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[Intervention Review]

Topical emollient for preventing infection in preterm infants

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ABSTRACT

Background

Breakdown of the developmentally immature epidermal barrier may permit entry for micro-organisms leading to invasive infection in preterm infants. Topical emollients may improve skin integrity and barrier function and thereby prevent invasive infection, a major cause of mortality and morbidity in preterm infants.

Objectives

To assess the effect of topical application of emollients (ointments, creams, or oils) on the risk of invasive infection and mortality in preterm infants.

Search methods

We searched CENTRAL via Cochrane Register of Studies (CRS) Web and MEDLINE via Ovid (updated 08 January 2021) and the reference lists of retrieved articles.

Selection criteria

Randomised or quasi-randomised controlled trials that assessed the effect of prophylactic application of topical emollient on the risk of invasive infection, mortality, other morbidity, and growth and development in preterm infants.

Data collection and analysis

We used the standard methods of Cochrane Neonatal. Two review authors separately evaluated trial quality, extracted data, and synthesised effect estimates using risk ratio (RR), risk difference (RD), and mean difference. We used the GRADE approach to assess the certainty of evidence for effects on mortality and invasive infection.

Main results

We included 22 trials with a total of 5578 infant participants. The main potential sources of bias were lack of clarity on the methods used to generate random sequences and conceal allocation in half of the trials, and lack of masking of parents, caregivers, clinicians, and investigators in all of the trials.

Eight trials (2086 infants) examined the effect of topical ointments or creams. Most participants were very preterm infants cared for in healthcare facilities in high-income countries. Meta-analyses suggested that topical ointments or creams may have little or no effect on invasive infection (RR 1.13, 95% confidence interval (CI) 0.97 to 1.31; low certainty evidence) or mortality (RR 0.94, 95% CI 0.82 to 1.08; low certainty evidence).

Fifteen trials (3492 infants) assessed the effect of topical plant or vegetable oils. Most of these trials were undertaken in low- or middle-income countries and were based in healthcare facilities. One large (2249 infants) community-based trial occurred in a rural field practice in

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India. Meta-analyses suggested that topical oils may reduce invasive infection (RR 0.71, 95% CI 0.52 to 0.96; I^2 = 52%; low certainty evidence) but have little or no effect on mortality (RR 0.94, 95% CI 0.82 to 1.08, I^2 = 3%; low certainty evidence).

One trial (316 infants) that compared petroleum-based ointment versus sunflower seed oil in very preterm infants in Bangladesh showed little or no effect on invasive infection (RR 0.91, 95% CI 0.57 to 1.46; low certainty evidence), but suggested that ointment may lower mortality slightly (RR 0.82, 95% CI 0.68 to 0.98; RD -0.12, 95% CI -0.23 to -0.01; number needed to treat for an additional beneficial outcome 8, 95% CI 4 to 100; low certainty evidence). One trial (64 infants) that assessed the effect of coconut oil versus mineral oil in preterm infants with birth weight 1500 g to 2000 g in India reported no episodes of invasive infection or death in either group (very low certainty evidence).

Authors' conclusions

The level of certainty about the effects of emollient therapy on invasive infection or death in preterm infants is low. Since these interventions are mostly inexpensive, readily accessible, and generally acceptable, further good-quality randomised controlled trials in healthcare facilities, and in community settings in low- or middle-income countries, may be justified.

PLAIN LANGUAGE SUMMARY

Topical emollient for preventing infection in preterm infants

Background

Preterm infants (born before 37 weeks' gestation) are susceptible to bloodstream and other serious infections partly because their immature skin is not a fully effective barrier to micro-organisms. Applying emollient (ointment, cream, or oil) may protect against skin breakdown and thereby prevent micro-organisms from spreading into the bloodstream and causing serious infection.

Study characteristics

Our search (updated January 2021) identified 22 eligible trials. In total, 5578 infants participated. Eight trials (2086 infants) examined the effect of topical ointments or creams in very preterm infants (born more than eight weeks early) cared for in hospitals, mostly in high-income countries. Fourteen trials (3492 infants) assessed the effect of sunflower and other vegetable oils, mostly in low- or middle-income countries in south Asia. All but one of these trials was conducted in hospitals. One large trial in India (2249 infants) was based in the community.

Key results

Regular application of ointments or creams to the skin of very preterm infants may have little or no effect on serious infection or death. Application of sunflower and other vegetable oils may reduce invasive infection but have little or no effect on mortality.

Certainty of evidence

These analyses provide low certainty evidence about the effects of emollient therapy on serious infection or death in preterm infants. Since these interventions are mostly inexpensive, readily accessible, and generally acceptable, further good-quality randomised controlled trials in healthcare facilities, and in community-settings in low- or middle-income countries, may be justified.

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SUMMARY OF FINDINGS

Summary of findings 1. Topical ointment or cream versus routine skin care for preventing infection in preterm infants

Topical ointment or cream versus routine skin care for preventing infection in preterm infants

Patient or population: preterm (< 37 weeks') and low birth weight (< 2500 g) infants
Settings: high-income countries, and low- and middle-income countries
Intervention: topical ointment or cream ¶

Comparison: routine skin care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine skin care	Topical ointment or cream				
Invasive infection until hospital discharge	**228 per 1000**	**257 per 1000** (221 to 298)	**RR 1.13** (0.97 to 1.31)	2086 (8)	⊕⊕⊖⊖ **low** [a,b]	Six trials were conducted in high-income countries, one in a middle-income country (Turkey), and one in a low-income country (Bangladesh). No evidence of subgroup difference.
Mortality until hospital discharge (or latest reported)	**203 per 1000**	**176 per 1000** (152 to 209)	**RR 0.87** (0.75 to 1.03)	2067 (7)	⊕⊕⊖⊖ **low** [a,c]	Five trials were conducted in high-income countries, one in a middle-income country (Turkey) and one in a low-income country (Bangladesh). No evidence of subgroup difference.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

¶ Most trials used proprietary emollient, most commonly Aquaphor (a water-free petroleum-based ointment) and Bepanthen (a water-containing lanolin and petroleum-based ointment).
[a]Downgraded one level due to serious risk of bias (unclear random sequence generation in many trials; caregivers and investigators not masked in any trials). In one trial (Darmstadt 2005), there was a disruption in the method of the randomisation process, which may have contributed to an unequal distribution of infants between groups.
[b]Downgraded one level due to imprecision. 95% CI (0.97 to 1.31) consistent with no effect or substantial harm.
[c]Downgraded one level due to imprecision. 95% CI (0.75 to 1.03) consistent with no effect or substantial benefit.

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Summary of findings 2. Topical oil versus routine skin care for preterm infants

Topical oil versus routine skin care for preventing infection in preterm infants

Patient or population: preterm (< 37 weeks) and low birth weight (< 2500 g) infants
Settings: high-income countries, and low- and middle-income countries
Intervention: topical oil ¶

Comparison: routine skin care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine skin care	Topical oil				
Invasive infection until hospital discharge	**55 per 1000**	**39 per 1000** (29 to 53)	**RR 0.71** (0.52 to 0.96)	3256 (9)	⊕⊕⊖⊖ **low** [a,b]	Eight trials were conducted in low- or middle-income countries, and one in a high income country (Germany). No evidence of subgroup difference.
Mortality until hospital discharge (or latest reported)	**254 per 1000**	**239 per 1000** (208 to 274)	**RR 0.94** (0.82 to 1.08)	1119 (11)	⊕⊕⊖⊖ **low** [a,c]	Seven trials were conducted in low- or middle-income countries, and two in a high income country (France, Germany). No evidence of subgroup difference.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

¶ Sunflower, sunflower seed, other vegetable oils.
[a]Downgraded one level due to serious risk of bias (unclear random sequence generation or allocation concealment; caregivers and investigators not masked in any trials).
[b]Downgraded one level due to inconsistency. There was evidence of unexplained moderate heterogeneity in this meta-analysis (I^2 = 52%).
[c]Downgraded one level due to imprecision. 95% CI (0.82 to 1.08) consistent with potentially important benefit or harm.

Summary of findings 3. Topical ointment or cream versus oil for preterm infants

Topical ointment or cream versus oil for preventing infection in preterm infants

Patient or population: preterm (< 37 weeks) and low birth weight (< 2500 g) infants
Settings: high-income countries, and low- and middle-income countries

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Intervention: topical ointment or cream

Comparison: topical oil

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine skin care	Topical oil				
Invasive infection until hospital discharge	**189 per 1000**	**172 per 1000** (108 to 275)	**RR 0.91** (0.57 to 1.46)	316 (1)	⊕⊕⊖⊖ **low** [a],[b]	
Mortality until hospital discharge (or latest reported)	**660 per 1000**	**542 per 1000** (449 to 647)	**RR 0.82** (0.68 to 0.98)	316 (1)	⊕⊕⊖⊖ **low** [a],[c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

¶ Sunflower, sunflower seed, other vegetable oils.
[a]Downgraded one level due to serious risk of bias (unclear random sequence generation or allocation concealment; caregivers and investigators not masked in any trials).
[b]Downgraded one level due to imprecision. 95% CI (0.57 to 1.46) consistent with potentially important benefit or harm.
[c]Downgraded one level due to imprecision. 95% CI (0.68 to 0.98) consistent with potentially important benefit or minimal effect.

Summary of findings 4. Topical oil versus another oil for preterm infants

Topical oil versus another oil for preventing infection in preterm infants

Patient or population: preterm (< 37 weeks) and low birth weight (< 2500 g) infants
Settings: high-income countries, and low- and middle-income countries
Intervention: topical oil

Comparison: another topical oil

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine skin care	Topical oil				
Invasive infection until hospital discharge	**0 per 1000**	**0 per 1000** (0 to 0)	not estimable	64 (1)	⊕⊖⊖⊖	No events

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					very low [a,b]	
Mortality until hospital discharge (or latest reported)	**0 per 1000**	**0 per 1000** (0 to 0)	not estimable	64 (1)	⊕⊖⊖⊖ **very low** [a,b]	No events

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

[a]Downgraded one level due to serious risk of bias (caregivers and investigators not masked).
[b]Downgraded two levels due to serious imprecision. There were no events in either arm.

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BACKGROUND

Description of the condition

Invasive infection is the most common serious complication associated with intensive care for preterm infants. In high-income countries, invasive infection occurs in about one-in-five very preterm (< 32 weeks) infants, reflecting their duration of exposure to invasive procedures (Samanta 2011; Vergnano 2011; Berrington 2012). Coagulase-negative staphylococci cause about half of all invasive infections (Isaacs 2003). Other pathogens include gram-negative bacilli (mainly enteric bacilli), *Staphylococcus aureus*, enterococci, and fungi (predominantly *Candida spp.)* (Stoll 2002; Isaacs 2004; Gordon 2006; Camacho-Gonzalez 2013). The epidemiology of invasive infection in preterm infants in low- or middle-income countries may differ from that in high-income countries (Zaidi 2005; Khan 2017). The incidence is higher but infections are more commonly due to gram-negative bacilli and are less likely to be directly associated with intensive care or invasive procedures.

Preterm infants with invasive infection have an elevated risk of mortality and a range of important morbidities including necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) (Adams-Chapman 2006; Berrington 2012). Mortality and serious morbidity are usually associated with gram-negative bacilli, *Staphylococcus aureus,* enterococcal infection, or fungal infection. Coagulase-negative staphylococcal infection, although common, is associated with a more benign clinical course. However, even 'low grade' coagulase-negative staphylococcal bloodstream infection may generate inflammatory cascades associated with both acute morbidity and white matter and other brain damage that may adversely affect neurodevelopment (Stoll 2004).

Description of the intervention

Maturation of the epidermis in utero does not occur until about 34 weeks' gestational age. Although skin maturation is accelerated ex utero, the stratum corneum, eccrine glands, and acid mantle of preterm infants remain physically and functionally immature for several weeks after birth (Harpin 1983). Compared with term infants, preterm infants have few dermal elastic fibres and a weak dermal-epidermal junction prone to disruption. Very preterm infants, furthermore, lack a vernix caseosa - a mixture of proteins, lipids, and water with anti-inflammatory and antimicrobial properties (Marchini 2002). As well as increasing the rate of transepidermal evaporative heat loss, immaturity of the epidermal barrier predisposes preterm infants to microbial colonisation and infection (Evans 1986; Rutter 1988; Cartlidge 2000; Rutter 2000). The risk of infection is increased further because preterm infants' fragile skin is susceptible to damage through several mechanisms, including thermal, chemical, adhesive, friction and pressure injuries, as well as iatrogenic skin breaks from blood sampling, cannula placement, or extravasation of intravenously-administered fluids or medicines (Dyer 2013; Ness 2013).

Emollients

Emollients are moisturising treatments applied directly to the skin to protect the stratum corneum, enhance epidermal barrier function and reduce evaporative losses (Pickens 2000). Most proprietary or commercially-available emollients are creams (oil-in-water suspensions) or ointments (oily creams/water-in-oil). Some preparations contain antimicrobial or hydrating agents. Natural vegetable or plant oils (for example, mustard, safflower, sesame, coconut, olive, and soybean oils) have emollient properties and in many countries, particularly in south Asia, application of these to the newborn infant's whole body surface is a widespread traditional practice (Darmstadt 2002a; Darmstadt 2002b).

How the intervention might work

As well as providing a physical barrier to skin disruption, emollient oils, creams, or ointments provide lipids that are integrated into the epidermis to further enhance skin barrier function. Topical oils may also be a transcutaneous nutritional source of essential fatty acids for preterm or low birth weight infants (Lee 1993).

Potential adverse effects of emollients

Although emollients may plausibly improve skin barrier function, the process of application, which may include massage, could disrupt skin integrity in preterm infants. Emollients may also reduce the antimicrobial function of the acid mantle which could potentially increase the risk of colonisation and infection. Many emollients contain excipients which have the potential to be absorbed through the immature epidermal barrier resulting in contact sensitivity, epidermal injury, cutaneous haemorrhagic necrosis, and uraemia (Ness 2013).

Another concern is that emollient preparations may become contaminated and colonised with potential pathogens, particularly preparations stored in non-sealed containers (BNF for Children 2020). An important practical limitation is that emollients may reduce the effectiveness of adhesives needed to secure intravenous catheters or endotracheal tubes.

Why it is important to do this review

Given the potential for topical emollient therapy to improve skin barrier function and prevent infection in preterm infants, we have assessed the available evidence to inform practice and research.

OBJECTIVES

To assess the effect of topical application of emollients (ointments, creams, or oils) on the risk of invasive infection and mortality in preterm infants.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random participant allocation. Cluster-randomised trials where the unit of randomisation was a group of infants (for example, in a neonatal unit) were eligible for inclusion. Cross-over studies that assessed the use of emollient therapy in the same infant were not eligible for inclusion as this design would not permit a meaningful assessment of the effect of the intervention on the primary outcome for this review.

Types of participants

Preterm infants (< 37 weeks gestation)

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Types of interventions

- Ointment or cream versus routine skin care
- Oil versus routine skin care
- Ointment or cream versus oil
- One oil (or combination) versus another oil (or combination)

Types of outcome measures

Primary outcomes

Invasive infection diagnosed more than 48 hours after birth as determined by culture from a normally sterile site: cerebrospinal fluid; blood; urine (obtained by sterile urethral catheterisation or suprapubic bladder tap); bone or joint, peritoneum, pleural space, or central venous line tip; or findings on autopsy examination consistent with invasive microbial infection. If sufficient data were available, we planned to examine specific effects on infection with these organisms:

- Coagulase-negative staphylococci
- Other bacteria (gram-negative bacilli, *S aureus,* enterococci)
- Fungi

Secondary outcomes

- Death (all cause) before hospital discharge (in facility-based trials), or at latest assessment in community trials
- Growth: weight gain (g/kg/day); linear growth (mm/week); head circumference (mm/week); skinfold thickness (mm/week) during the trial period
- Neurodevelopmental outcomes assessed at more than 12 months post-term (measured using validated assessment tools) and classifications of disability, including auditory and visual disability. A composite outcome of 'severe neurodevelopmental disability' was defined as any one or combination of the following: non-ambulant cerebral palsy, severe developmental delay, auditory impairment and visual impairment.
- Bronchopulmonary dysplasia (BPD) (oxygen supplementation at 36 weeks' postmenstrual age)
- Necrotising enterocolitis (NEC) (Bell stage 2 or 3) (Bell 1978)
- Retinopathy of prematurity (ROP) requiring treatment (medical or surgical) (ICCROP 2005)

Search methods for identification of studies

Electronic searches

We conducted a comprehensive search in January 2021 including: Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 1, 01 January 2015 to 08 January 2021) in the Cochrane Library and Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (01 January 2015 to 08 January 2021). We have included the search strategies for each database in Appendix 1. We did not apply language restrictions.

We searched clinical trial registries for ongoing or recently completed trials. We searched the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp/search/en/), and the United States' National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov) via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry (http://www.isrctn.com/) for any unique trials not found through the Cochrane CENTRAL search.

Previous search details are listed in Appendix 2.

Searching other resources

We searched the reference lists of any articles selected for inclusion in this review.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

One review author (JC) screened titles and abstracts of all records identified by the search and coded records as 'order' or 'exclude'. A second review author (WM) assessed all records coded as 'order' and made the final decision about which records were ordered as full-text articles. Both authors read the full texts and used a checklist to assess each article's eligibility for inclusion on the basis of pre-specified inclusion and exclusion criteria.

Data extraction and management

Both authors extracted data independently using a data collection form to aid extraction of information on design, methods, participants, interventions, outcomes, and treatment effects from each included study. We discussed disagreements until we reached consensus. If data from the trial reports were insufficient, we contacted trialists for further information.

Assessment of risk of bias in included studies

Both authors independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).

We resolved any disagreements through discussion or by consulting a third assessor. See Appendix 3 for a description of risk of bias for each domain.

Measures of treatment effect

We analysed treatment effects in the individual trials using Review Manager 5 (Review Manager 2020), and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for one additional beneficial outcome (NNTB) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually-randomised trials. For cluster-randomised trials, we undertook analyses at the level of the individual while accounting for inter-cluster correlations in the data using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Cross-over studies were not eligible for inclusion.

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Dealing with missing data

We requested additional data from trial investigators when data on important outcomes were missing or were reported unclearly. If unavailable, we planned to undertake sensitivity analyses to assess the potential impact of missing outcome data.

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting the forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high (I^2 > 50%) heterogeneity, we planned to explore possible causes (differences in study design, participants, interventions, or outcome assessments).

Assessment of reporting biases

We planned to assess funnel plot asymmetry visually and with Harbord's modification of Egger's test in meta-analyses with data from more than nine trials contributing events (Harbord 2006).

Data synthesis

We used a fixed-effect model for meta-analysis (as per Cochrane Neonatal recommendations). When moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup (see below) and sensitivity (by methodological quality) analyses.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup comparisons.

- Very preterm (< 32 weeks) infants versus infants born at 32 weeks gestation or later.
- Low- and middle-income versus high-income countries. (For classification, see: datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income.)

