Prevention and treatment of neonatal infections in facility and community settings of low- and middle-income countries: a descriptive review

Supplementary Material

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Appendix 1: Search Strategies

1.1 Strategies to Reduce Antimicrobial Resistance Review

Databases searched were Ovid MEDLINE, Ovid EMBASE, CINAHL, Global Index Medicus, and Cochrane CENTRAL. MEDLINE search strategy is shown below. This search strategy was adapted to all databases.

Table 1 Search strategy for Ovid MEDLINE, with date of final search on June 26, 2024

| 1 | (newborn* or neonat* or infant* or baby or babies or birth* or deliver* or labo?r).ti. |
|---|---|
| 2 | exp Infant, Newborn/ or Neonatology/ or Perinatology/ or Intensive Care, Neonatal/ |
| 3 | 1 or 2 |
| 4 | (((antibiotic* or antimicrobial*) and (resistan* or stewardship)) or AMR).ti. |
| 5 | Drug Resistance, Microbial/ or exp Drug Resistance, Bacterial/ or Drug Resistance, Multiple, Bacterial/ or Antimicrobial Stewardship/ |

| 6 | 4 or 5 |
|----|---|
| 7 | ("bacterial infection*" or "nosocomial infection*" or HAI* or "healthcare-associated infection*" or "health care-associated infection*" or sepsis or coloni#* or hygien* or cleaning or disinfect* or sterili\$* or saniti\$* or sanitary or susceptibility or culture* or antibiogram* or surveillance or monitoring or management or administration or utilization or usage or over-use or over-use or prescribing or prescription* or prophylaxis or therapy or treatment* or regimen*).ti. |
| 8 | exp Bacterial Infections/ or exp Cross Infection/ or exp Infection Control/ or Intensive Care Units, Neonatal/ or Antibiotic Prophylaxis/ or exp Microbial Sensitivity Tests/ |
| 9 | 7 or 8 |
| 10 | (afghanistan or albania or algeria or "american samoa" or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrian or bangladesh or barbados or "republic of belarus" or belarus or bylearus or belorussia or bylearussian or belize or "british honduras" or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or "burkina faso" or "burkina fasso" or "upper volta" or burundi or urundi or "cabo verde" or "cape verde" or cambodia or kampuchea or "khmer republic" or cameroon or cameroon or cameroon or central african republic" or "ubangi shari" or chad or chile or china or colombia or comoros or "comoroor islands" or "iles comores" or mayotte or "democratic republic" or the congo" or "democratic republic congo" or congo or zaire or "costa rica" or "cote d'ivoire" or "cote divoire" |

or "global south" or "africa south of the sahara" or "sub-saharan africa" or "subsaharan africa" or "africa, central" or "central africa" or "africa, northern" or "north africa" or "northern africa" or magreb or maghrib or sahara or "africa, southern" or "southern africa" or "africa, eastern" or "east africa" or "eastern africa" or "africa, western" or "west africa" or "western africa" or "west indies" or "indian ocean islands" or caribbean or "central america" or "latin america" or "south and central america" or "south america" or "asia, central" or "central asia" or "asia, northern" or "north asia" or "northern asia" or "asia, southeastern" or "southeastern asia" or "south eastern asia" or "southeast asia" or "south east asia" or "asia, western" or "western asia" or "europe, eastern" or "east europe" or "eastern europe" or "developing country" or "developing countries" or "developing nation?" or "developing population?" or "developing world" or "less developed countr*" or "less developed nation?" or "less developed population?" or "less developed world" or "lesser developed countr*" or "lesser developed nation?" or "lesser developed population?" or "lesser developed nation?" or "lesser developed nation?" or "lesser developed population?" or "lesser developed nation?" or "lesser developed nation." or "les developed world" or "under developed countr*" or "under developed nation?" or "under developed population?" or "under developed world" or "underdeveloped countr*" or "underdeveloped nation?" or "underdeveloped population?" or "underdeveloped world" or "middle income countr*" or "middle income nation?" or "middle income population?" or "low income countr*" or "low income nation?" or "low income population?" or "lower income countr*" or "lower income nation?" or "lower income population?" or "underserved countr*" or "underserved nation?" or "underserved population?" or "underserved world" or "under served countr*" or "under served nation?" or "under served population?" or "under served world" or "deprived countr*" or "deprived nation?" or "deprived population?" or "deprived world" or "poor countr*" or "poor nation?" or "poor population?" or "poor world" or "poorer countr*" or "poorer nation?" or "poorer population?" or "poorer world" or "developing econom*" or "less developed econom*" or "lesser developed econom*" or "under developed econom*" or "underdeveloped econom*" or "middle income econom*" or "low income econom*" or "lower income econom*" or "low gdp" or "low gnp" or "low gross domestic" or "low gross national" or "lower gdp" or "lower gnp" or "lower gross domestic" or "lower gross national" or lmic or lmics or "third world" or "lami countr*" or "transitional" countr*" or "emerging economies" or "emerging nation?" or "low-resource setting*" or "low-resource nation*" or "low-resource countr*" or "resource-limiting setting*" or "resource-limiting nation*" or "resource-limiting countr*").ti,sh.

