randomised controlled clinical trial in a low-resource setting is justified based on our analysis. Such a trial would require rigorously defined inclusion criteria such as in the Rouse et al. studies [30, 41]. These patients were nulliparous, more than 32 weeks gestation and exclusion criteria were: contraindication to digital cervical examination, active genital herpes, chorioamnionitis prior to randomisation and allergy to chlorhexidine. The studies also carried out double-blinding and computer randomisation.

The use of intrapartum vaginal chlorhexidine should also be considered separately to neonatal skin cleansing, to provide more specific information regarding the efficacy of such interventions. As there are still unanswered questions regarding the optimum concentration of chlorhexidine, the frequency and timing (pre/post rupture of membranes) of the intervention and the method used (wipes/gel/cream versus douching), further studies may need to also address these issues.

Abbreviation
GBS: Group B streptococci

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
Searches were completed by CB, LH and TA. Screening and assessment for inclusion/exclusion - CB, LH. Disagreement resolution - TA, DL. Data extraction and risk of bias analysis - TA, VR. Disagreement resolution - CB, LH. Methodological support, AW, DL. All authors drafted, edited and approved the final manuscript. DL and AW were funded as part of the Antibiotics in miscarriage surgery trial, by the Medical Research Council, Wellcome Trust, UK Aid, Joint global health trials programme; Trial registration ISRCTN97143849.

Ethics approval and consent to participate
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Received: 24 November 2017 Accepted: 19 April 2018
Published online: 08 May 2018

References
1. World Health Organisation. World health statistics 2015. Luxembourg: WHO Press; 2015.
2. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN maternal mortality estimation inter-agency group. Lancet. 387(10017):462–74.
3. Sankar MJ, Chandrasekarana A, Ravindranath A, Aganwala R, Paul VK. Umbilical cord cleansing with chlorhexidine in neonates: a systematic review. J Perinatol. 2016;36(51):512–20.
4. Liu L, Johnson HL, Cousins S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since. Lancet. 2000;375(9663):2151–61.
5. Say L, Chou D, Gemmill A, &c, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(9):e323–33.
6. Gogia S, Sachdev HPS. Home-based neonatal care by community health workers for preventing mortality in neonates in low- and middle-income countries: a systematic review. J Perinatol. 2016;36(51):555–73.
7. Lawn JE, Cousins S, Zupan J. 4 million neonatal deaths: When? Where? Why? The Lancet. 2005;365(9462):891–900.
8. Lim WT, Lien R, Huang Y-C, Chiang M-C, Fu R-H, Chu S-M, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediat Neonatol. 2012;53(4):228–34.
9. Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE. Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV). Cochrane Database Syst Rev. 2014, Issue 9. Art No.: CD004070. https://doi.org/10.1002/14651858.CD004070.pub3.
10. Moyo SR, Hägerstrand I, Nyström L, Tswana SA, Blomberg J, Bergström S, et al. Stillbirths and intrapartum infection, histologic chorioamnionitis and microbiological findings. Int J Gynecol Obstet. 1996;54(2):115–23.
11. McClure EM, Goldenberg RL, Brandes N, Darmstadt GL, Wright LL. The use of chlorhexidine to reduce maternal and neonatal mortality and morbidity in low-resource settings. Int J of Gynecol Obstet. 2007;97(2):89–94.
12. Mullaney LC, Darmstadt GL, Tielisch JM. Safety and impact of chlorhexidine antisepsis interventions for improving neonatal health in developing countries. Pediatr Infect Dis J. 2006;25(8):665–75.
13. Christensen K, Christensen P, Dykes A, Kahlmeter G. Chlorhexidine for prevention of neonatal colonization with group B streptococci. III. Effect of vaginal washing with chlorhexidine before rupture of the membranes. Eur J Obstet Gynaecol Reprod Biol. 1985;19(4):231–6.
14. Sanderson PJ, Haji TC. Transfer of group B streptococci from mothers to neonates: effect of whole body washing of mothers with chlorhexidine. J Hospital Infect. 1985;6(3):257–64.
15. Dykes A-K, Christensen KK, Christensen P, Kahlmeter G. Chlorhexidine for prevention of neonatal colonization with group B streptococci. I. Chlorhexidine concentrations and recovery of group B streptococci following vaginal washing in pregnant women. Eur J Obstet Gynecol. 1983;16(3):167-72.

16. Kollée LAA, Speyer J, van Kuijk MAP, Koopman R, Dorny JM, Bakker JH, et al. Prevention of group B streptococcal transmission during delivery by vaginal application of chlorhexidine gel. Eur J Obstet Gynecol. 1989;31(1):47-51.

17. Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE. Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (including Group B Streptococcal and HIV). Cochrane Database Syst Rev. 2004(4).

18. Stade BC, Shah VS, Ohlsson A. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Cochrane Database Syst Rev. 2004(3).

19. Ohlsson A, Shah VS, Stade BC. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Cochrane Database Syst Rev. 2014(12).

20. Burman LG, Fryklund B, Helgesson AM, Christensen P, Christensen K, Svenningsen NW, et al. Prevention of excess neonatal morbidity associated with Group B streptococci by vaginal chlorhexidine disinfection during labour. Lancet. 1992;340(8811):65-9.

21. Dykes A-K, Christensen KK, Christensen P. Chlorhexidine for prevention of neonatal colonization with group B streptococci. IV. Depressed puerperal carriage following vaginal washing with chlorhexidine during labour. Eur J Obstet Gynecol Reprod Biol. 1987;24(4):293-7.

22. Henneguin Y, Tecco L, Vokaer A. Use of chlorhexidine during labor: how effective against neonatal group B streptococci colonization? Acta Obstet Gynecol Scand. 1995;74(2):168.

23. Adriaanse AH, Bb prevention of neonatal septicemia due to group B streptococci. Baillieres Clin Obstet Gynaecol. 1995;9(3):545-52.

24. Schuchat A. Impact of intrapartum chemoprophylaxis on neonatal sepsis. Pediatr Infect Dis J. 2003;22(12):1087-8.

25. Rouse DJ, Hauth JC, Andrews WW, Mills BB, Maher JE. Chlorhexidine vaginal irrigation for the prevention of peripartum infection: a placebo-controlled randomized clinical trial. Am J Obstet Gynecol. 1997;176(3):617-22.

26. Stray-Pedersen B, Bergan T, Hafstad A, Normann E, Graagda J, Vangdal M. Vaginal disinfection with chlorhexidine during childbirth. Int J Antimicrob Agents. 1999;12(3):245-51.

27. Pereira L, Chipato T, Mashu A, Mushangwe V, Rusakaniko S, Bangdiwala SI, et al. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol. 1995;61(2):135-41.

28. Eriksen NL, Sweeten KM, Blanco JD. Chlorhexidine vs. sterile vaginal wash during labor to prevent neonatal infection. Infect Dis Obstet Gynecol. 1997;5(4):286-90.

29. Mushangwe V, Tolosa JE, Pereira I, Mashu A, Bangdiwala S, Rusakaniko S, et al. Chlorhexidine washing of the vagina in labor effectively reduces bacterial colonization: A study by the global network for perinatal & reproductive health. Am J Obstet Gynecol. 2006;195(6):566.

30. Taha TE, Biggar RJ, Bradlow RL, Mitmavajle LAR, Motti PG, Jutessen AB, et al. Effect of cleansing the birth canal with an antisepic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. BJM. 1997;315(7102):216.