Sensitivity analysis

We planned sensitivity analyses to determine how estimates of effect on invasive infection and mortality were affected by including only studies at low risk of selection bias (adequate randomisation and allocation concealment), detection or performance bias (adequate masking of intervention and measurement), attrition bias (< 20% loss to follow-up for primary outcome assessment), or reporting bias (selective reporting).

Summary of findings and assessment of the certainty of the evidence

Both authors (independently) used 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE) methods to assess the certainty of the evidence for effects on all-cause mortality and invasive infection (Schünemann 2013). We considered evidence from RCTs as high certainty but 'downgraded' one level for serious (or two levels for very serious) limitations based on: design weaknesses (risk of bias), inconsistency across studies, indirectness, imprecision of estimates, and presence of publication bias. This approach results in an assessment of the certainty of a body of evidence as one of four grades:

- high certainty: we have a lot of confidence that the true effect is similar to the estimated effect; further research is very unlikely to change our confidence in the estimate of effect;
- moderate certainty: we believe that the true effect is probably close to the estimated effect; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- low certainty: the true effect might be markedly different from the estimated effect; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- very low certainty: the true effect is probably markedly different from the estimated effect; we are very uncertain about the estimate.

We used GRADEpro GDT software to create ‘Summary of findings’ tables to report the certainty of the evidence.

RESULTS

Description of studies

Results of the search

See Figure 1.

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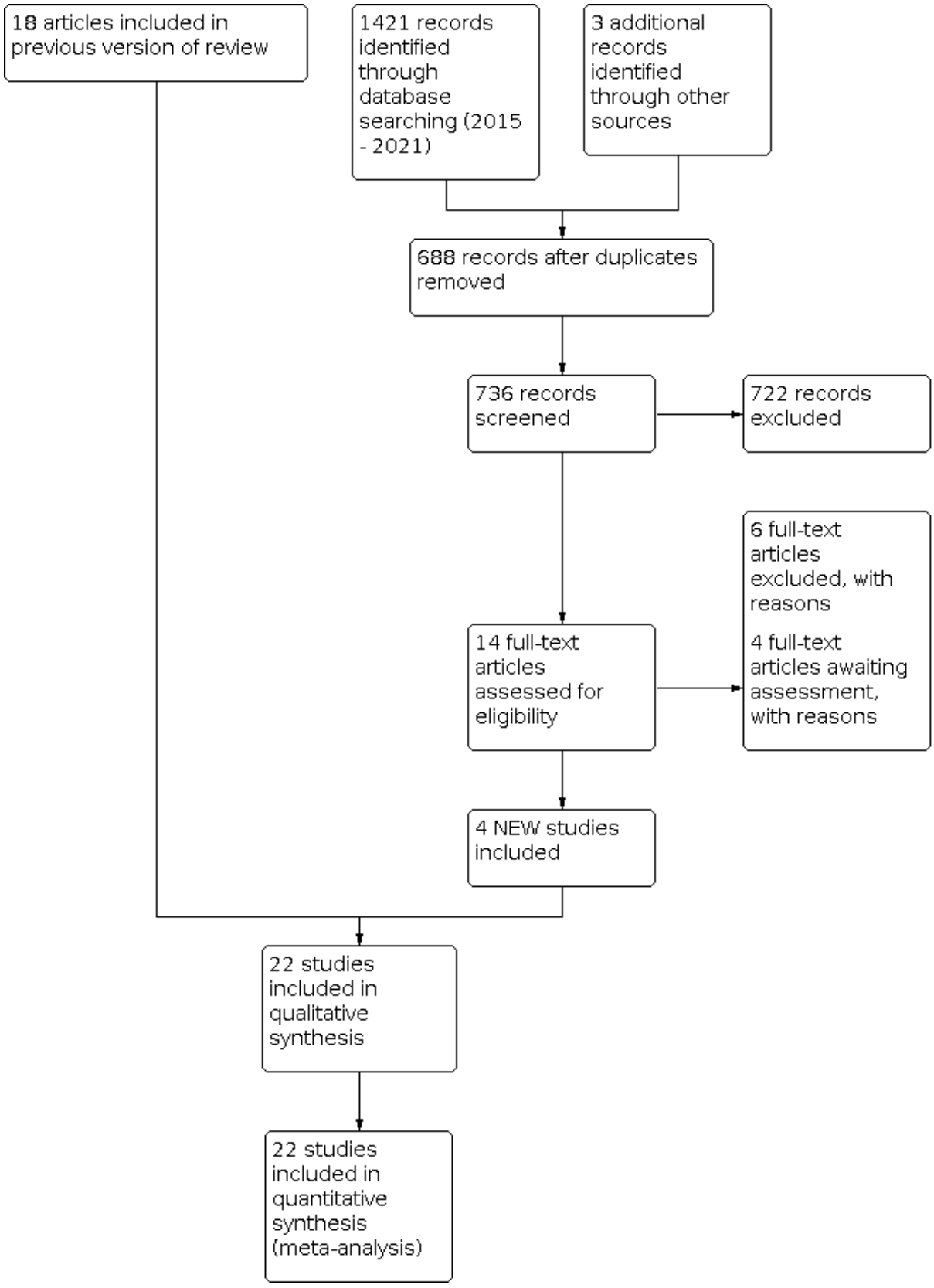
Figure 1. Study flow diagram: 2021 review update



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Included studies

We included trial reports from 22 primary publications (Characteristics of included studies). Most reports were of two-arm trials. Four were of three-arm trials (Arora 2005; Darmstadt 2005; Sankaranarayanan 2005; Kiechl-Kohlendorfer 2008).

Participants and setting

The included trials were conducted since the late 1990s in neonatal care centres in high-income countries (USA, Saudi Arabia, Germany, Austria, Australia, and France), middle-income countries (Turkey, India, Egypt, Iran, and Brazil), and a low-income country (Bangladesh).

In total, 5578 infants participated. Most trials were single-centre and facility-based. One large (N = 2249) community-based trial occurred in a "rural field practice" in West Bengal, India between 2014 and 2018 (Konar 2019).

Birth weight or gestational age inclusion criteria:

- Lane 1993: 29 to 36 weeks
- Nopper 1996: less than 33 weeks
- Pabst 1999: 26 to 30 weeks
- Soriano 2000: less than 1700 g
- Darmstadt 2004: less than 34 weeks
- Edwards 2004: less than 31 weeks and 501 g to 1000 g
- Arora 2005: less than 1500 g
- Darmstadt 2005: less than 33 weeks
- Sankaranarayanan 2005: 1500 g to 2000 g
- Kiechl-Kohlendorfer 2008: 25 to 36 weeks
- Vaivre-Douret 2008: 31 to 34 weeks
- Farhat 2010: less than 2000 g and less than 37 weeks
- Fallah 2013: 1500 g to 1999 g and 33 to 37 weeks
- Kumar 2013: less than 1800 g and less than 35 weeks
- Alkharfy 2014: less than 1250 g and less than 33 weeks
- Kanti 2014: 1500 g to 2500 g
- Erdemir 2015: less than 34 weeks
- Salam 2015: 26 to 36 weeks and more than 750 g
- Jabraeile 2016: 1500 g to 1000 g and 28 to 32 weeks
- Kukreja 2018: 1000 g to 2000 g
- Strunk 2018; less than 30 weeks
- Konar 2019: less than 37 weeks

Interventions

The intervention was generally commenced within a few days after birth and continued until about one to four weeks postnatally, or until hospital discharge. The ointments or oils were massaged between two and six times each day into the whole skin surface (except the face or head) by either the infant's mother or nurse or other caregiver.

Comparison 1

Eight trials compared treatment with emollient ointment (mainly proprietary preparations) versus routine skin care:

- Aquaphor(Nopper 1996; Pabst 1999; Edwards 2004; Darmstadt 2005; Erdemir 2015)
- Bepanthen(Kiechl-Kohlendorfer 2008)
- Eucerin (Lane 1993)
- petroleum jelly (Alkharfy 2014)
- olive oil/lanolin cream (Kiechl-Kohlendorfer 2008)

Comparison 2

Fifteen trials compared treatment with a natural vegetable or plant oil versus routine skin care:

- sunflower oil (Darmstadt 2004; Arora 2005; Darmstadt 2005; Farhat 2010; Fallah 2013; Kumar 2013; Kanti 2014; Kukreja 2018)
- coconut oil (Sankaranarayanan 2005; Salam 2015; Strunk 2018; Konar 2019)
- soybean oil (Soriano 2000)
- almond oil or vegetable oil (Vaivre-Douret 2008)
- olive oil (Jabraeile 2016)

Comparison 3

One trial compared ointment or cream versus topical oil:

- Aquaphor versus sunflower seed oil (Darmstadt 2005)

Comparison 4

One trial compared one oil with another oil

- coconut oil versus mineral oil (Sankaranarayanan 2005)

Outcomes

Most trials reported data on invasive infection and mortality. Several trials of topical oil versus standard care primarily assessed growth parameters but unpublished data on the rate of infection and death were available from the study investigators (Soriano 2000; Arora 2005; Sankaranarayanan 2005; Kumar 2013; Kukreja 2018; Konar 2019). None of the studies assessed any growth or neurodevelopmental outcomes beyond infancy.

Excluded studies

We screened the full texts of 32 articles of studies which did not meet inclusion criteria (see Characteristics of excluded studies). Five potentially eligible studies remain to be assessed when further information is available from the authors or via publication of the full report (Hu 2014; Saeidi 2014; Nangia 2015; Maamouri 2018; Summers 2019).

Risk of bias in included studies

See Figure 2

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

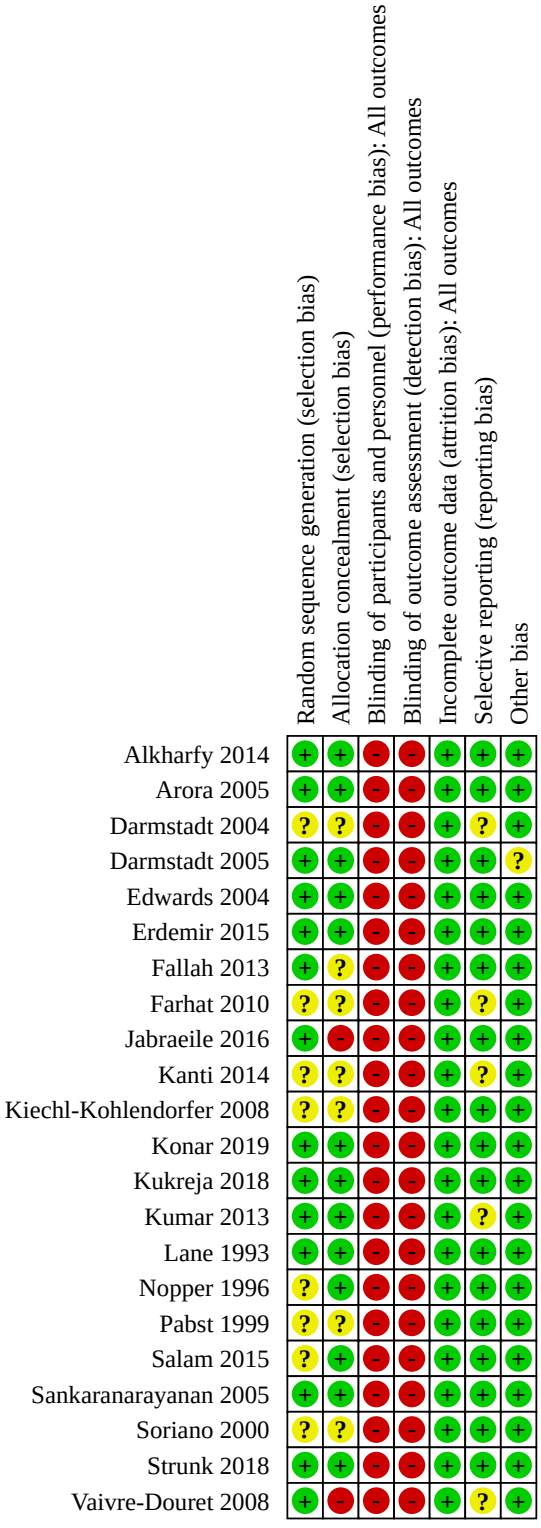

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Figure 2. (Continued)

Allocation

None of the included trials employed quasi-random allocation methods, but the methods used to generate the random sequence and conceal allocation are not described in about half of the trial reports.

Blinding

The caregivers and investigators were not masked to the intervention in any of the trials.

Incomplete outcome data

Attrition bias does not appear to be an issue in most trials (outcome data reported for > 80% of randomised cohorts).

Selective reporting

Most reports did not provide access to the trial protocol. It is unlikely, however, that reporting bias was an issue in most trials (low risk of bias) where the review's primary and infant-important outcomes were reported. In some trials, where the aim was to assess surrogate outcomes such as skin condition or hydration, clinical outcome data were generally available from the investigators.

Other potential sources of bias

We did not find evidence of important between-group differences in reported baseline characteristics in any of the included trials.

Effects of interventions

See: **Summary of findings 1** Topical ointment or cream versus routine skin care for preventing infection in preterm infants; **Summary of findings 2** Topical oil versus routine skin care for preterm infants; **Summary of findings 3** Topical ointment or cream versus oil for preterm infants; **Summary of findings 4** Topical oil versus another oil for preterm infants

Comparison 1. Topical ointment or cream versus routine skin care

Invasive infection

Meta-analysis did not show an effect (RR 1.13, 95% CI 0.97 to 1.31; I^2 = 36%; 8 trials, 2086 infants). There was no evidence of subgroup differences in trials conducted in low- and middle-income versus high-income countries (Chi^2 = 1.97, df = 1 (P = 0.16); Analysis 1.1; Figure 3). Sensitivity meta-analysis of trials at low risk of selection, attrition, or reporting bias showed a higher risk of infection in the intervention group (RR 1.18, 95% CI 1.01 to 1.38; I^2 = 12%; RD 0.04, 95% CI 0.00 to 0.08; 5 trials, 1834 infants).

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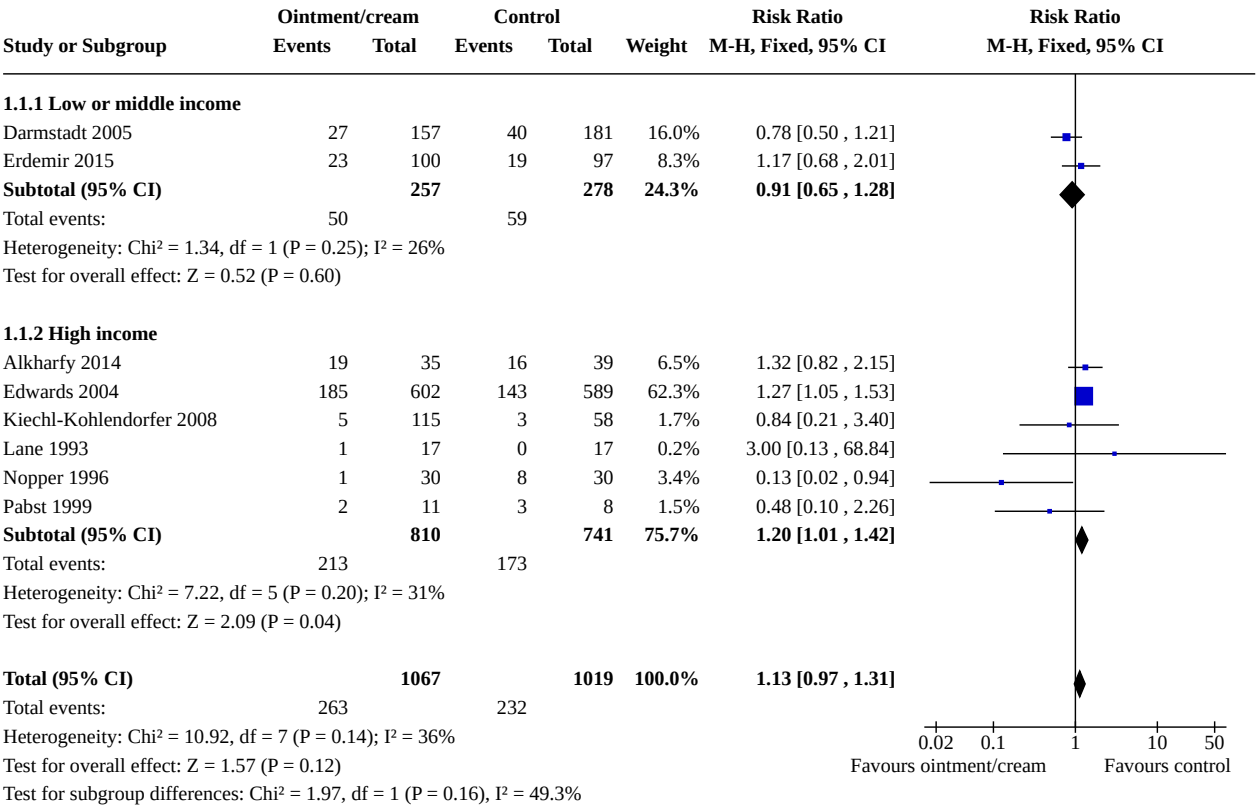
Figure 3. Forest plot of comparison: 1 Topical ointment or cream versus routine skin care, outcome: 1.1 Invasive infection (any organism).



Two trials (1210 infants) restricted participation to very preterm infants (Pabst 1999; Edwards 2004). Meta-analysis showed a higher rate of invasive infection in the intervention group (RR 1.25, 95% CI 1.04 to 1.50; I^2 = 32%; RD 0.06, 95% CI 0.01 to 0.11; number needed to treat for an additional harmful outcome (NNTH) 17, 95% CI 9 to 100; Analysis 1.2). The other trials did not report subgroup data for very preterm infants.

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 1).

Infection with specific organisms

Six trials (1839 infants) provided data on the type of infecting organism (Lane 1993; Nopper 1996; Pabst 1999; Edwards 2004; Darmstadt 2005; Erdemir 2015). The meta-analyses showed a higher risk of infection with coagulase-negative staphylococci but not infection with other bacteria or fungi:

- Coagulase-negative staphylococci: RR 1.30, 95% CI 1.03 to 1.65; I^2 = 36% (Analysis 1.3)
- Other bacteria (gram-negative bacilli, *S. aureus,* enterococci): RR 0.84, 95% CI 0.63 to 1.12; I^2 = 0% (Analysis 1.4)
- Fungi: RR 1.27, 95% CI 0.78 to 2.06, I^2 = 0% (Analysis 1.5)

Mortality

Meta-analysis did not show an effect (RR 0.87, 95% CI 0.75 to 1.03; I^2 = 39%; 6 trials, 2067 infants). There was no evidence of subgroup differences in trials conducted in low- and middle-income versus high-income countries (Chi^2 = 0.80, df = 1 (P = 0.37); Analysis 1.6; Figure 4). Sensitivity meta-analysis of trials at low risk of selection, attrition, or reporting bias did not show an effect (RR 0.87, 95% CI 0.74 to 1.02; I^2 = 54%; 5 trials, 1834 infants).