3 and 6 and 9 and 10

1.2 Prevention of Hospital-Acquired Infections Review

Please refer to Fitzgerald 2022 [1] for search strategy details.

1.3 Clean Birth Kits Review

Please refer to Lassi 2020 [2] for search strategy details.

1.4 Chlorhexidine Cleansing Review

Please refer to Zhou 2022 [3] and WHO recommendations on maternal and newborn care for a positive postnatal experience (WHO 2022) [4] for search strategy details.

1.5 Topical Emollients Review

For the topic of emollients for preterm neonates, please refer to *Cleminson 2021* [5] for search strategy details. For the topic of emollients for term neonates, please refer to *Priyadarshi 2022* [6] for search strategy details.

1.6 Probiotics Supplementation Review

Please refer to reviews by Sharif 2020 [7] and Imdad 2020 [8] for search strategy details.

1.7 Synbiotics Supplementation Review

Please refer to reviews by Sharif 2022 [9] and Imdad 2020 [8] for search strategy details.

1.8 Prophylactic Systemic Antifungal Agents Review

Please refer to Cleminson 2015 [10] for search strategy details.

1.9 Mixed Setting & Community-Based Antibiotic Delivery for PSBIs Review

Please refer to Duby 2019 [11] for search strategy details.

Appendix 2: Eligibility Criteria

Table 2 Eligibility criteria for de novo, updated, and as-is reviews

| Topic | Population | Intervention | Comparator | Outcomes | Included studies |
|---|----------------------------|---|---|--|---|
| Strategies to reduce AMR – de novo review | Preterm & term neonates | Interventions conducted in a neonatal unit or community setting, reporting on an intervention, policy, or strategy designed to promote antibiotic stewardship and/or mitigate the development of antimicrobial resistance | Standard practices, or no intervention | All-cause neonatal mortality, lab confirmed and suspected EOS -community or hospital onset, lab confirmed and suspected LOS -community or hospital onset, localized infections (e.g., omphalitis, UTI, meningitis) – all, localized infections – due to MDROs, confirmed blood stream infections – all, confirmed blood stream infections – MDROs, & colonization with multidrug resistant bacteria. | Randomized or quasi- randomized trials, observational studies, program evaluations, and implementation studies |
| | | | | Secondary outcomes: Duration of antibiotic therapy, proportion of neonates receiving any antibiotic, length of hospital stay | |

| | | | | (inpatient newborns), & use of WHO watch and reserve antimicrobials. | |
|---|---|--|---|---|--|
| HAI prevention – as-is review from Fitzgerald 2022 [1] | Hospitalized neonates, including neonatal ward and/or NICU settings | Included both single interventions [e.g., probiotics, KMC, breastfeeding, fluconazole prophylaxis] and bundled interventions (e.g., vascular device care, hand hygiene and healthcare worker education combined) | Standard of care | the effect of the interventions on (1) incidence of infection or (2) attributable mortality, depending on study definitions. Fungal or bacterial hospital-acquired invasive infections in hospitalized neonates were the primary events for study. Secondary outcomes: impact on incidence of laboratory-confirmed urinary tract infection, thrombophlebitis, NEC, device-associated infections (clinically suspected or culture proven) and clinically suspected infection where laboratory cultures were negative or not available. | RCTs, controlled and noncontrolled before-after, controlled and noncontrolled ITS and cohort studies |
| Clean birth kits - updated review from Lassi 2020 [2] | Pregnant mothers | 3 main interventions (1) Training of TBAs, LHWs and CHWs (2) Distribution of CBKs (3) Health education/messages/counselling | Standard of care | -Neonatal mortality -Any omphalitis | RCTs (individual and cluster), and quasi experimental studies |
| Chlorhexidine cleansing - updated review from an existing WHO guideline [4] (i.e., Chlorhexidine Umbilical | Neonates | Routine application of chlorhexidine to the umbilical cord stump | Dry cord care or usual cord practices | -Neonatal mortality (defined as deaths due to all causes occurring any time during the first 28 days of postnatal life) -Omphalitis (Any omphalitis: Redness or pus limited to stump; Moderate omphalitis: Redness extending to the skin at the base of the cord stump less than 2 cm, with or without pus; Severe omphalitis: Redness extending more than 2 cm from the skin, with or without pus) | RCTs (individual and cluster) |