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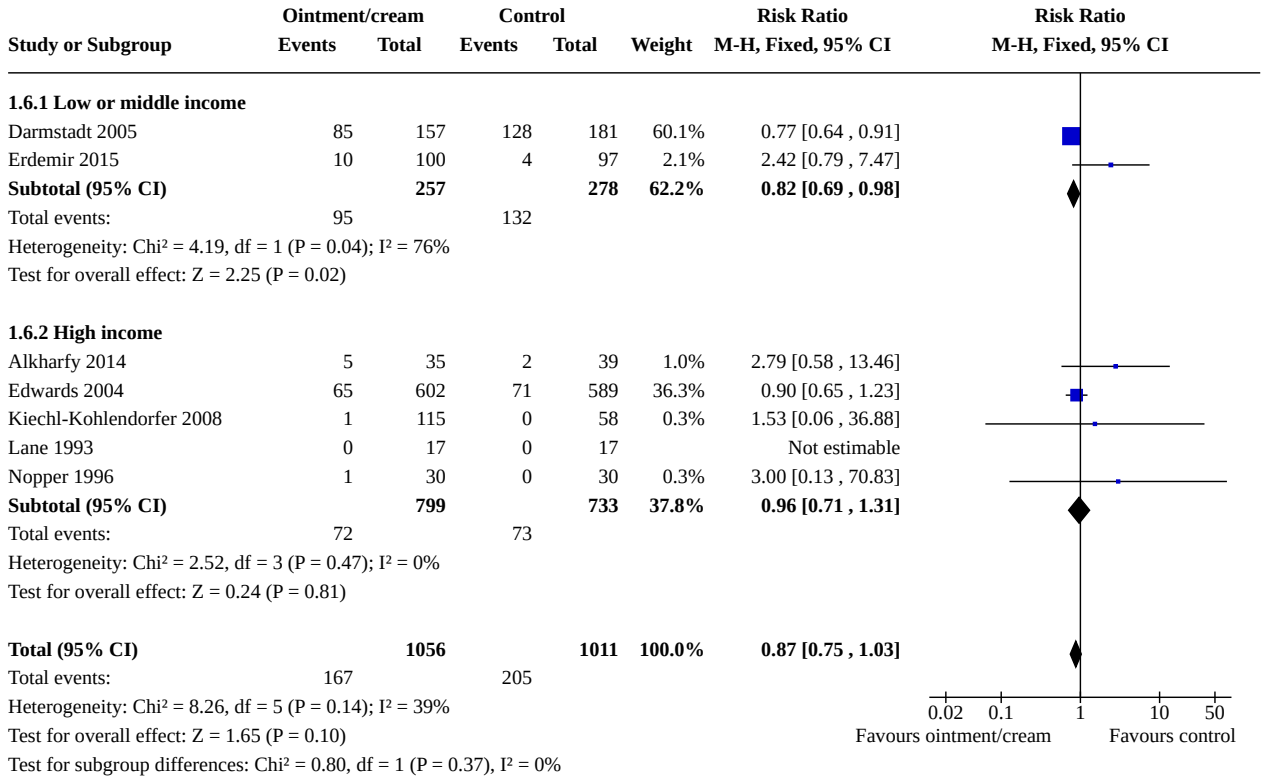
Figure 4. Forest plot of comparison: 1 Topical ointment or cream versus routine skin care, outcome: 1.6 Mortality.



One trial restricted participation to very preterm infants (Edwards 2004). Analysis did not show a difference (RR 0.90, 95% CI 0.65 to 1.23; 1 trial, 1191 infants; Analysis 1.7). The other trials did not report subgroup data for very preterm infants.

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 1).

Growth

Not reported.

Neurodevelopmental outcomes

Not reported.

BPD

Meta-analysis did not show a difference (RR 1.00, 95% CI 0.88 to 1.14; I^2 = 29%; 2 trials, 1009 infants; Analysis 1.8).

NEC

Meta-analysis did not show a difference (RR 1.25, 95% CI 0.89 to 1.76; I^2 = 0%; 4 trials, 1472 infants; Analysis 1.9).

ROP

Analysis did not show a difference (RR 0.99, 95% CI 0.77 to 1.28; 1 trial, 952 infants; Analysis 1.10).

Comparison 2. Topical oil versus routine skin care

Invasive infection

Meta-analysis showed a lower rate in the intervention group (RR 0.71, 95% CI 0.52 to 0.96; I^2 = 52%; RD -0.02, 95% CI -0.03 to 00.0; 9 trials, 3256 infants). There was no evidence of subgroup differences in trials conducted in low- and middle-income versus high-income countries (Chi^2 = 0.54, df = 1 (P = 0.46); Analysis 2.1; Figure 5). Sensitivity meta-analysis of trials at low risk of selection, attrition, or reporting bias did not show an effect (RR 0.91, 95% CI 0.65 to 1.30; I^2 = 24%; 6 trials, 1914 infants).

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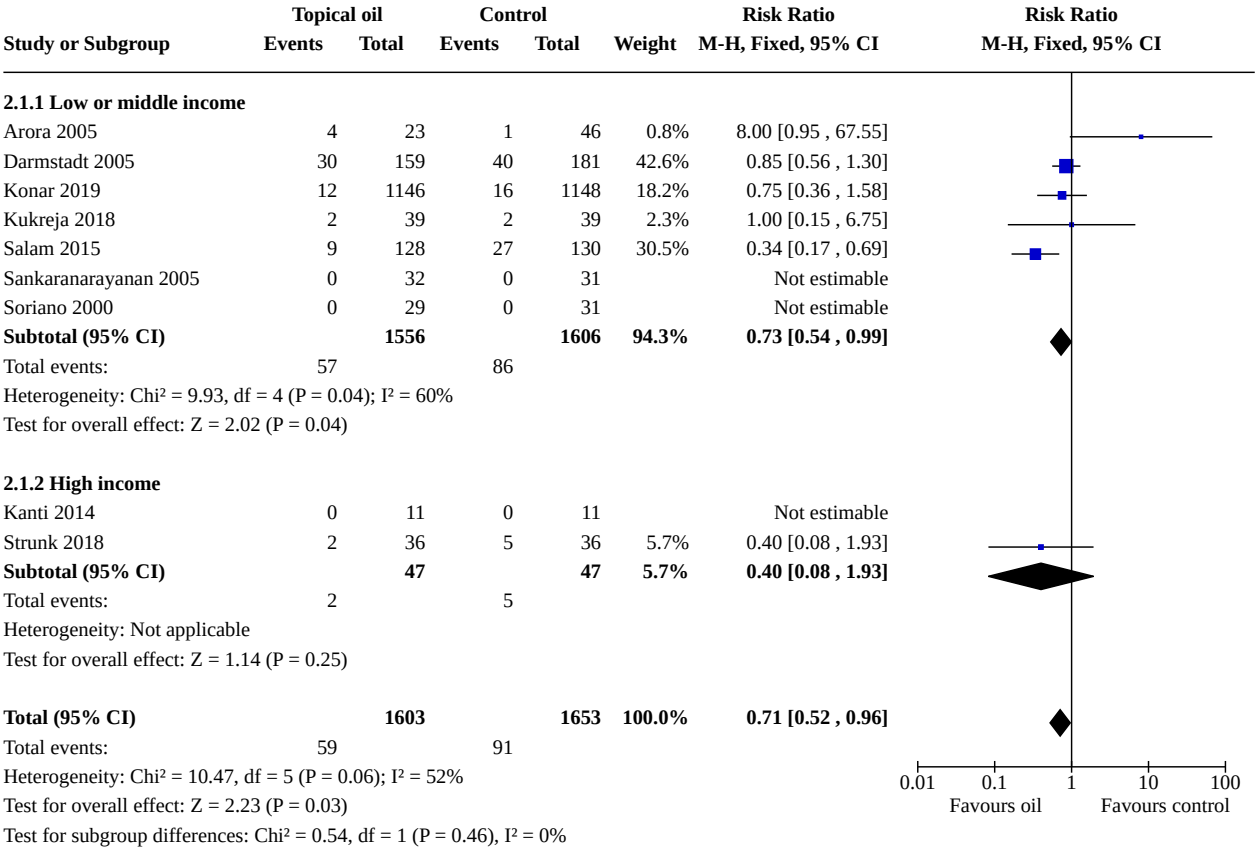
Figure 5. Forest plot of comparison: 2 Topical oil versus routine skin care, outcome: 2.1 Invasive infection (any organism).



One trial (78 infants) restricted participation to very preterm infants (Strunk 2018). Analysis did not show an effect (RR 0.40, 95% CI 0.08 to 1.93; Analysis 2.1). The other trials did not report subgroup data for very preterm infants.

Darmstadt 2004 stated that the rate of invasive infection was lower in the intervention group but did not report the number of infants in each group who had at least one episode of invasive infection. These data are not available from the principal investigator.

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and inconsistency (Summary of findings 2).

Infection with specific organisms

Four reports provided data on the type of infecting organism (Darmstadt 2005; Salam 2015; Kukreja 2018; Strunk 2018). None of the participants in three other trials had an episode of invasive infection (Soriano 2000; Sankaranarayanan 2005; Kanti 2014). None of the meta-analyses (7 trials, 893 infants) showed an effect:

- Coagulase-negative staphylococci: RR 0.22, 95% CI 0.05 to 1.02; I^2 = 0% (Analysis 2.2)
- Other bacteria (gram-negative bacilli, *Staphylococcus aureus,* enterococci): RR 0.71, 95% CI 0.48 to 1.04; I^2 = 0% (Analysis 2.3)
- Fungi: typical RR 1.93, 95% CI 0.42 to 8.78; I^2 = 52% (Analysis 2.4)

Mortality

Meta-analysis did not show an effect (RR 0.94, 95% CI 0.82 to 1.08; I^2 = 3%; 11 trials, 1119 infants). There was no evidence of subgroup differences in trials conducted in low- and middle-income versus high-income countries (Chi^2 = 2.11, df = 1 (P = 0.15); Analysis 2.5; Figure 6). Sensitivity meta-analysis of trials at low risk of selection, attrition, or reporting bias did not show an effect (RR 0.94, 95% CI 0.82 to 1.09; I^2 = 44%; 5 trials, 621 infants).

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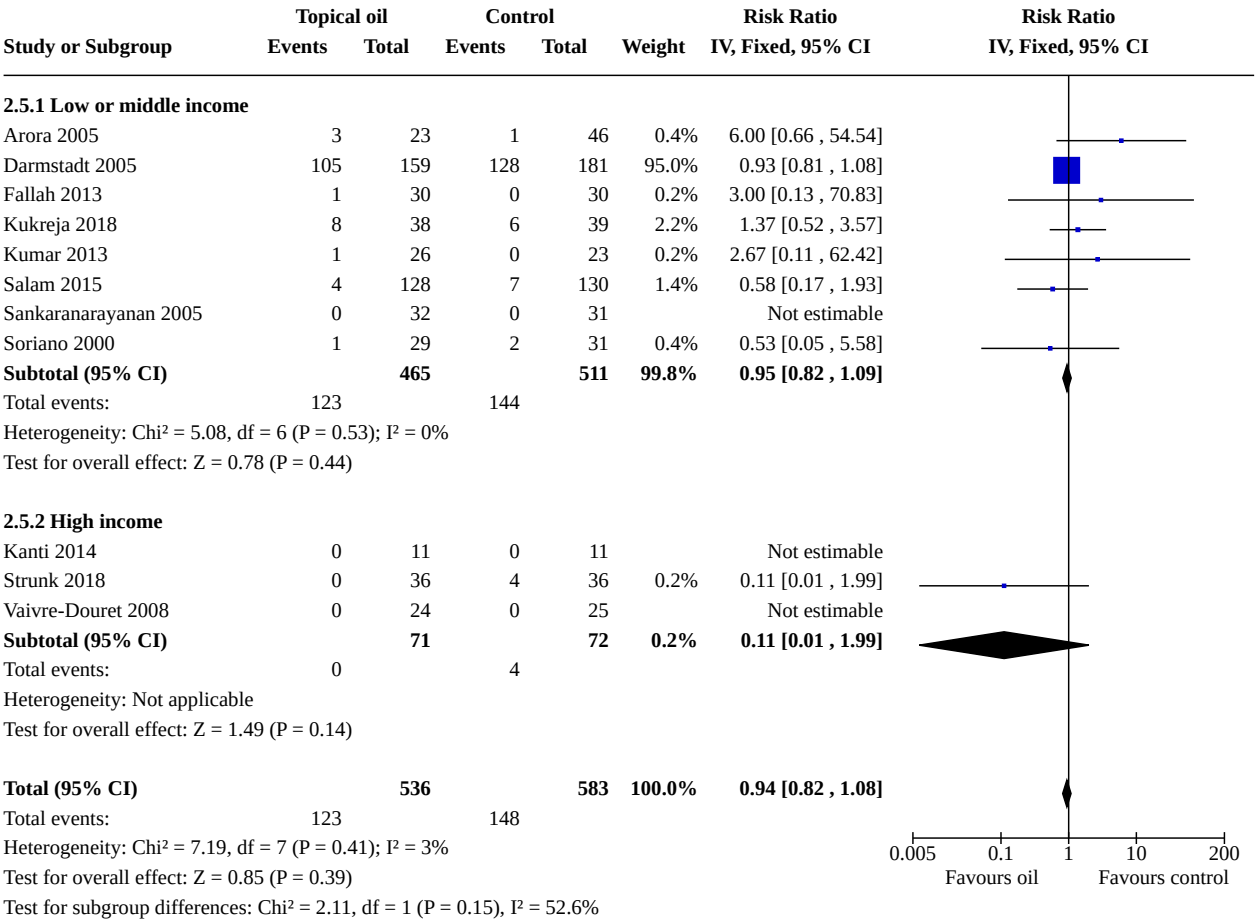
Figure 6. Forest plot of comparison: 2 Topical oil versus routine skin care, outcome: 2.5 Mortality.



One trial (78 infants) restricted participation to very preterm infants (Strunk 2018). Analysis did not show an effect (RR 0.11, 95% CI 0.01 to 1.99; Analysis 2.5). The other trials did not report subgroup data for very preterm infants.

Darmstadt 2004 reported infection-attributed mortality but not all-cause mortality data. We contacted the principal investigator but this information is not available for inclusion.

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 2).

Growth during the trial period

Data were available from seven trials (Soriano 2000; Arora 2005; Sankaranarayanan 2005; Farhat 2010; Fallah 2013; Kumar 2013; Jabraeile 2016). Meta-analyses showed that infants in the emollient group had higher rates of weight gain (MD 2.93 g/kg/day, 95% CI 2.11 to 3.76; I^2 = 62%) and linear growth (MD 1.34 mm/week, 95% CI 0.20 to 2.47; I^2 = 0%), but not head circumference growth (MD 0.66 mm/week, 95% CI -0.54 to 0.70; I^2 = 0%) or triceps skinfold thickness rate of change (MD 0.04 mm/week, 95% CI -0.03 to 0.11; I^2 = 0%; Analysis 2.6).

Two trials reported data on weight change that could not be meta-analysed:

- Strunk 2018: median weight after 21 days of infants in the emollient group was 100 g higher than the controls
- Kukreja 2018: average weight loss during the 10 days study period was not different (41 g/kg versus 39 g/kg)

Sensitivity analysis

The moderate heterogeneity (I^2 = 62%) in the meta-analysis of effect on weight gain is attributed to one 'outlier' (Jabraeile 2016). Exclusion of this trial removes the heterogeneity, but the effect size is similar (MD 2.62 g/kg/day, 95% CI 1.78 to 3.47; I^2 = 0%). Participants and interventions were similar to the other trials, and quality assessment scores were similar with the exception of allocation concealment. Investigators are likely to have been prospectively aware of group allocation. The mean weight at baseline differed between the groups (1321 g versus 1145 g; MD 176 g, 95% CI 119 to 233), which may have affected care practices and rate of weight gain over the ensuing 10 days.

Neurodevelopmental outcomes

One trial assessed neurodevelopment beyond infancy (Strunk 2018). Analysis did not show a difference in the prevalence of moderate or severe neurodevelopmental delay at 24 months (corrected age) in cognitive, language, motor or socio-emotional domains assessed using Bayley Scales of Infant Development (3rd Edition) (Analysis 2.7):

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- Cognitive: RR 0.25, 95% CI 0.06 to 1.11
- Language: RR 0.48, 95% CI 0.21 to 1.11
- Motor: RR 0.25, 95% CI 0.06 to 1.11
- Socio-emotional: RR 0.30, 95% CI 0.07 to 1.33

BPD

One trial (72 infants) assessed BPD (Strunk 2018). Analysis did not show a difference: RR 0.93, 95% CI 0.53 to 1.64 (Analysis 2.8).

NEC

One trial (72 infants) assessed NEC (Strunk 2018). Analysis did not show a difference: RR 0.20, 95% CI 0.01 to 4.03 (Analysis 2.9).

ROP

One trial (72 infants) assessed ROP (Strunk 2018). Analysis did not show a difference: RR 1.00, 95% CI 0.27 to 3.69 (Analysis 2.10).

Comparison 3. Topical ointment or cream versus oil

Invasive infection

One trial (316 infants) reported invasive infection (Darmstadt 2005). Analysis did not show a difference: RR 0.91, 95% CI 0.57 to 1.46 (Analysis 3.1).

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 3).

Infection with specific organisms

(i) Coagulase-negative staphylococci: no events detected (Analysis 3.2).

(ii) Other bacteria (gram-negative bacilli, *Staphylococcus aureus,* enterococci): RR 0.90, 95% CI 0.53 to 1.50 (Analysis 3.3).

(iii) Fungi: RR 1.35, 95% CI 0.31 to 5.94 (Analysis 3.4).

Mortality

One trial (316 infants) reported mortality (Darmstadt 2005). Analysis showed a reduced risk in the ointment/cream group: RR 0.82, 95% CI 0.68 to 0.98; RD -0.12, 95% CI -0.23 to -0.01; number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 4 to 100 (Analysis 3.5).

We assessed the certainty of evidence as low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 3).

Growth outcomes

Not reported.

Neurodevelopmental outcomes

Not reported.

BPD

Not reported.

NEC

Not reported.

ROP

Not reported.

Comparison 4. Topical oil versus another oil

Invasive infection

One trial (64 infants) reported invasive infection (Sankaranarayanan 2005). No events were detected (Analysis 4.1).

We assessed the certainty of evidence as very low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 4).

Mortality

One trial (64 infants) reported mortality (Sankaranarayanan 2005). No events were detected (Analysis 4.2).

We assessed the certainty of evidence as very low using GRADE methods, downgraded for serious study design limitations (lack of masking) and imprecision (Summary of findings 4).

Growth during the trial period

One trial (64 infants) assessed growth parameters (Sankaranarayanan 2005). Analysis showed a higher rate of weight gain in the coconut oil group compared to the mineral oil group (MD 2.00 g/kg/day, 95% CI 0.84 to 3.16). Rates of change in length (MD 0.40 mm/week, 95% CI -0.29 to 1.09) and head circumference (MD 0.10 mm/week, 95% CI -0.17 to 0.37) were not different (Analysis 4.3).

Neurodevelopmental outcomes

Not reported.

BPD

Not reported.

NEC

Not reported.

ROP

Not reported.

DISCUSSION

Summary of main results

Topical ointment or cream versus routine skin care

We included eight randomised controlled trials in which a total of 2086 preterm infants participated. The trials were undertaken during the past 25 years. Six were conducted in high-income countries, one in a middle-income country (Turkey) and one in a low-income country (Bangladesh). Most trials used proprietary emollient, most commonly Aquaphor (a water-free petroleum-based ointment) and Bepanthen (a water-containing lanolin and petroleum-based ointment). Most participants were preterm infants born before 32 weeks gestation, and in the largest trial, all participants were extremely low birth weight (N = 1191) (Edwards 2004).

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Meta-analyses did not show differences in the risk of invasive infection, mortality or morbidity (BPD, ROP, NEC) before discharge from hospital. We did not find evidence of a subgroup effect in a pre-specified analysis of trials set in high-income versus low- or middle-income countries. The certainty of the evidence for the effect on infection was assessed as low by GRADE methods because of concerns about the risk of selection, performance or detection bias in the included trials, and imprecision of the effect estimates.

Topical oil versus routine skin care

We included 15 randomised controlled trials in which a total of 3492 preterm infants participated. The trials were undertaken within the past 25 years. Nine were conducted in low- or middle-income countries, and two in high-income countries (Vaivre-Douret 2008; Kanti 2014). The most commonly used emollients were sunflower and other plant or vegetable oils. All but one of the trials were based in healthcare facilities. One large (2249 infants) community-based trial occurred in a rural field practice in West Bengal, India (Konar 2019). Most of the trials had some methodological limitations, particularly lack of masking of caregivers and clinicians, and uncertainty about the mechanics of the randomisation procedure.

Meta-analysis showed a lower rate of invasive infection in the intervention group, but this analysis showed moderate statistical heterogeneity (I^2 = 52%). A sensitivity meta-analysis of trials at low risk of bias did not show an effect. Meta-analyses did not show differences in mortality or other morbidity.

Infants massaged with vegetable oil had a higher rate of weight gain (about 2 g/kg/day) and linear growth (about 0.8 mm/week), though not head growth. These meta-analysis contained considerable heterogeneity. There are not yet any data at all on long-term growth and developmental outcomes.

Topical ointment or cream versus topical oil

Only one trial compared ointment (Aquaphor) versus sunflower seed oil (Darmstadt 2005). Analysis suggested a reduction in mortality in the ointment group but no evidence of an effect on the invasive infection rate.

Different oils

One small trial that compared coconut oil versus mineral oil did not detect any episodes of invasive infection or mortality in either group (Sankaranarayanan 2005).

Overall completeness and applicability of evidence

Topical ointment or cream versus routine skin care

These data provide low certainty evidence that topical ointments or creams may have little or no effect on invasive infection or mortality in preterm infants. Analysis of trials set in high-income countries suggests that routine topical application of ointments might increase the risk of infection. These trials recruited predominantly very preterm infants and most participants in the largest trial were of extremely low birth weight. This finding is consistent with those of a recent Cochrane Review that suggested that use of topical emollients during the first year of life in healthy term infants probably increases the risk of skin infection, perhaps related to suboptimal hand hygiene practices (Kelleher 2021).

The commonest organisms causing bloodstream infection were coagulase-negative staphylococci. Although some care practices, including infection control measures, feeding policies, and exposure to invasive procedures, may have changed since the larger trials were conducted more than 20 years ago, these findings are likely to remain applicable to the modern context of neonatal intensive care in high-income countries. A plausible mechanism for the increased risk of infection with coagulase-negative staphylococci is that application of the ointment causes skin trauma and epidermal micro-abrasion which permits transcutaneous migration of skin commensals. This is not consistent, however, with the finding in these trials that topical emollient improves skin condition as measured by skin score and evaporative water loss. Another possibility is that contamination may have occurred during the application process and that the ointment provided an environment conducive to the proliferation of bacteria. Analyses did not demonstrate an effect on infection due to other bacteria (gram-negative bacilli, enterococci, *S. aureus*) or fungi but these infections occurred infrequently compared with coagulase-negative staphylococcal infection and the 95% CI for these estimates are broad. Larger trials would be needed to obtain more precise estimates of the specific effect on these less common, though much more virulent, infections.

The finding from one trial that treatment with a topical ointment (Aquaphor), compared to routine skin care or application of vegetable oil, results in a substantial reduction in neonatal mortality should be interpreted and applied cautiously (Darmstadt 2005). Uncertainty exists concerning the method used to randomly allocate participants (discussed below).

Topical oil versus routine skin care

Trial data suggest that treatment with vegetable oils versus standard skin care may reduce the risk of invasive infection in preterm infants. This finding should be interpreted with caution as the 95% CI around the point estimate is broad and the meta-analysis is moderately heterogeneous. More precise estimates of effect sizes may be obtained when further data from a large ongoing trial are available (Kumar 2020).

The mechanism by which massage with vegetable oils increases the rates of weight and length gain is not clear. Transcutaneously absorbed lipids may be an additional source of calories or essential fatty acids. Reducing evaporative heat loss is another plausible mechanism. Applying topical oils by massage may have a calming effect that reduces energy expenditure or promotes more effective enteral feeding behaviours. Given the high risk of nutritional compromise that exists for preterm infants, particularly in low- and middle-income countries, it may be appropriate to undertake further trials to assess whether topical vegetable oils may have clinically important benefits during this potentially critical phase of growth and growth-programming (Mullany 2005).

Quality of the evidence

We assessed the evidence for the main outcomes (risk of infection and death) to be low certainty. Many of the trials contained methodological weaknesses; specifically, uncertainty about adequate allocation concealment methods in about half of the trials and lack of masking in all of the trials. Parents, caregivers, clinicians, and investigators were likely to have been aware of the treatment group to which infants had been allocated

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and this knowledge may have affected some care-giving practices or investigation strategies, including thresholds for screening for invasive infection, that may have affected the outcomes assessed.

A further concern exists with regard to the random allocation process used in one of the largest of the included trials (Darmstadt 2005). The report states that infants were randomised within "blocks of six with two assignments per block for all three of the groups". This form of block randomisation would be expected to generate roughly equal numbers of participants in each of the three study arms. However, the report indicates unequal distribution of infants. The principal investigator has provided further information (post hoc withdrawal of a fourth arm and change in the sequence generation and allocation methods) that may have contributed to this discrepancy. Given the potential for these post hoc changes to have disrupted the integrity of the randomisation process, it may be most appropriate to interpret and apply the findings of this trial with caution.

Potential biases in the review process

The main concern with the review process is the possibility that the findings are subject to publication and other reporting biases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of the major international perinatal conferences to identify trial reports that are not (or not yet) published in full form in academic journals. The meta-analyses that we performed did not contain sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

We have not been able to obtain data from two trials for inclusion in meta-analyses. Darmstadt 2004 did not report the number of infants in each group who acquired an infection (only the total number of infections which includes multiple infections in individual infants) or all-cause mortality (only infection-attributed mortality). These data have not yet been made available by the investigators. One trial has been completed but has yet to report methodological details and numerical data (Hu 2014). Four other potentially eligible trials have not reported clinical outcome data. We have sought these data from the investigators and, when available, we will include them in an updated version of this review.

Agreements and disagreements with other studies or reviews

Our findings are broadly consistent with other systematic reviews of topical emollient for preventing infection in preterm infants (Salam 2013; Pupala 2019). Our review differs from others in some respects:

- we included trials that assessed any emollient, but pre-specified separate comparisons of ointments/creams and oils;
- we conducted subgroup analyses to explore differences in effect sizes depending upon whether the trial was set in a low- or middle-income country versus a high-income country;
- we pre-specified sensitivity analyses to determine how trial methodological quality affected effect size estimates; and
- we included a GRADE assessment of the certainty of the evidence at outcomes level to help inform policy, practice, and research.

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic topical application of emollient ointment, particularly for very preterm infants in high-income countries, has not been shown to reduce the risk of infection or its associated morbidity or mortality, and may increase the risk of infection with coagulase-negative staphylococci.

In low- and middle-income countries, the available data provide low certainty evidence that topical emollients (either proprietary ointments or inexpensive vegetable oils) reduce the risk of infection (though not mortality). Some evidence exists that massage with vegetable oil results in higher rates of weight gain and linear growth but the effect on long-term growth and development is unknown.

Implications for research

Given the potential for this simple, low-cost, and readily available intervention to reduce the huge burden of infectious morbidity and mortality in preterm infants, particularly in low- and middle-income countries, further pragmatic randomised controlled trials are justified in order to improve the precision of the estimates of effect sizes. We are aware of one such trial awaiting analysis and reporting (Kumar 2020).

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Jon Dorling and Robert Boyle have peer reviewed the 2021 review update.

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Edwards WH, Conner JM, Soll RF et al. The effect of Aquaphor Original Emollient Ointment on nosocomial sepsis rates and skin integrity in infants of birth weight 501 to 1000 grams. *Pediatric Research* 2001;**49**:388A.

Soll 1998

Soll RF, Edwards WH. Emollient ointment for preventing infection in preterm infants. *Cochrane Database of*

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Systematic Reviews 1998, Issue 3. Art. No: CD001150. [DOI: 10.1002/14651858.CD001150]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alkharfy 2014

Study characteristics	
Methods	Randomised controlled trial.
Participants	Infants weighing 501 grams to 1250 grams at birth and with a gestational age of < 33 weeks.
Interventions	1. Twice-daily topical therapy of 2 g/kg petroleum jelly (N = 35) 2. Standard skin care (N = 39) Intervention applied until 34 weeks' postmenstrual age.
Outcomes	Invasive infection. NEC. BPD. Mortality.
Notes	Setting: Department of Pediatrics, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia (January 2008 to December 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sealed envelopes kept in closed closet, managed by study co-ordinator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked clinicians and investigators
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

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Arora 2005

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants of birth weight < 1500 grams, and < 10 days old, who were receiving enteral feeds.
Interventions	1. Massage with sunflower oil: N = 23 2. Massage without oil: N = 23 3. No massage (or oil): N = 23 Intervention applied for at least 10 days after enrolment. We combined groups 2 and 3 as a single control group for meta-analyses.
Outcomes	Growth. Invasive infection. Mortality.
Notes	Setting: Regional Neonatal Unit, Associated Lok Nayak Hospital, New Dehli, India (March to December 2001). Infection and mortality data courtesy of Professor Kumar. SD for change in length and head circumference imputed from Soriano 2000.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow-up assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

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Darmstadt 2004

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants of gestational age < 34 weeks and postnatal age < 72 hours. Exclusions: Infants considered likely to die within 48 hours, infants with major congenital anomalies, infants requiring major surgery, infants with immunodeficiency.
Interventions	1. Cutaneous application of sunflower seed oil to whole body apart from face and head (4 grams/kg/dose): N = 51. Infants received emollient thrice daily for 14 days, then twice daily until 28 days or discharge from hospital. 2. No emollient: N = 52. Control infants received standard skin care for preterm infants, which included minimal to no use of topical emollients.
Outcomes	Mortality attributed to sepsis. Invasive infection.
Notes	Setting: Kasr El-Aini NICU, Cairo University (dates not stated but trial likely to have been undertaken during late 1990s or early 2000s).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome assessment
Selective reporting (reporting bias)	Unclear risk	Mortality attributed to sepsis (all-cause mortality not reported or available from investigators). Invasive infection diagnosed more than 2 days after birth: the report did not state the number of infants in each group who had (at least one) episode of invasive infection. We contacted the principal investigator to seek these data but these have not yet been provided.
Other bias	Low risk	No evidence of baseline imbalance

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Darmstadt 2005

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants of gestational age at birth < 33 weeks and aged < 72 hours. Exclusions: Infants considered likely to die within 48 hours, infants with major congenital anomalies, infants requiring major surgery, infants with established skin infections.
Interventions	Massage (whole body apart from face and head) thrice daily for 14 days, then twice daily until discharge from hospital with: 1. Sunflower seed oil: N = 159 2. Aquaphor: N = 157 3. No emollient (control): N = 181
Outcomes	Invasive infection. Mortality.
Notes	Setting: Special Care Nursery, Dhaka Shishu Hospital, Bangladesh (1998 to 2003).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Manual generation of blocks of six with two assignments per block for all three of the groups, then computer-generated sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow-up assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Unclear risk	The report states that infants were randomised within "blocks of six with two assignments per block for all three of the groups". However, this process appears to be inconsistent with the allocated distribution of infants: 1. sunflower seed oil (N = 159), or 2. Aquaphor (N = 157), or 3. no emollient (control) (N = 181). The principal investigator of the trial has explained that this inconsistency may be due to two possible factors: 1. The trial originally had a fourth arm (emollient therapy with safflower oil) which was deemed unacceptable to parents and caregivers and removed from the trial when 24 infants had been randomised to the arms. These infants were not included in the final analyses.

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Darmstadt 2005 *(Continued)*

	2. The allocation sequence generation method was changed from the original manual process (selecting from a block of six envelopes) to a computer-generated sequence that did not maintain the balance of assignments within blocks.

Edwards 2004

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants, < 31 weeks gestation and birth weight 501 g to 1000 g, aged < 48 hours without evidence of skin disease and expected to survive beyond 48 hours.
Interventions	1. Prophylactic application of preservative free ointment (Aquaphor, Beiersdorf Inc.) twice daily: N = 602 2. Routine skin care: N = 589 (could include local application of Aquaphor to area of dermatitis if required) Intervention applied for 14 days.
Outcomes	Invasive infection. Mortality. BPD. NEC. ROP.
Notes	53 centres across Vermont Oxford Network in USA (trial performed during late 1990s to early 2000s). Dr Soll provided information on randomisation method and data on fungal infections.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near complete outcome assessment

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Edwards 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Erdemir 2015

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants (< 34 weeks) and < 24 hours old. Exclusions: Admitted after 24 hours, major congential abnormalities, infection (skin or systemic).
Interventions	1. Aquaphor once daily to entire body surface except head: N = 100 2. Routine skin care without emollient: N = 97 Intervention applied for 14 days.
Outcomes	Infection. Mortality. NEC.
Notes	Setting: Tepecik Hospital, Turkey (2010 to 2012). Additional information courtesy of investigators.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	Unlikely

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Erdemir 2015 *(Continued)*

Other bias	Low risk	No evidence of baseline imbalance

Fallah 2013

Study characteristics	
Methods	Randomised controlled trial.
Participants	Newborn infants (< 10 days old) of gestational age 33 to 37 weeks, and birth weight 1500 g to 1999 g. Exclusions: multiple pregnancy, birth asphyxia, sepsis, major congenital malformation, small for gestational age.
Interventions	1. Massage with sunflower oil, three times daily (N = 30) 2. Massage without oil (N = 30) Intervention applied for 14 days.
Outcomes	Growth parameters. Mortality. Infection data not available from investigators (May 2014).
Notes	Setting: Shahid Saddoughi Hospital, Yazd, Iran (2011). Growth parameters reported as mean at baseline and end of intervention. We calculated mean change and imputed the associated SD for weight gain from Kumar 2013 and SD for change in length and head circumference from Soriano 2000 (similar population, and same timescale of measurement).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow-up: 5 infants (2 in intervention group, and 3 controls) were lost to follow-up (and growth parameter data not available).
Selective reporting (reporting bias)	Low risk	Unlikely

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Fallah 2013 *(Continued)*

Other bias	Low risk	No evidence of baseline imbalance

Farhat 2010

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants (< 37 weeks) or birth weight < 2000 g and receiving 150 mL/kg/day of breast milk
Interventions	1. Daily massage with sunflower oil: N = 30 2. Routine skin care (no massage): N = 29 Intervention applied for seven days.
Outcomes	Weight change [mean estimated from graph, SD imputed from Kumar 2013]
Notes	Setting: Emamreza Hospital, Mashhad, Iran (2007-9). Further data on infection and mortality not available from investigators (May 2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete assessment of weight change outcome
Selective reporting (reporting bias)	Unclear risk	Data on infection and mortality not reported or available from investigators (May 2014).
Other bias	Low risk	No evidence of baseline imbalance

Jabraeile 2016

Study characteristics	

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Jabraeile 2016 *(Continued)*

Methods	Randomised controlled trial.
Participants	Preterm infants 28 to 32 weeks' gestation, or birth weight 1000 g to 1500 g. Exclusions: infants with congenital anomalies, or signs of physiological instability.
Interventions	1. Olive oil massage thrice daily: N = 45 2. Massage without emollient: N = 45 Intervention applied for up to 10 days.
Outcomes	Duration of hospitalisation. Weight gain during the 10 days intervention period.
Notes	Setting: Neonatal Intensive Care Unit, Al-Zahra Hospital, Tabriz, Iran (2018). The mean weight at baseline differed between the groups (1321 g versus 1145 g; MD 176 g, 95% CI 119 to 233).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	High risk	Investigators likely to have been prospectively aware of group allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete (86/90)
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Kanti 2014

Study characteristics

Methods	Randomised controlled trial
Participants	Preterm infants (< 48 hours after birth) with birth weight 1500 grams to 2500 grams

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Kanti 2014 *(Continued)*

Interventions	1. Sunflower seed oil daily applied to whole body every 3 to 4 hours for 10 days: N = 11 2. Control (no oil): N = 11
Outcomes	Transepidermal water loss, stratum corneum hydration, skin pH and sebum level (no episodes of invasive infection or death)
Notes	Setting: Department of Neonatology, Charité Universitätsmedizin Berlin, Germany (2009 to 2011).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment
Selective reporting (reporting bias)	Unclear risk	Data on clinical outcomes courtesy of Dr Bartels (2015).
Other bias	Low risk	No evidence of baseline imbalance

Kiechl-Kohlendorfer 2008

Study characteristics

Methods	Randomised controlled trial
Participants	Preterm infants (25 to 36 weeks) admitted to NICU (neonatal intensive care unit)
Interventions	1. Water-in-oil emollient cream (Bepanthen): N = 57 2. Olive oil cream (70% lanolin, 30% olive oil): N = 58 3. Routine skin care (control group): N = 58 Emollients applied twice daily to body surface except head for 4 weeks
Outcomes	Invasive infection. Mortality.

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Kiechl-Kohlendorfer 2008 *(Continued)*

Notes	Setting: Department of Pediatrics, Innsbruck Medical University, Innsbruck, Austria (2004 to 2006). We combined groups 1 and 2 as a single intervention (ointment) group for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Konar 2019

Study characteristics

Methods	Randomised controlled trial
Participants	Preterm infants < 37 weeks (modified Ballard scoring) Exclusions: infants with congenital anomalies, skin rash or infection, critically ill.
Interventions	1. Coconut oil (5 mL) massaged on entire body except face and scalp four times daily: N = 1146 2. Massage only (no emollient): N = 1148 Intervention applied for seven days.
Outcomes	Skin condition during neonatal period. Neurodevelopmental score (motor/mental) in infancy Invasive infection (> 72 h after birth) defined as "clinical signs with positive sepsis screen with or without positive blood culture".
Notes	Setting: "Rural field practice", Department of Community Medicine, Burdwan Medical College, India (2014 to 2018).