| Prevention | and Treatment | of Neonatal | Infections in | LMICs |
|------------|---------------|-------------|---------------|--------------|
|------------|---------------|-------------|---------------|--------------|

| Prevention and Tr | reatment of Neor | natal Infections in LMICs | | | |
|-------------------|------------------|--|------------------|---|------------------------------|
| Review Group's | | | | -Possible serious bacterial infections (PSBIs) (Any PSBI: | |
| IPD meta- | | | | Presence of any one of the following symptoms or signs: | |
| analysis) and a | | | | stopped feeding, severe chest indrawing, movements | |
| review from | | | | only on stimulation, fever (>38°C axillary), hypothermia | |
| Zhou 2022 [3] | | | | (<35.5°C axillary), convulsions; Severe PSBI: Presence of | |
| | | | | any one of the following symptoms or signs: | |
| | | | | convulsions, stopped feeding well, lethargy, | |
| | | | | hypothermia (<35.5°C)) | |
| Topical | Preterm infants | Ointment or cream versus | Standard of care | Primary outcomes: | Controlled trials |
| emollients for | | routine skincare | | • | using random or |
| preterm | (< 37 weeks' | | | Invasive infection diagnosed more than 48 hours after | quasi-random |
| neonates | gestation) | Oil versus routine skincare | | birth as determined by culture from a normally sterile | participant |
| | | | | site: cerebrospinal fluid; blood; urine (obtained by | allocation. |
| – as-is review | | Ointment or cream versus oil | | sterile urethral catheterisation or suprapubic bladder | Cluster- |
| from Cleminson | | •One oil (or combination) versus | | tap); bone or joint, peritoneum, pleural space, or central | randomized trials |
| 2021 [5] | | •One oil (or combination) versus | | venous line tip; or findings on autopsy examination | where the unit of |
| | | another oil (or combination) | | consistent with invasive microbial infection. If sufficient | randomization |
| | | | | data were available, we planned to examine specific | |
| | | | | effects on infection with these organisms: | was a group of infants (for |
| | | | | Coagulase-negative staphylococci | example, in a neonatal unit) |
| | | | | Other bacteria (gram-negative bacilli, Saureus, | were eligible for |
| | | | | enterococci) | inclusion. |
| | | | | • 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 | |
| | | | | | |

| Topical emollients for term neonates – as-is review from Priyadarshi 2022 [6] | Term healthy neonates (babies up to 28 completed days of life) | Emollients can be used as an additive in bath/wash products or applied on the body as leave-on emollients. Studies were included if one group had received a routine application of leave-on emollients (including oil, cream, ointment, lotion, or moisturizer) and another group did not receive any form of emollient. Included studies | Standard of care | 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. • BPD (oxygen supplementation at 36 weeks' postmenstrual age) • NEC (Bell stage 2 or 3) (Bell 1978) • ROP requiring treatment (medical or surgical) (ICCROP 2005) Key outcomes were neonatal mortality (all-cause death in the first 28 days of life); systemic infections (sepsis, pneumonia, or possible serious bacterial infection); atopic dermatitis (meeting the diagnostic criteria of at least one of the established tools, such as UK Working Party diagnostic criteria, up to one year of age); skin condition (based on a validated skin assessment score or erythema, rash, itching, oedema, exanthema, dry skin, and urticaria), and adverse events related to emollient application. | RCTs |
|--|---|--|--------------------|---|----------------|
| Probiotics | Included very | where the intervention was started in the neonatal period. Included enteral administration | Standard of care | Primary outcomes: | Included RCTs |
| supplementation – as-is review from Sharif 2020 [7] | preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants (pre- specified | of any probiotic or probiotic combination for at least one week compared to placebo or no treatment. Categorised probiotic preparations at the genus level | Stallual u Oi Cale | NEC, confirmed at surgery or autopsy or diagnosed by at least two of the following clinical features (Walsh 1986): abdominal radiograph showing pneumatosis intestinalis or | and quasi-RCTs |

| Prevention and Tr | eatment of Neonatal Infections in LMICs |
|-------------------|---|
| | |