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Konar 2019 *(Continued)*

	Unpublished data on infants with positive blood culture supplied by Dr Konar.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed, opaque, envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Kukreja 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants with birth weight 1000 g to 2000 g. Exclusions: infants with major congenital anomalies, skin disease, need for mechanical ventilation for >12 h.
Interventions	1. Topical sunflower seed oil (4 mL/kg) applied to entire body below neck thrice daily: N = 39 2. Standard skin care (no emollient): N = 39 Intervention applied for seven days.
Outcomes	Invasive infection (until day 28). Skin condition and microbial colonisation.
Notes	Setting: Neonatal Unit, Maulana Azad Medical College, New Dehli, India (2015 to 2016). Mortality data courtesy of Prof Ajay Kumar (February 2021)
Risk of bias	

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Kukreja 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Serial, sealed, opaque, envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Kumar 2013

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants of birth weight < 1800 grams and < 35 weeks' gestation, who were receiving ≥ 100 ml/kg/day enteral feeds. Exclusions: Infants receiving supplemental oxygen > 48 hours after birth, infants with major congenital anomalies, intracranial haemorrhage, meningitis or encephalopathy.
Interventions	1. Massage with sunflower oil four times daily: N = 27 2. Standard care (no massage): N = 25 Intervention applied for up to 28 days.
Outcomes	Growth parameters. Mortality.
Notes	Setting: Neonatal Intensive Care Unit (NICU), LLRM Medical College, Meerut, India (2009 to 2010). Cross-over contamination was limited by "segregating the two groups in separate NICU rooms". SD for change in length and head circumference imputed from Soriano 2000. Data on invasive infection not available from investigators (May 2014).
Risk of bias	

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Kumar 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete growth data assessment (3 randomised infants not included because of protocol violation or loss to follow-up)
Selective reporting (reporting bias)	Unclear risk	Data on invasive infection not available from investigators
Other bias	Low risk	No evidence of baseline imbalance

Lane 1993

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants (gestational age 29 to 36 weeks), aged < 24 hours.
Interventions	1. Prophylactic application of water-in-oil emollient (Eucerin Creme, Beiersdorf, Inc.) twice daily: N = 17 2. No emollient (standard skin care): N = 17 Intervention applied for 16 days.
Outcomes	Invasive infection. Mortality (no deaths).
Notes	Setting: Departments of Dermatology and Pediatrics, Stanford University, California, early 1990s (single centre). Clarification of methods and outcomes courtesy of Professor Alfred Lane (May 2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table

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Lane 1993 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Nopper 1996

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants (gestational age < 33 weeks), aged < 96 hours, without evidence of skin disease.
Interventions	1. Prophylactic application of preservative-free ointment (Aquaphor, Beiersdorf, Inc.) applied twice daily: N = 30 2. Standard skin care (which could include a water-in-oil emollient if required (Eucerin, Beiersdorf, Inc.): N = 30 Intervention applied for 14 days.
Outcomes	Invasive infection. Mortality. Weight change. Time to regain birth weight.
Notes	Setting: Departments of Dermatology and Pediatrics, Stanford University, California, early-mid 1990s (single centre). Clarification of methods and outcomes courtesy of Professor Alfred Lane (May 2014).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

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Nopper 1996 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Pabst 1999

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants (gestational age 26 to 30 weeks), aged < 24 hours.
Interventions	1. Prophylactic application of preservative-free ointment (Aquaphor Ointment, Beiersdorf, Inc.) applied twice daily: N = 11 2. Standard skin care (no emollients): N = 8 Intervention applied for 14 days.
Outcomes	Weight change. Invasive infection. [Mortality not reported]
Notes	Setting: Department of Pediatrics, University of Maryland, Baltimore, US (mid-1990s).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Unmasked parents and caregivers

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Pabst 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Salam 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Hospital-born preterm infants (gestational age > 26 weeks).
Interventions	1. Coconut oil massage twice daily: N = 128 2. Routine skin care: N = 130 Twice daily topical application of coconut oil by nurses from birth until discharge and continued thereafter by mothers at home until completion of the 28th day of life.
Outcomes	Invasive infection. Neonatal mortality.
Notes	Setting: Nursery and neonatal intensive care unit at Aga Khan University Hospital, Pakistan. ClinicalTrials.gov Identifier: NCT01396642

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Staff "blinded to randomisation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators

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Salam 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

Sankaranarayanan 2005

Study characteristics	
Methods	Randomised controlled trial.
Participants	Appropriate for gestational age preterm infants with birth weight 1500 g to 2000 g
Interventions	1. Coconut oil massage: N = 38 2. Mineral oil massage: N = 37 3. Massage with baby powder: N = 37 Intervention applied from day 2 until day 31 after birth (4 times daily for 5 minutes).
Outcomes	Growth parameters.
Notes	Setting: Department of Neonatology, LTM Medical College and General Hospital, Mumbai, India. Infection and mortality data courtesy of Dr Sankaranarayanan.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment
Selective reporting (reporting bias)	Low risk	Unlikely

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Sankaranarayanan 2005 *(Continued)*

Other bias	Low risk	No evidence of baseline imbalance

Soriano 2000

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants (gestational age 28 to 34 weeks and birth weight < 1700 grams). Infants were fully enterally fed before entering the trial. Exclusions: Infants receiving supplemental oxygen, ventilation, inotropic agents, corticosteroids, and infants with congenital anomalies.
Interventions	1. Thrice daily cutaneous application of soybean oil (6 grams/kg/day of linoleic acid) for 30 days: N = 29 2. No cutaneous treatment: N = 31
Outcomes	Growth parameters. Invasive infection. Mortality.
Notes	Setting: Newborn Nursery, Hospital das Clinicas de Ribeirao Preto, Sao Paulo, Brazil (1992 to 1993). Further data courtesy of Dr Francisco Martinez.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome assessment
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

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Strunk 2018

Study characteristics	
Methods	Randomised controlled trial.
Participants	Preterm infants < 30 weeks' gestation, postnatal age < 24 hours. Exclusions: infants with major congenital anomalies, or signs of pre-existing skin infection.
Interventions	1. Topical coconut oil (5 mL/kg) twice daily: N = 36 2. Standard skin care (no emollient): N = 36 Intervention applied for up to 21 days.
Outcomes	Skin condition until day 21. Weight gain. Invasive infection. Necrotising enterocolitis (NEC). Mortality. Cognitive, language, motor or socio-emotional delay assessed at 24 months (corrected age) using Bayley Scales of Infant Development (3rd Edition).
Notes	Setting: Neonatal Intensive Care Unit, Edward Memorial Hospital, Perth, Australia (2018).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed, coded, opaque, serially-numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete for in hospital outcomes (25% attrition for neurodevelopmental assessments)
Selective reporting (reporting bias)	Low risk	Unlikely
Other bias	Low risk	No evidence of baseline imbalance

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Vaivre-Douret 2008

Study characteristics	
Methods	Randomised controlled trial
Participants	Preterm infants (31 to 34 weeks). Exclusions: Mechanical ventilation or supplemental oxygen requirement, maternal drug misuse, congenital abnormalities.
Interventions	1. Almond oil or vegetable oil massage twice daily for ten days: N = 24 2. Saline massage or no intervention (routine care): N = 25
Outcomes	Growth (weight and length percentage change) reported but data suitable for inclusion in meta-analyses not available. Mortality (no deaths). Infection not reported and data not available from investigators.
Notes	Setting: Tertiary Neonatal Unit, Poitou-Charentes, France (2002 to 2004). We have sought but have not received further clarification and data from the investigators (May 2014).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	High risk	Clinician allocation (likely to have been aware)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked parents and caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unmasked clinicians and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete growth parameters data reported
Selective reporting (reporting bias)	Unclear risk	Infection not reported and data not available from investigators
Other bias	Low risk	No evidence of baseline imbalance

Characteristics of excluded studies *[ordered by study ID]*

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Study	Reason for exclusion
Abdallah 2013	Quasi-experimental design (epoch-comparison).
Ang 2012	No emollient in intervention.
Beeram 2006	Retrospective case control study.
Berger 2009	Duplicate. Article reporting same research as Kiechl-Kohlendorfer 2008.
Brandon 2010	No Sting (not an emollient) versus emollient; no routine care as control arm.
Brice 1981	Comparison of paraffin mixture with thermal blankets.
Caglar 2020	Randomised controlled trial. Preterm infants 32- 37 weeks' gestation. Measured effect of topical sunflower oil versus almond oil versus no emollient on skin condition and hydration over first five days. No data on outcome measures of interest.
Campbell 2000	Case control study.
Diego 2008	No emollient in intervention.
Ferber 2005	No emollient in intervention.
Fernandez 1987	Case control study.
Fernandez 2005	Not a randomised controlled trial.
Guzzetta 2011	No emollient in intervention.
Jansi 2008	Partcipants predominantly term babies - outcomes for preterm infants not reported.
Mathai 2001	Quasi-randomised trial of massage using powder or mineral oil - no routine care as control arm.
Mendes 2008	No emollient in intervention.
Montaseri 2020	Randomised controlled trial. Preterm infants 30 to 36 weeks' gestation. Measured effect of massage with olive oil versus no emollient on weight change after first five days. No data on outcome measures of interest. Irct20170520034039N
Rutter 1981	Non-random: "before-and-after" (epoch-comparison) study.
Smith 2013	No emollient in intervention.
Solanki 2005a	Randomised controlled trial. Measured effect of topical safflower oil versus coconut oil versus no oil on fatty acid profiles and triglyceride levels in blood.

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Study	Reason for exclusion
	No data on outcome measures of interest.
Taheri 2018	Randomised controlled trial. Assessed effect of sunflower oil massage on weight change over first five days after birth. No data on outcome measures of interest.
Wananukul 2001	Comparison of topical application of liquid paraffin mixture to one side of the body with no application to the other side.
Wananukul 2002	Effect of liquid paraffin emollient on trans-epidermal water loss and ambient skin temperature. Outcomes measured for 5 hours only.

Characteristics of studies awaiting classification *[ordered by study ID]*

Hu 2014

Methods	Randomised controlled trial
Participants	428 preterm infants < 34 weeks' gestational age and < 72 hours old were considered eligible for the study during September 2010 to June 2012
Interventions	Infants were randomly assigned to sunflower seed oil group (153 cases) or Johnson oil group (140 cases) or control group (135 cases)
Outcomes	Skin condition Infection
Notes	

Maamouri 2018

Methods	Unclear whether this is an RCT: "The subjects were placed in two groups" (clarification sought from investigators)
Participants	60 preterm infants (< 34 weeks)
Interventions	1. Sunflower oil (N = 27) 2. Control group (N = 33) The body surface of these infants was massaged with sunflower oil three times a day for 2 weeks and then twice for up to 28 days.
Outcomes	Skin condition Blood culture-confirmed infection
Notes	Setting: Neonatal Intensive Care Unit, Ghaem Hospital in Mashhad, Iran (2016): Irct20130120012197N

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Nangia 2015

Methods	Randomised controlled trial
Participants	Preterm infants with birth weight 751 g to 1499 g. Exclusions: infants with major congenital anomalies or asphyxia or hydrops.
Interventions	1. Topical coconut oil (4 mL) applied to trunk below neck twice daily: N = 37 2. Standard skin care (no emollient): N = 37 Intervention applied for seven days.
Outcomes	Trans-epidermal water loss. Microbial skin colonisation after seven days.
Notes	Setting: Neonatal Unit, Kalawati Saran Children's Hospital, New Dehli, India (2006). Data on invasive infection and mortality sought March 2021.

Saeidi 2014

Methods	Randomised controlled trial.
Participants	Preterm infants < 37 weeks' gestation, postnatal age < 28 days. Exclusions: infants with major congenital anomalies, pre-existing skin conditions, or receiving respiratory support.
Interventions	1. Massage with medium chain triglyceride (likely coconut) oil (4 mL) applied below neck four times daily: N = 40 2. Massage only (no emollient): N = 41 Intervention applied for seven days.
Outcomes	Weight change until day 7.
Notes	Setting: Neonatal Intensive Care Unit, Qaem Educational Hospital, Mashhad, Iran (trial period not reported). Data on invasive infection and mortality sought March 2021.

Summers 2019

Methods	Cluster randomised controlled trial.
Participants	Preterm infants of gestational age at birth < 37 weeks Exclusions: Infants considered likely to die within 48 hours, infants with major congenital anomalies, infants requiring major surgery, infants with established skin infections.
Interventions	"Full-body" massage with: 1. Sunflower seed oil: N = 195

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Summers 2019 *(Continued)*	2. Mustard oil: N = 204 Promoted daily massage by mothers for 28 days.
Outcomes	Trans-epidermal water loss. Skin condition and pH.
Notes	Community-based; Sarlahi, Nepal (2012 to 2014) Data on invasive infection and mortality sought March 2021.

Characteristics of ongoing studies *[ordered by study ID]*

Kumar 2020	
Study name	Impact of topical application of cold-pressed sunflower seed oil with improved massage practices on neonatal mortality: a cluster-randomised controlled trial in rural North India
Methods	Cluster-randomised controlled trial
Participants	All newborns identified within the study area until 7 days after their delivery are considered eligible for the trial
Interventions	1. Sunflower seed oil massage (10 mL, three times daily) by families through the neonatal period 2. Usual care
Outcomes	Neonatal mortality rate after 24 hours of birth.
Starting date	01/01/2015
Contact information	Dr Vishwajeet Kumar, Uttar Pradesh, Lucknow, India (vishwajeet.kumar@shivgarh.org)
Notes	ISRCTN38965585 WHO Reference No.: RPC667 The Universal Trial Number (UTN): U1111-1158-4665 [subgroup data for preterm infants will be sought]

DATA AND ANALYSES

Comparison 1. Topical ointment or cream versus routine skin care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Invasive infection (any organism)	8	2086	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.97, 1.31]
1.1.1 Low or middle income	2	535	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.28]
1.1.2 High income	6	1551	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.01, 1.42]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Invasive infection (trials with only very preterm infants participating)	2	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.04, 1.50]
1.3 Invasive infection (coagulase negative staphylococci)	6	1839	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.03, 1.65]
1.3.1 Low or middle income	2	535	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.71, 2.22]
1.3.2 High income	4	1304	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.02, 1.70]
1.4 Invasive infection (other bacteria)	6	1839	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.12]
1.4.1 Low or middle income	2	535	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.46, 1.18]
1.4.2 High income	4	1304	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.63, 1.29]
1.5 Invasive infection (fungi)	6	1839	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.78, 2.06]
1.5.1 Low or middle income	2	535	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.46, 6.65]
1.5.2 High income	4	1304	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.72, 2.02]
1.6 Mortality	7	2067	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.03]
1.6.1 Low or middle income	2	535	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
1.6.2 High income	5	1532	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.31]
1.7 Mortality (trials with only very preterm infants participating)	1	1191	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.23]
1.8 BPD	2	1009	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.88, 1.14]
1.9 NEC	4	1472	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.89, 1.76]
1.10 ROP (severe)	1	952	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.28]

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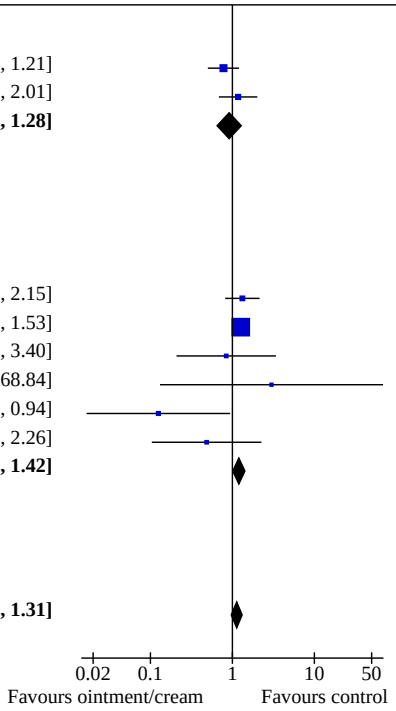
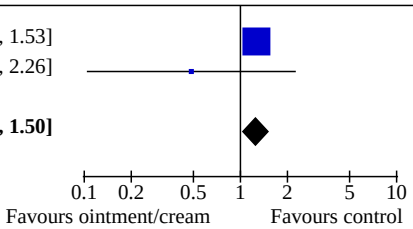
Analysis 1.1. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 1: Invasive infection (any organism)

Study or Subgroup	Ointment/cream Events	Ointment/cream Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Low or middle income						
Darmstadt 2005	27	157	40	181	16.0%	0.78 [0.50 , 1.21]
Erdemir 2015	23	100	19	97	8.3%	1.17 [0.68 , 2.01]
Subtotal (95% CI)		**257**		**278**	**24.3%**	**0.91 [0.65 , 1.28]**
Total events:	50		59			
Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² = 26%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.1.2 High income						
Alkharfy 2014	19	35	16	39	6.5%	1.32 [0.82 , 2.15]
Edwards 2004	185	602	143	589	62.3%	1.27 [1.05 , 1.53]
Kiechl-Kohlendorfer 2008	5	115	3	58	1.7%	0.84 [0.21 , 3.40]
Lane 1993	1	17	0	17	0.2%	3.00 [0.13 , 68.84]
Nopper 1996	1	30	8	30	3.4%	0.13 [0.02 , 0.94]
Pabst 1999	2	11	3	8	1.5%	0.48 [0.10 , 2.26]
Subtotal (95% CI)		**810**		**741**	**75.7%**	**1.20 [1.01 , 1.42]**
Total events:	213		173			
Heterogeneity: Chi² = 7.22, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**1067**		**1019**	**100.0%**	**1.13 [0.97 , 1.31]**
Total events:	263		232			
Heterogeneity: Chi² = 10.92, df = 7 (P = 0.14); I² = 36%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 1.97, df = 1 (P = 0.16), I² = 49.3%						



Analysis 1.2. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 2: Invasive infection (trials with only very preterm infants participating)

Study or Subgroup	Ointment/cream Events	Ointment/cream Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 2004	185	602	143	589	97.7%	1.27 [1.05 , 1.53]
Pabst 1999	2	11	3	8	2.3%	0.48 [0.10 , 2.26]
Total (95% CI)		**613**		**597**	**100.0%**	**1.25 [1.04 , 1.50]**
Total events:	187		146			
Heterogeneity: Chi² = 1.47, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Not applicable						



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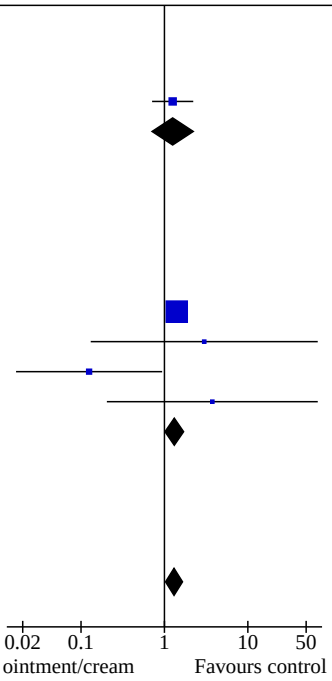
Analysis 1.3. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 3: Invasive infection (coagulase negative staphylococci)

Study or Subgroup	Ointment/cream Events	Ointment/cream Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Low or middle income						
Darmstadt 2005	0	157	0	181		Not estimable
Erdemir 2015	22	100	17	97	16.4%	1.26 [0.71 , 2.22]
Subtotal (95% CI)		**257**		**278**	**16.4%**	**1.26 [0.71 , 2.22]**
Total events:	22		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.3.2 High income						
Edwards 2004	112	602	78	589	75.0%	1.40 [1.08 , 1.83]
Lane 1993	1	17	0	17	0.5%	3.00 [0.13 , 68.84]
Nopper 1996	1	30	8	30	7.6%	0.13 [0.02 , 0.94]
Pabst 1999	2	11	0	8	0.5%	3.75 [0.20 , 68.89]
Subtotal (95% CI)		**660**		**644**	**83.6%**	**1.31 [1.02 , 1.70]**
Total events:	116		86			
Heterogeneity: Chi² = 6.24, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**917**		**922**	**100.0%**	**1.30 [1.03 , 1.65]**
Total events:	138		103			
Heterogeneity: Chi² = 6.29, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 2.22 (P = 0.03)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



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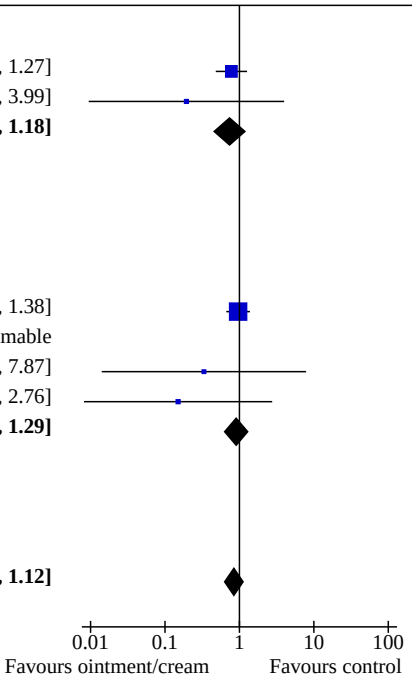
Analysis 1.4. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 4: Invasive infection (other bacteria)

Study or Subgroup	Ointment/cream Events	Ointment/cream Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Low or middle income						
Darmstadt 2005	23	157	34	181	34.3%	0.78 [0.48 , 1.27]
Erdemir 2015	0	100	2	97	2.8%	0.19 [0.01 , 3.99]
Subtotal (95% CI)		**257**		**278**	**37.1%**	**0.74 [0.46 , 1.18]**
Total events:	23		36			
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
1.4.2 High income						
Edwards 2004	52	602	53	589	58.2%	0.96 [0.67 , 1.38]
Lane 1993	0	17	0	17		Not estimable
Nopper 1996	0	30	1	30	1.6%	0.33 [0.01 , 7.87]
Pabst 1999	0	11	2	8	3.1%	0.15 [0.01 , 2.76]
Subtotal (95% CI)		**660**		**644**	**62.9%**	**0.90 [0.63 , 1.29]**
Total events:	52		56			
Heterogeneity: Chi² = 1.95, df = 2 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**917**		**922**	**100.0%**	**0.84 [0.63 , 1.12]**
Total events:	75		92			
Heterogeneity: Chi² = 3.18, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.24)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						



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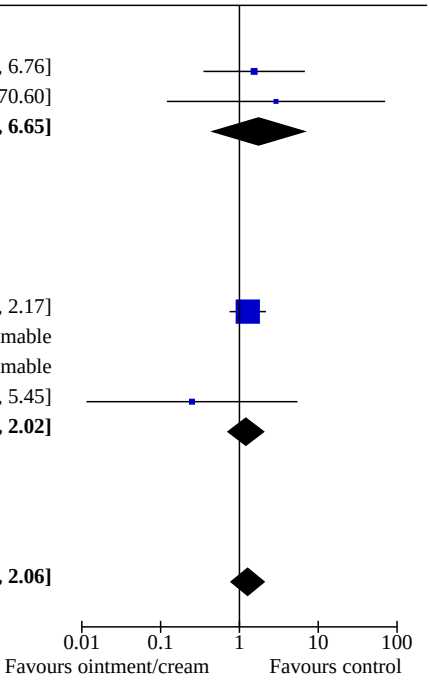
Analysis 1.5. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 5: Invasive infection (fungi)

Study or Subgroup	Ointment/cream Events	Ointment/cream Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Low or middle income						
Darmstadt 2005	4	157	3	181	9.9%	1.54 [0.35 , 6.76]
Erdemir 2015	1	100	0	97	1.8%	2.91 [0.12 , 70.60]
Subtotal (95% CI)		**257**		**278**	**11.7%**	**1.75 [0.46 , 6.65]**
Total events:	5		3			
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.5.2 High income						
Edwards 2004	30	602	23	589	82.3%	1.28 [0.75 , 2.17]
Lane 1993	0	17	0	17		Not estimable
Nopper 1996	0	30	0	30		Not estimable
Pabst 1999	0	11	1	8	6.1%	0.25 [0.01 , 5.45]
Subtotal (95% CI)		**660**		**644**	**88.3%**	**1.21 [0.72 , 2.02]**
Total events:	30		24			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 4%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**917**		**922**	**100.0%**	**1.27 [0.78 , 2.06]**
Total events:	35		27			
Heterogeneity: Chi² = 1.39, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



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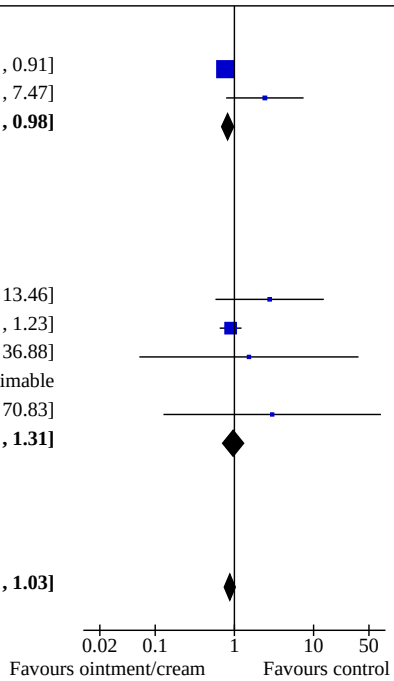
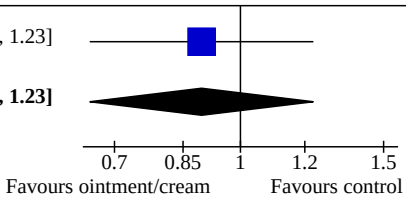
Analysis 1.6. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 6: Mortality

Study or Subgroup	Ointment/cream Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Low or middle income						
Darmstadt 2005	85	157	128	181	60.1%	0.77 [0.64 , 0.91]
Erdemir 2015	10	100	4	97	2.1%	2.42 [0.79 , 7.47]
Subtotal (95% CI)		**257**		**278**	**62.2%**	**0.82 [0.69 , 0.98]**
Total events:	95		132			
Heterogeneity: Chi² = 4.19, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.6.2 High income						
Alkharfy 2014	5	35	2	39	1.0%	2.79 [0.58 , 13.46]
Edwards 2004	65	602	71	589	36.3%	0.90 [0.65 , 1.23]
Kiechl-Kohlendorfer 2008	1	115	0	58	0.3%	1.53 [0.06 , 36.88]
Lane 1993	0	17	0	17		Not estimable
Nopper 1996	1	30	0	30	0.3%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**799**		**733**	**37.8%**	**0.96 [0.71 , 1.31]**
Total events:	72		73			
Heterogeneity: Chi² = 2.52, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**1056**		**1011**	**100.0%**	**0.87 [0.75 , 1.03]**
Total events:	167		205			
Heterogeneity: Chi² = 8.26, df = 5 (P = 0.14); I² = 39%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%						



Analysis 1.7. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 7: Mortality (trials with only very preterm infants participating)

Study or Subgroup	Ointment/cream Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 2004	65	602	71	589	100.0%	0.90 [0.65 , 1.23]
Total (95% CI)		**602**		**589**	**100.0%**	**0.90 [0.65 , 1.23]**
Total events:	65		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



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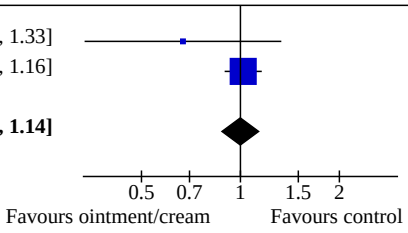
Analysis 1.8. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 8: BPD

Study or Subgroup	Ointment/cream Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alkharfy 2014	9	35	15	39	5.9%	0.67 [0.34 , 1.33]
Edwards 2004	232	466	229	469	94.1%	1.02 [0.90 , 1.16]
Total (95% CI)		**501**		**508**	**100.0%**	**1.00 [0.88 , 1.14]**
Total events:	241		244			

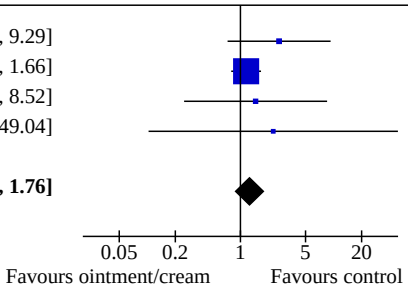
Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 29%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 9: NEC

Study or Subgroup	Ointment/cream Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alkharfy 2014	7	35	3	39	5.3%	2.60 [0.73 , 9.29]
Edwards 2004	56	595	48	587	89.9%	1.15 [0.80 , 1.66]
Erdemir 2015	3	100	2	97	3.8%	1.46 [0.25 , 8.52]
Pabst 1999	1	11	0	8	1.1%	2.25 [0.10 , 49.04]
Total (95% CI)		**741**		**731**	**100.0%**	**1.25 [0.89 , 1.76]**
Total events:	67		53			

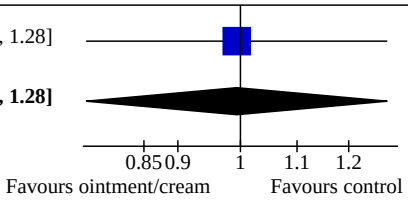
Heterogeneity: Chi² = 1.63, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Topical ointment or cream versus routine skin care, Outcome 10: ROP (severe)

Study or Subgroup	Ointment/cream Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 2004	95	475	96	477	100.0%	0.99 [0.77 , 1.28]
Total (95% CI)		**475**		**477**	**100.0%**	**0.99 [0.77 , 1.28]**
Total events:	95		96			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Comparison 2. Topical oil versus routine skin care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Invasive infection (any organism)	9	3256	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.96]
2.1.1 Low or middle income	7	3162	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.54, 0.99]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.2 High income	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 1.93]
2.2 Invasive infection (coagulase negative staphylococci)	7	893	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 1.02]
2.2.1 Low or middle income	5	799	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.16]
2.2.2 High income	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.27]
2.3 Invasive infection (other bacteria)	7	893	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.04]
2.3.1 Low or middle income	5	799	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.48, 1.05]
2.3.2 High income	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.75]
2.4 Invasive infection (fungi)	7	893	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.42, 8.78]
2.4.1 Low or middle income	5	799	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.42, 8.78]
2.4.2 High income	2	94	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.5 Mortality	11	1119	Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.82, 1.08]
2.5.1 Low or middle income	8	976	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.82, 1.09]
2.5.2 High income	3	143	Risk Ratio (IV, Fixed, 95% CI)	0.11 [0.01, 1.99]
2.6 Growth	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 Rate of weight gain (g/kg/day)	7	433	Mean Difference (IV, Fixed, 95% CI)	2.93 [2.11, 3.76]
2.6.2 Change in crown-heel length (mm/week)	6	358	Mean Difference (IV, Fixed, 95% CI)	1.34 [0.20, 2.47]
2.6.3 Change in head circumference (mm/week)	6	358	Mean Difference (IV, Fixed, 95% CI)	0.66 [-0.54, 1.85]
2.6.4 Change in triceps skinfold thickness (mm/week)	2	99	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.03, 0.11]
2.7 Moderate-severe neurodevelopmental delay	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 BSID III cognitive score (<85)	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.11]
2.7.2 BSID III language score (<85)	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.21, 1.11]
2.7.3 BSID III motor score (<85)	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.11]
2.7.4 Socio-emotional score (<85)	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.07, 1.33]

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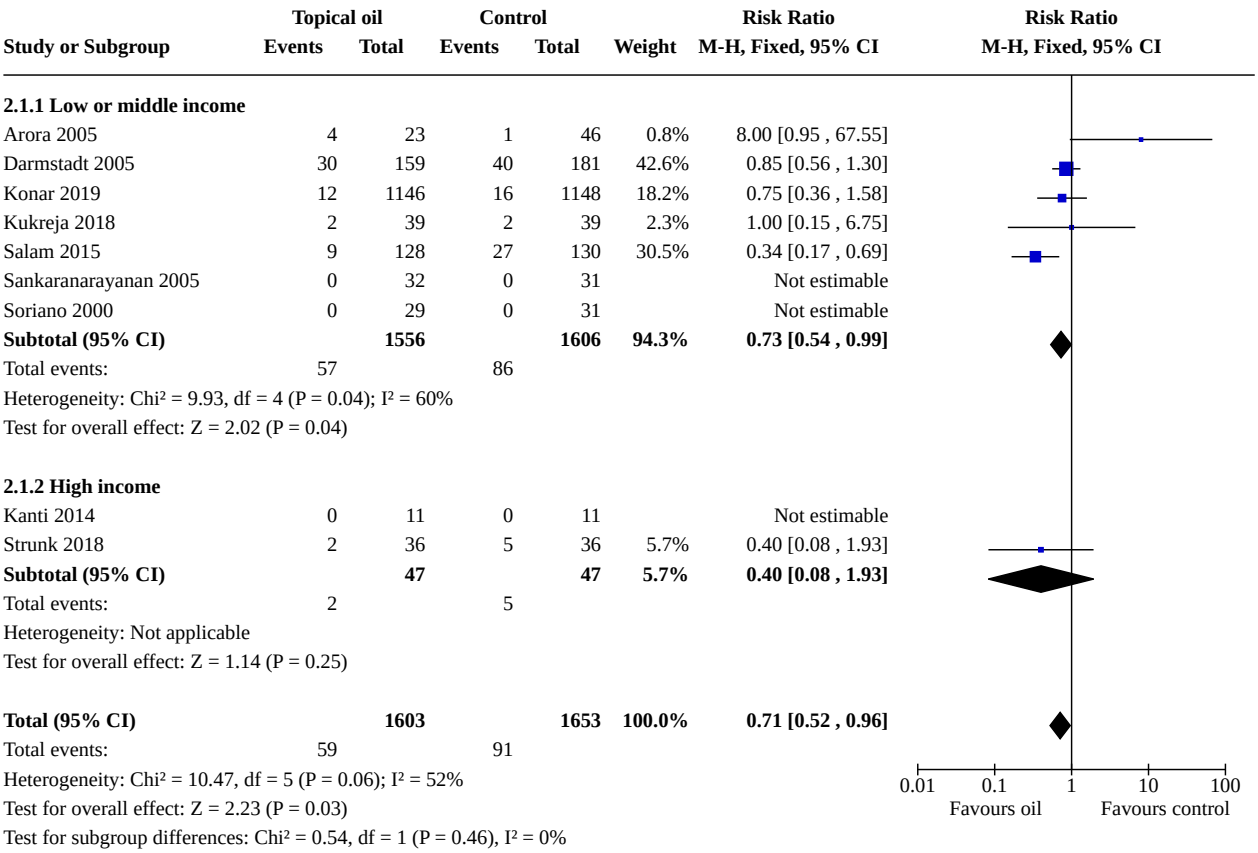
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 BPD	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.53, 1.64]
2.9 NEC	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.03]
2.10 ROP (severe)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.69]
2.11 Severe neurodevelopmental disability	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.11.1 BSID (3rd Ed): Cognitive <70	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.60]
2.11.2 BSID (3rd Ed): Language <70	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.95]
2.11.3 BSID (3rd Ed): Motor <70	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.42]
2.11.4 BSID (3rd Ed): Social-emotional <70	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.54]

Analysis 2.1. Comparison 2: Topical oil versus routine skin care, Outcome 1: Invasive infection (any organism)



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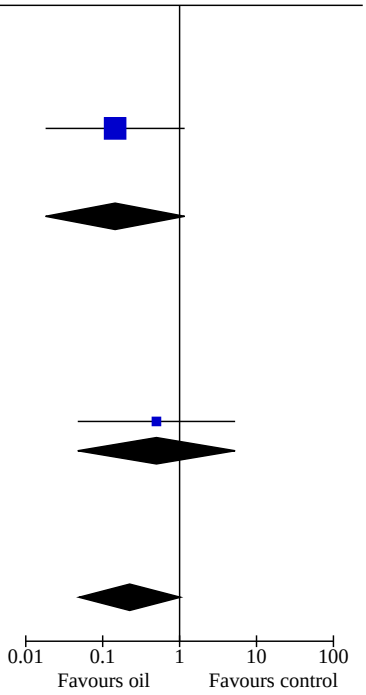
Analysis 2.2. Comparison 2: Topical oil versus routine skin care, Outcome 2: Invasive infection (coagulase negative staphylococci)

Study or Subgroup	Topical oil Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Low or middle income						
Darmstadt 2005	0	159	0	181		Not estimable
Kukreja 2018	0	39	0	39		Not estimable
Salam 2015	1	128	7	130	77.6%	0.15 [0.02 , 1.16]
Sankaranarayanan 2005	0	32	0	31		Not estimable
Soriano 2000	0	29	0	31		Not estimable
Subtotal (95% CI)		**387**		**412**	**77.6%**	**0.15 [0.02 , 1.16]**
Total events:	1		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.2.2 High income						
Kanti 2014	0	11	0	11		Not estimable
Strunk 2018	1	36	2	36	22.4%	0.50 [0.05 , 5.27]
Subtotal (95% CI)		**47**		**47**	**22.4%**	**0.50 [0.05 , 5.27]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**434**		**459**	**100.0%**	**0.22 [0.05 , 1.02]**
Total events:	2		9			
Heterogeneity: $Chi^2 = 0.61$, df = 1 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: $Chi^2 = 0.60$, df = 1 (P = 0.44), $I^2 = 0\%$						



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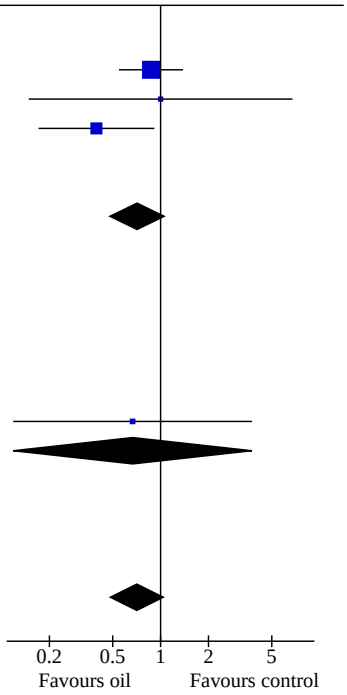
Analysis 2.3. Comparison 2: Topical oil versus routine skin care, Outcome 3: Invasive infection (other bacteria)

Study or Subgroup	Topical oil Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Low or middle income						
Darmstadt 2005	26	159	34	181	58.2%	0.87 [0.55 , 1.38]
Kukreja 2018	2	39	2	39	3.7%	1.00 [0.15 , 6.75]
Salam 2015	7	128	18	130	32.7%	0.39 [0.17 , 0.91]
Sankaranarayanan 2005	0	32	0	31		Not estimable
Soriano 2000	0	29	0	31		Not estimable
Subtotal (95% CI)		**387**		**412**	**94.5%**	**0.71 [0.48 , 1.05]**
Total events:	35		54			
Heterogeneity: Chi² = 2.74, df = 2 (P = 0.25); I² = 27%						
Test for overall effect: Z = 1.70 (P = 0.09)						
2.3.2 High income						
Kanti 2014	0	11	0	11		Not estimable
Strunk 2018	2	36	3	36	5.5%	0.67 [0.12 , 3.75]
Subtotal (95% CI)		**47**		**47**	**5.5%**	**0.67 [0.12 , 3.75]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**434**		**459**	**100.0%**	**0.71 [0.48 , 1.04]**
Total events:	37		57			
Heterogeneity: Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						



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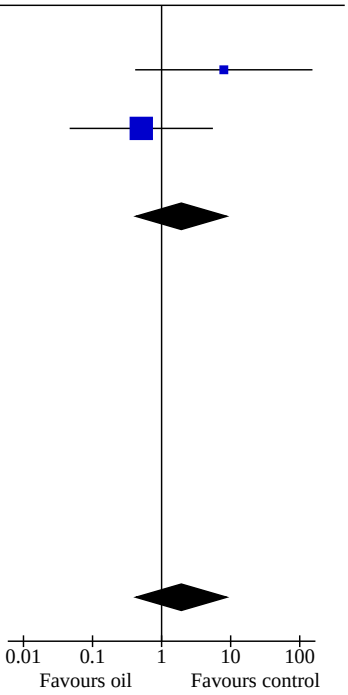
Analysis 2.4. Comparison 2: Topical oil versus routine skin care, Outcome 4: Invasive infection (fungi)

Study or Subgroup	Topical oil Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Low or middle income						
Darmstadt 2005	3	159	0	181	19.1%	7.96 [0.41 , 152.98]
Kukreja 2018	0	39	0	39		Not estimable
Salam 2015	1	128	2	130	80.9%	0.51 [0.05 , 5.53]
Sankaranarayanan 2005	0	32	0	31		Not estimable
Soriano 2000	0	29	0	31		Not estimable
Subtotal (95% CI)		**387**		**412**	**100.0%**	**1.93 [0.42 , 8.78]**
Total events:	4		2			
Heterogeneity: Chi² = 2.08, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.85 (P = 0.39)						
2.4.2 High income						
Kanti 2014	0	11	0	11		Not estimable
Strunk 2018	0	36	0	36		Not estimable
Subtotal (95% CI)		**47**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**434**		**459**	**100.0%**	**1.93 [0.42 , 8.78]**
Total events:	4		2			
Heterogeneity: Chi² = 2.08, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Not applicable						



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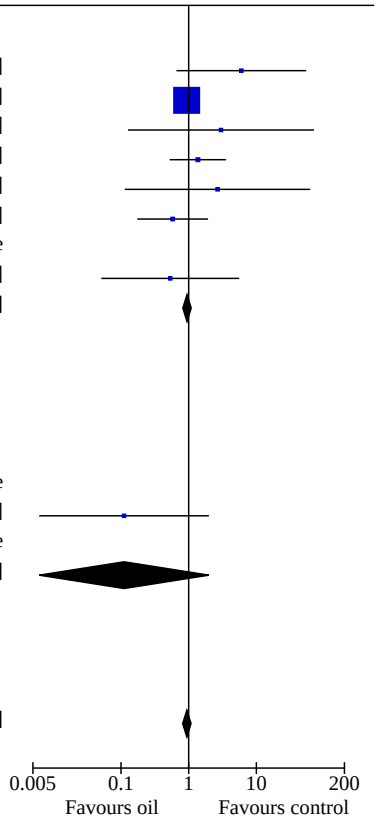
Analysis 2.5. Comparison 2: Topical oil versus routine skin care, Outcome 5: Mortality

Study or Subgroup	Topical oil Events	Topical oil Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
2.5.1 Low or middle income						
Arora 2005	3	23	1	46	0.4%	6.00 [0.66 , 54.54]
Darmstadt 2005	105	159	128	181	95.0%	0.93 [0.81 , 1.08]
Fallah 2013	1	30	0	30	0.2%	3.00 [0.13 , 70.83]
Kukreja 2018	8	38	6	39	2.2%	1.37 [0.52 , 3.57]
Kumar 2013	1	26	0	23	0.2%	2.67 [0.11 , 62.42]
Salam 2015	4	128	7	130	1.4%	0.58 [0.17 , 1.93]
Sankaranarayanan 2005	0	32	0	31		Not estimable
Soriano 2000	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**465**		**511**	**99.8%**	**0.95 [0.82 , 1.09]**
Total events:	123		144			
Heterogeneity: Chi² = 5.08, df = 6 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						
2.5.2 High income						
Kanti 2014	0	11	0	11		Not estimable
Strunk 2018	0	36	4	36	0.2%	0.11 [0.01 , 1.99]
Vaivre-Douret 2008	0	24	0	25		Not estimable
Subtotal (95% CI)		**71**		**72**	**0.2%**	**0.11 [0.01 , 1.99]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**536**		**583**	**100.0%**	**0.94 [0.82 , 1.08]**
Total events:	123		148			
Heterogeneity: Chi² = 7.19, df = 7 (P = 0.41); I² = 3%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Chi² = 2.11, df = 1 (P = 0.15), I² = 52.6%						



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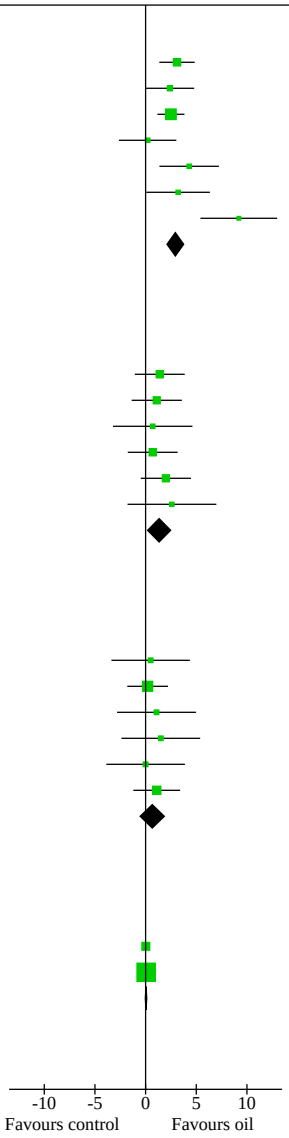
Analysis 2.6. Comparison 2: Topical oil versus routine skin care, Outcome 6: Growth

Study or Subgroup	Topical oil Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 Rate of weight gain (g/kg/day)								
Soriano 2000	18	3.3	29	14.9	3.6	31	22.2%	3.10 [1.35 , 4.85]
Arora 2005	10.9	4.4	20	8.5	4.7	42	11.8%	2.40 [0.00 , 4.80]
Sankaranarayanan 2005	11	2.6	32	8.5	2.8	31	38.0%	2.50 [1.16 , 3.84]
Farhat 2010	8	5.6	30	7.8	5.5	29	8.5%	0.20 [-2.63 , 3.03]
Fallah 2013	10.9	5.6	28	6.6	5.5	27	7.9%	4.30 [1.37 , 7.23]
Kumar 2013	11.6	5.6	25	8.4	5.5	23	6.9%	3.20 [0.06 , 6.34]
Jabraeile 2016	16	7.7	42	6.8	10.1	44	4.7%	9.20 [5.41 , 12.99]
Subtotal (95% CI)			**206**			**227**	**100.0%**	**2.93 [2.11 , 3.76]**
Heterogeneity: Chi² = 15.60, df = 6 (P = 0.02); I² = 62%								
Test for overall effect: Z = 6.98 (P < 0.00001)								
2.6.2 Change in crown-heel length (mm/week)								
Soriano 2000	8.4	2.5	29	7	6.5	31	21.3%	1.40 [-1.06 , 3.86]
Arora 2005	7.5	2.1	20	6.4	7.6	42	21.1%	1.10 [-1.38 , 3.58]
Sankaranarayanan 2005	6.3	6.8	32	5.6	8.9	31	8.4%	0.70 [-3.22 , 4.62]
Kumar 2013	6.5	2.3	25	5.8	5.6	23	21.4%	0.70 [-1.76 , 3.16]
Fallah 2013	8	2.5	28	6	6.1	27	21.0%	2.00 [-0.48 , 4.48]
Jabraeile 2016	10.3	10.1	33	7.7	8.4	37	6.7%	2.60 [-1.78 , 6.98]
Subtotal (95% CI)			**167**			**191**	**100.0%**	**1.34 [0.20 , 2.47]**
Heterogeneity: Chi² = 0.99, df = 5 (P = 0.96); I² = 0%								
Test for overall effect: Z = 2.30 (P = 0.02)								
2.6.3 Change in head circumference (mm/week)								
Soriano 2000	7.7	7.5	29	7.2	7.8	31	9.5%	0.50 [-3.37 , 4.37]
Sankaranarayanan 2005	4.9	2.8	32	4.7	5	31	35.4%	0.20 [-1.81 , 2.21]
Arora 2005	7.2	6.3	20	6.12	9.1	42	9.4%	1.08 [-2.82 , 4.98]
Fallah 2013	5.5	7.4	28	4	7.3	27	9.5%	1.50 [-2.39 , 5.39]
Kumar 2013	6	7	25	6	6.7	23	9.5%	0.00 [-3.88 , 3.88]
Jabraeile 2016	5.7	5.2	33	4.6	4.6	37	26.7%	1.10 [-1.21 , 3.41]
Subtotal (95% CI)			**167**			**191**	**100.0%**	**0.66 [-0.54 , 1.85]**
Heterogeneity: Chi² = 0.68, df = 5 (P = 0.98); I² = 0%								
Test for overall effect: Z = 1.08 (P = 0.28)								
2.6.4 Change in triceps skinfold thickness (mm/week)								
Soriano 2000	0.16	0.27	29	0.14	0.28	31	25.0%	0.02 [-0.12 , 0.16]
Arora 2005	0.1	0.1	20	0.05	0.15	19	75.0%	0.05 [-0.03 , 0.13]
Subtotal (95% CI)			**49**			**50**	**100.0%**	**0.04 [-0.03 , 0.11]**
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Chi² = 52.76, df = 3 (P < 0.00001), I² = 94.3%								



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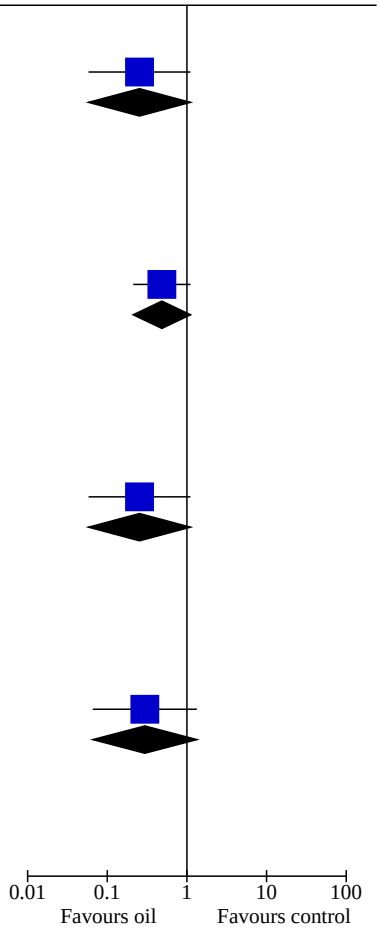
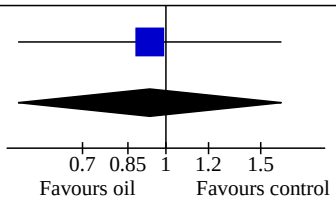
Analysis 2.7. Comparison 2: Topical oil versus routine skin care, Outcome 7: Moderate-severe neurodevelopmental delay

Study or Subgroup	Oil Events	Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 BSID III cognitive score (<85)						
Strunk 2018	2	27	7	24	100.0%	0.25 [0.06 , 1.11]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.25 [0.06 , 1.11]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.7.2 BSID III language score (<85)						
Strunk 2018	6	27	11	24	100.0%	0.48 [0.21 , 1.11]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.48 [0.21 , 1.11]**
Total events:	6		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
2.7.3 BSID III motor score (<85)						
Strunk 2018	2	27	7	24	100.0%	0.25 [0.06 , 1.11]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.25 [0.06 , 1.11]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.7.4 Socio-emotional score (<85)						
Strunk 2018	2	27	6	24	100.0%	0.30 [0.07 , 1.33]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.30 [0.07 , 1.33]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 0.99, df = 3 (P = 0.80), I² = 0%						



Analysis 2.8. Comparison 2: Topical oil versus routine skin care, Outcome 8: BPD

Study or Subgroup	Oil Events	Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strunk 2018	14	36	15	36	100.0%	0.93 [0.53 , 1.64]
Total (95% CI)		**36**		**36**	**100.0%**	**0.93 [0.53 , 1.64]**
Total events:	14		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Not applicable						



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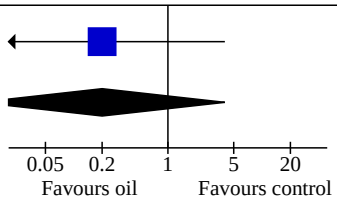
Analysis 2.9. Comparison 2: Topical oil versus routine skin care, Outcome 9: NEC

Study or Subgroup	Oil Events	Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strunk 2018	0	36	2	36	100.0%	0.20 [0.01 , 4.03]
Total (95% CI)		**36**		**36**	**100.0%**	**0.20 [0.01 , 4.03]**
Total events:	0		2			

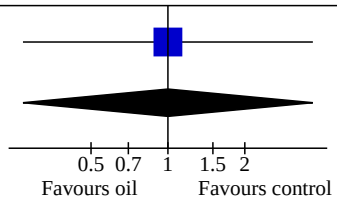
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Topical oil versus routine skin care, Outcome 10: ROP (severe)

Study or Subgroup	Oil Events	Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strunk 2018	4	36	4	36	100.0%	1.00 [0.27 , 3.69]
Total (95% CI)		**36**		**36**	**100.0%**	**1.00 [0.27 , 3.69]**
Total events:	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



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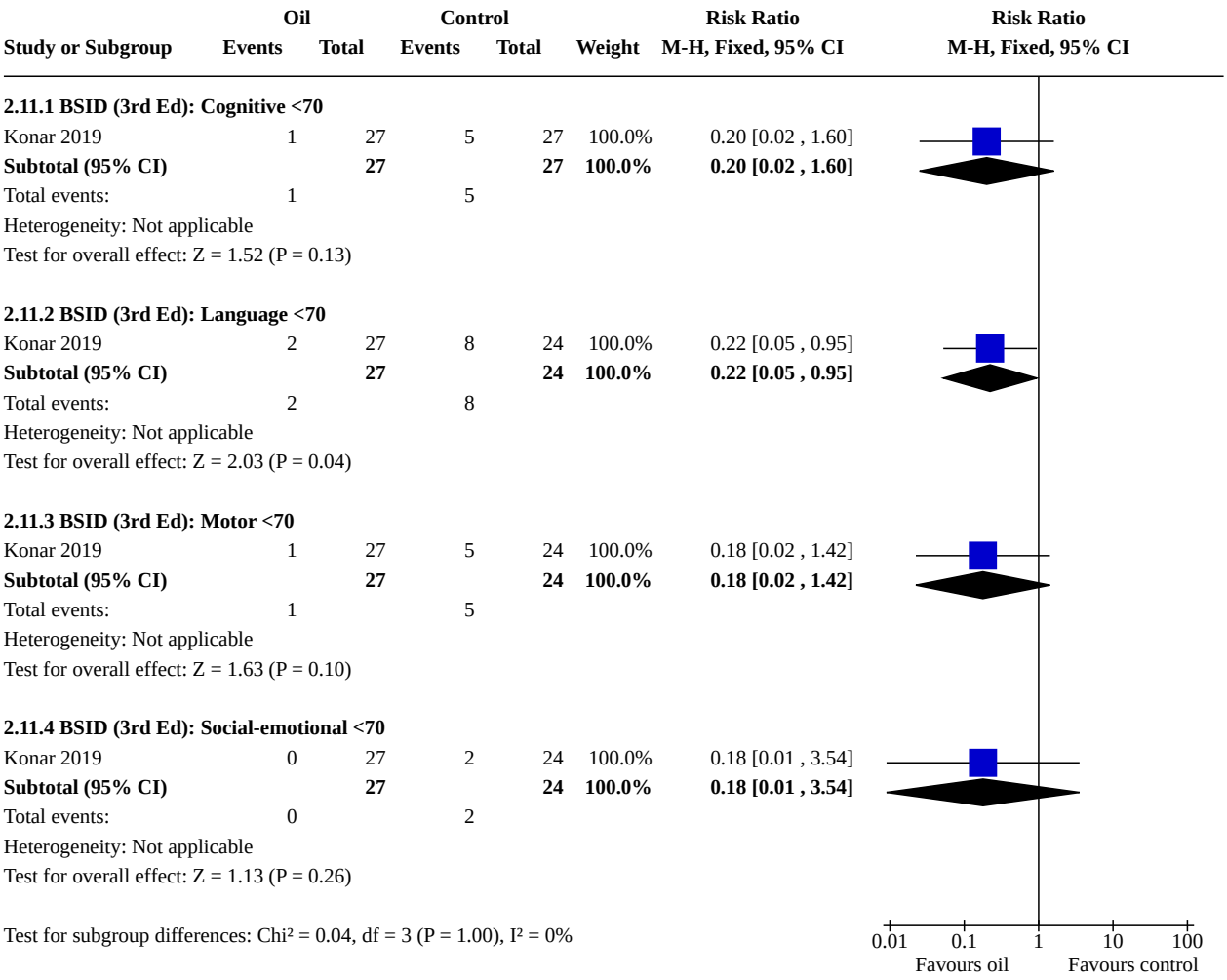
Analysis 2.11. Comparison 2: Topical oil versus routine skin care, Outcome 11: Severe neurodevelopmental disability



Comparison 3. Topical ointment or cream vs. topical oil.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Invasive infection (any organism)	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.57, 1.46]
3.2 Invasive infection (coagulase negative staphylococci)	1	316	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Invasive infection (other bacteria)	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.53, 1.50]
3.4 Invasive infection (fungi)	1	316	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.31, 5.94]
3.5 Mortality	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.68, 0.98]

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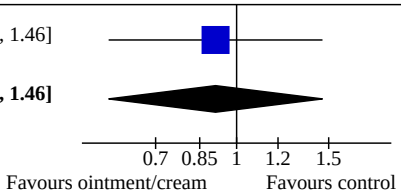
Analysis 3.1. Comparison 3: Topical ointment or cream vs. topical oil., Outcome 1: Invasive infection (any organism)

Study or Subgroup	Ointment or cream Events	Total	Oil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darmstadt 2005	27	157	30	159	100.0%	0.91 [0.57 , 1.46]
Total (95% CI)		**157**		**159**	**100.0%**	**0.91 [0.57 , 1.46]**
Total events:	27		30			

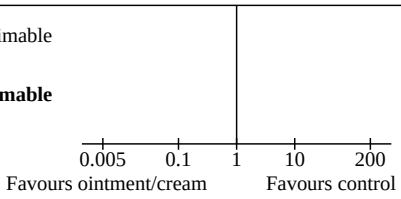
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Topical ointment or cream vs. topical oil., Outcome 2: Invasive infection (coagulase negative staphylococci)

Study or Subgroup	Ointment or cream Events	Total	Oil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darmstadt 2005	0	157	0	159		Not estimable
Total (95% CI)		**157**		**159**		**Not estimable**
Total events:	0		0			

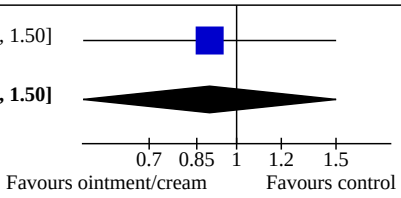
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Topical ointment or cream vs. topical oil., Outcome 3: Invasive infection (other bacteria)

Study or Subgroup	Ointment or cream Events	Total	Oil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darmstadt 2005	23	157	26	159	100.0%	0.90 [0.53 , 1.50]
Total (95% CI)		**157**		**159**	**100.0%**	**0.90 [0.53 , 1.50]**
Total events:	23		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable



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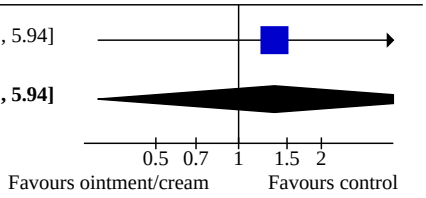
Analysis 3.4. Comparison 3: Topical ointment or cream vs. topical oil., Outcome 4: Invasive infection (fungi)

Study or Subgroup	Ointment or cream Events	Total	Oil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darmstadt 2005	4	157	3	159	100.0%	1.35 [0.31 , 5.94]
Total (95% CI)		**157**		**159**	**100.0%**	**1.35 [0.31 , 5.94]**
Total events:	4		3			

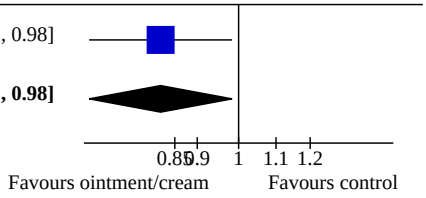
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Topical ointment or cream vs. topical oil., Outcome 5: Mortality

Study or Subgroup	Ointment or cream Events	Total	Oil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darmstadt 2005	85	157	105	159	100.0%	0.82 [0.68 , 0.98]
Total (95% CI)		**157**		**159**	**100.0%**	**0.82 [0.68 , 0.98]**
Total events:	85		105			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Comparison 4. One topical oil (or combination) vs. another oil (or combination)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Invasive infection	1	64	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Mortality	1	64	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Growth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.3.1 Rate of weight gain (g/kg/day)	1	64	Mean Difference (IV, Fixed, 95% CI)	2.00 [0.84, 3.16]
4.3.2 Change in crown-heel length (mm/week)	1	64	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.29, 1.09]
4.3.3 Change in head circumference (mm/week)	1	64	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.17, 0.37]

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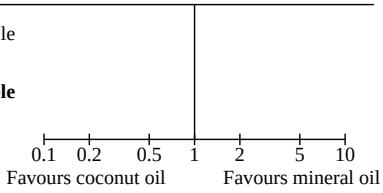
Analysis 4.1. Comparison 4: One topical oil (or combination) vs. another oil (or combination), Outcome 1: Invasive infection

Study or Subgroup	Coconut oil Events	Coconut oil Total	Mineral oil Events	Mineral oil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan 2005	0	32	0	32		Not estimable
Total (95% CI)		**32**		**32**		**Not estimable**
Total events:	0		0			

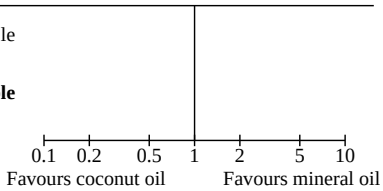
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: One topical oil (or combination) vs. another oil (or combination), Outcome 2: Mortality

Study or Subgroup	Coconut oil Events	Coconut oil Total	Mineral oil Events	Mineral oil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan 2005	0	32	0	32		Not estimable
Total (95% CI)		**32**		**32**		**Not estimable**
Total events:	0		0			

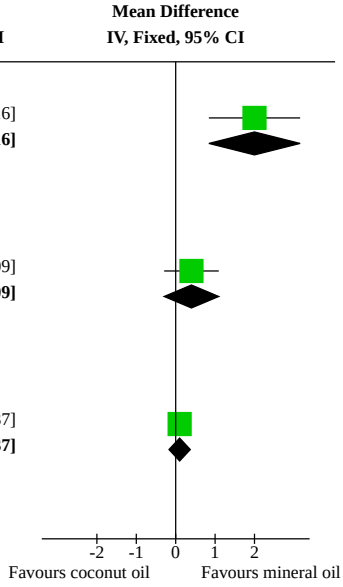
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: One topical oil (or combination) vs. another oil (or combination), Outcome 3: Growth

Study or Subgroup	Coconut oil Mean	Coconut oil SD	Coconut oil Total	Mineral oil Mean	Mineral oil SD	Mineral oil Total	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 Rate of weight gain (g/kg/day)								
Sankaranarayanan 2005	11	2.6	32	9	2.1	32	100.0%	2.00 [0.84 , 3.16]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**2.00 [0.84 , 3.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.39 (P = 0.0007)								
4.3.2 Change in crown-heel length (mm/week)								
Sankaranarayanan 2005	6.3	1.2	32	5.9	1.6	32	100.0%	0.40 [-0.29 , 1.09]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**0.40 [-0.29 , 1.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								
4.3.3 Change in head circumference (mm/week)								
Sankaranarayanan 2005	4.9	0.5	32	4.8	0.6	32	100.0%	0.10 [-0.17 , 0.37]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**0.10 [-0.17 , 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								

Test for subgroup differences: Chi² = 10.09, df = 2 (P = 0.006), I² = 80.2%



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APPENDICES

Appendix 1. 2021 Search methods

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2019). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist; please see the Search Methodology section at https://neonatal.cochrane.org/resources-authors/author-resources-new-reviews.

CENTRAL via CRS Web:

Date ranges: 01 January 2015 to 08 January 2021
Terms:
1 MESH DESCRIPTOR Emollients EXPLODE ALL AND CENTRAL:TARGET
2 emollient* AND CENTRAL:TARGET
3 MESH DESCRIPTOR Skin Cream EXPLODE ALL AND CENTRAL:TARGET
4 skin cream* AND CENTRAL:TARGET
5 MESH DESCRIPTOR Ointments EXPLODE ALL AND CENTRAL:TARGET
6 MESH DESCRIPTOR Dermatologic Agents EXPLODE ALL AND CENTRAL:TARGET
7 dermatological agent* AND CENTRAL:TARGET
8 MESH DESCRIPTOR Plant Oils EXPLODE ALL AND CENTRAL:TARGET
9 MESH DESCRIPTOR Coconut Oil EXPLODE ALL AND CENTRAL:TARGET
10 MESH DESCRIPTOR Lanolin EXPLODE ALL AND CENTRAL:TARGET
11 lanolin AND CENTRAL:TARGET
12 MESH DESCRIPTOR Mineral Oil EXPLODE ALL AND CENTRAL:TARGET
13 MESH DESCRIPTOR Olive Oil EXPLODE ALL AND CENTRAL:TARGET
14 MESH DESCRIPTOR Petrolatum EXPLODE ALL AND CENTRAL:TARGET
15 petrolatum or petroleum jelly AND CENTRAL:TARGET
16 MESH DESCRIPTOR Soybean Oil EXPLODE ALL AND CENTRAL:TARGET
17 MESH DESCRIPTOR Sunflower Oil EXPLODE ALL AND CENTRAL:TARGET
18 ((plant* or vegetable* or coconut* or mineral* or olive* or soy or soybean* or sunflower* or almond*) ADJ3 oil*) AND CENTRAL:TARGET
19 aquaphor AND CENTRAL:TARGET
20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21 MESH DESCRIPTOR Skin EXPLODE ALL AND CENTRAL:TARGET
22 skin AND CENTRAL:TARGET
23 MESH DESCRIPTOR Administration, Cutaneous EXPLODE ALL AND CENTRAL:TARGET
24 cutaneous* AND CENTRAL:TARGET
25 MESH DESCRIPTOR Administration, Topical EXPLODE ALL AND CENTRAL:TARGET
26 topical* AND CENTRAL:TARGET
27 MESH DESCRIPTOR Skin Care EXPLODE ALL AND CENTRAL:TARGET
28 MESH DESCRIPTOR Skin Diseases, Bacterial EXPLODE ALL AND CENTRAL:TARGET
29 MESH DESCRIPTOR Skin Diseases EXPLODE ALL AND CENTRAL:TARGET
30 MESH DESCRIPTOR Massage EXPLODE ALL AND CENTRAL:TARGET
31 massage AND CENTRAL:TARGET
32 MESH DESCRIPTOR Skin Absorption EXPLODE ALL AND CENTRAL:TARGET
33 MESH DESCRIPTOR Skin Physiological Phenomena EXPLODE ALL AND CENTRAL:TARGET
34 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
35 #34 AND #20
36 ((skin* or topical* or dermal or epidermal or cutaneous) ADJ6 (cream* or oil* or unguent* or gel* or moisturi* or honey or humectant* or ointment* or foam* or lotion* or conditioner*)) AND CENTRAL:TARGET
37 (topical* ADJ2 (agent* or treatment* or therap*)) AND CENTRAL:TARGET
38 skin care product* AND CENTRAL:TARGET
39 #35 OR #36 OR #37 OR #38
40 MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET
41 infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET
42 #41 OR #40
43 #42 AND #39
44 2015 TO 2021:YR AND CENTRAL:TARGET
45 #44 AND #43

MEDLINE via Ovid - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R):

Date ranges: 01 January 2015 to 08 January 2021

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Terms:
1. exp Emollients/
2. emollient*.mp.
3. exp Skin Cream/
4. skin cream*.mp.
5. exp Ointments/
6. exp Dermatologic Agents/
7. dermatological agent*.mp.
8. exp Plant Oils/
9. exp Coconut Oil/
10. exp Lanolin/
11. lanolin.mp.
12. exp Mineral Oil/
13. exp Olive Oil/
14. exp Petrolatum/
15. (petrolatum or petroleum jelly).mp.
16. exp Soybean Oil/
17. exp Sunflower Oil/
18. ((plant* or vegetable* or coconut* or mineral* or olive* or soy or soybean* or sunflower* or almond*) adj3 oil*).mp.
19. aquaphor.mp.
20. or/1-19
21. exp Skin/
22. skin.mp.
23. exp Administration, Cutaneous/
24. cutaneous*.mp.
25. exp Administration, Topical/
26. topical*.mp.
27. exp Skin Care/
28. exp Skin Diseases, Bacterial/
29. exp Skin Diseases/
30. exp Massage/
31. massage.mp.
32. exp Skin Absorption/
33. exp Skin Physiological Phenomena/
34. or/21-33
35. 20 and 34
36. ((skin* or topical* or dermal or epidermal or cutaneous) adj6 (cream* or oil* or unguent* or gel* or moisturi* or honey or humectant* or ointment* or foam* or lotion* or conditioner*)).mp.
37. (topical* adj2 (agent* or treatment* or therap*)).mp.
38. skin care product*.mp.
39. or/35-38
40. exp infant, newborn/
41. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.
42. 40 or 41
43. randomized controlled trial.pt.
44. controlled clinical trial.pt.
45. randomized.ab.
46. placebo.ab.
47. drug therapy.fs.
48. randomly.ab.
49. trial.ab.
50. groups.ab.
51. or/43-50
52. exp animals/ not humans.sh.
53. 51 not 52
54. 42 and 53
55. randomi?ed.ti,ab.
56. randomly.ti,ab.
57. trial.ti,ab.
58. groups.ti,ab.
59. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.

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60. placebo*.ti,ab.
61. 55 or 56 or 57 or 58 or 59 or 60
62. 41 and 61
63. limit 62 to yr="2019 -Current"
64. 54 or 63
65. 39 and 64
66. limit 65 to yr="2015 -Current"

ISRCTN:

Date searched: 2015 to 08 January 2021
Terms:
Interventions: Topical emollient AND Participant age range: Neonate
topical emollient within Participant age range: Neonate
skin within Interventions: Emollient AND Participant age range: Neonate
Condition: Infection AND Interventions: Skin* or topical* or dermal or epidermal or cutaneous AND Participant age range: Neonate
skin* or topical* or dermal or epidermal or cutaneous AND (Condition: Infection AND Participant age range: Neonate)
"skin* or topical* or dermal or epidermal or cutaneous AND (Interventions: Lotion AND Participant age range: Neonate)
skin infection AND (Interventions: Lotion AND Participant age range: Neonate)
skin within Interventions: Lotion AND Participant age range: Neonate

Appendix 2. Previous Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 7, 2015), MEDLINE (1966 to August 2015), EMBASE (1980 to August 2015, CINAHL (1982 to August 2015), and LILACS (1982 to August 2014) using the following text words and MeSH terms:

[exp Infant, Newborn/ OR Premature Birth/ OR (neonat$ or neo nat$).ti,ab. OR (newborn$ or new born$ or newly born$).ti,ab. OR (preterm or preterms or pre term or pre terms).ti,ab. OR (preemie$ or premie or premies).ti,ab. OR (prematur$ adj3 (birth$ or born or deliver $)).ti,ab. OR (low adj3 (birthweight$ or birth weight$)).ti,ab. OR (lbw or vlbw or elbw).ti,ab. OR infan$.ti,ab. OR (baby or babies).ti,ab.] AND [emollients/ OR Skin cream/ OR Ointments/ OR Dermatological agents/ OR Plant oils/ OR emollient$.ti,ab. (skin adj6 (cream$ or oil$ or unguent$ or gel$ or moisturi$ or honey or humectant$ or ointment$ or foam$ or lotion$ or conditioner$)).ti,ab. OR (topical adj2 (agent$ or treatment$ or therap$)).ti,ab. OR skin care product$.ti,ab.]

The search outputs were limited with the relevant search filters for clinical trials. We did not apply any language restriction.

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and ClinicalTrials.gov (www.clinicaltrials.gov/) for completed or ongoing trials.

We examined reference lists in previous reviews and included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to present), the European Society for Paediatric Research (1995 to 2014), the Royal College of Paediatrics and Child Health (2000 to 2015), the Perinatal Society of Australia and New Zealand (2000 to 2015), the European Society for Paediatric Infectious Diseases (2005 to 2014), and the Infectious Diseases Society of America (2003 to 2014). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Appendix 3. 'Risk of bias' tool

Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

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Blinding of personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for personnel.

Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared pre-specified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

WHAT'S NEW

Date	Event	Description
7 May 2021	New citation required and conclusions have changed	Conclusions changed
7 May 2021	New search has been performed	Expanded and revised review.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1998

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Date	Event	Description
24 July 2003	New citation required and conclusions have changed	Substantive amendment
24 July 2003	New search has been performed	This review updates the previously published review titled "Emollient ointment for preventing infection in preterm infants", The Cochrane Library, Issue 3, 1998 (Soll 1998). The updated review includes data from two additional randomized trials (Pabst 1999, Edwards 2001). Additional outcomes are noted including fungal infection, patent ductus arteriosus, bronchopulmonary dysplasia, and chronic lung disease. Results and conclusions have changed with inclusion of two more randomized trials.

CONTRIBUTIONS OF AUTHORS

Jemma Cleminson and William McGuire updated the search strategy, appraised the identified literature, extracted data from included studies and drafted the revised review.

DECLARATIONS OF INTEREST

None.

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  Logistical

External sources

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  This report is independent research funded by a UK NIHR Evidence Synthesis Programme Grant.
- World Health Organization, Switzerland

  Editorial and administrative support for this review has been provided by a grant from World Health Organization to Cochrane Neonatal.
- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Expanded and revised protocol and review, with pre-specified analyses of trials conducted in low- and middle-income versus high-income countries. We planned sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

- As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. RCTs and controlled clinical trials (CCTs) from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see How CENTRAL is created). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL (Ovelman 2020).
- Since July 2019, Cochrane Neonatal no longer searches for RCTs and CCTs on the following platforms: ClinicalTrials.gov or from the World Health Organization's International Clinical Trials Registry Platform (ICTRP), as records from both platforms are added to CENTRAL on a monthly basis (see How CENTRAL is created). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN Registry (at www.isrctn.com/, formerly Controlled-trials.com), is searched separately.

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- Starting in September 2020, Cochrane Neonatal no longer searches for RCTs and quasi-RCTs from CINAHL, as records are identified and added to CENTRAL on a monthly basis through Cochrane's Centralised Search Service project (see 'How CENTRAL is created' at: www.cochranelibrary.com/central/central-creation#CINAHL%20section).
- For the 2021 update, we ran searches in the following databases: CENTRAL via Cochrane Register of Studies (CRS) Web and MEDLINE via Ovid. The search strategies are available in Appendix 1. The previous search methods are available in Appendix 2.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Bacterial Infections [mortality] [*prevention & control]; Bias; Cross Infection [mortality] [*prevention & control]; Dermatitis [*prevention & control]; Emollients [*therapeutic use]; Infant, Extremely Premature; Infant, Premature; Infant, Premature, Diseases [*prevention & control]; Mycoses [mortality] [*prevention & control]; Ointments [therapeutic use]; Randomized Controlled Trials as Topic; Skin Care

MeSH check words

Humans; Infant, Newborn

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