| Trevention und Tr | extremely preterm (< 28 weeks' gestation) or ELBW (< 1000 g) infants) | (Bifidobacterium spp., Lactobacillus spp., Saccharomyces spp., Streptococcal spp., others, and combinations thereof). | | gas in the portal venous system or free air in the abdomen; abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both); blood in stool elethargy, hypotonia or apnoea (or combination of these). | |
|-------------------------------|--|---|---------------------------------------|---|---|
| | | | | All-cause mortality before discharge from hospital Secondary outcomes: | |
| | | | | Late-onset invasive infection, as determined by culture of bacteria or fungus from blood or cerebrospinal fluid or from a normally sterile body space (> 48 hours after birth) | |
| | | | | • Late-onset infection with the supplemented probiotic microorganism | |
| | | | | •Duration of hospitalization (days) | |
| | | | | Neurodevelopmental impairment assessed by a validated | |
| | | | | test after 12 months' post-term: neurological evaluations, developmental scores, and classifications of disability, including cerebral palsy and auditory and visual impairment | |
| Probiotics supplementation | Included neonates regardless of health status, including low | Neonatal oral probiotics/synbiotics supplementation | No probiotic supplementation/ placebo | Primary outcomes: -All-cause neonatal mortality (death between 0–28 days of life) | Studies selected for inclusion in this review were either experimental or |

| Prevention and T | Freatment of Neonatal Infections in LMICs | | |
|------------------|---|--|---|
| – as-is review | birth weight and | -All-cause infant mortality at 6 months (death between | quasi- |
| from Imdad | preterm infants | 0 days to 6 months of life) | experimental |
| 2020 [8] | | -All-cause infant mortality at 12 months (death between 0 days to 12 months life). | studies that were designed as RCTs. Other study |
| | | In the event that the outcomes were not reported in the follow-up periods mentioned (e.g., 28 days, | designs were considered, such as before-after |
| | | 6 months, and 12 months), we first contacted the authors to obtain this data. If that data were not available from the authors, the following actions were taken: Mortality within the first six weeks of life was included as neonatal mortality at day 28, between 3–6 months were included as 6 months, and between 9–12 months were included as 12 months. If there was not a clear follow-up, the mortality data from the longest follow-up was included. | studies, regression discontinuity designs, interrupted time series (ITS) but none of these studies were included. |
| | | Secondary outcomes: | |
| | | -Sepsis specific mortality measured between 0–28 days, 0 days to 6 months and 0 days to 12 months of life | |
| | | -Neonatal sepsis (as defined by authors) in the first six weeks of life | |
| | | -Necrotizing enterocolitis (as defined by the authors) | |
| | | -Vitamin A Deficiency | |
| | | -Prevention of Hypoglycemia (as defined by authors) during the neonatal period -Treatment of Hypoglycemia (recurrence of hypoglycemia after the episode treated) - Any adverse reactions during the intervention period | |
| | | -Serious adverse events | |

| revention and m | eatment of Neon | atal Infections in LMICs | | -Neurodevelopmental outcomes at 12 and 24 months and the longest follow-up A neurodevelopment outcome is an event that involves any cognitive, neurologic, and/or sensory outcomes. | |
|--|---|--|--|--|--|
| Probiotics supplementation – as-is review from Thomas 2023 [12] | Very low birth weight (VLBW) neonates | Enteral supplementation of one or more species of probiotics | Another probiotic species/genera, or placebo/no probiotics | Primary outcomes: -All-cause neonatal mortality -Sepsis/severe infection at discharge or 28 days or the latest follow- up. (Sepsis was identified by a positive culture of bacteria or fungus from blood, cerebrospinal fluid, urine, or from a normally sterile body space or as defined by the authors of the individual studies.) Secondary outcomes: -Necrotizing enterocolitis (NEC)— stage 2 or more as per modified Bell's staging. | Randomized controlled trials (RCT) or quasi- RCTs |
| Synbiotics supplementation – as-is review from Sharif 2022 [9] | Very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants | Prophylactic enteral synbiotics: any combination or dose of probiotic organisms and prebiotic oligosaccharides, commenced within 14 days of birth and continued daily (or more frequently) for at least one week. Probiotics and prebiotics need not be given simultaneously, but should be given on the same day. | Standard of care | Primary outcomes: NEC before discharge from hospital, confirmed at surgery or autopsy or using standardized clinical and radiological criteria (VON 2020): at least one of: bilious gastric aspirate or emesis; or abdominal distention; or blood in stool; and at least one of: abdominal radiograph showing pneumatosis intestinalis; or gas in the portal venous | Randomized or quasi- randomized (predictable allocation) controlled trials, including cluster- RCTs. |

| Prevention and Tr | eatment of Neon | atal Infections in LMICs | | | | | | | |
|--|--|---|-------------------------------|--|---|--|--|--|--|
| | J | · | | Secondary outcomes: | | | | | |
| | | | | • Late-onset invasive infection, as determined by the culture of bacteria or fungus from blood or cerebrospinal fluid or from a normally sterile body space (> 48 hours after birth until discharge from hospital) | | | | | |
| | | | | Invasive infection with the supplemented probiotic micro- organism until discharge from hospital | | | | | |
| | | | | Duration of hospitalization since birth Neurodevelopmental impairment assessed by a validated | | | | | |
| | | | | test after 12 months' post-term: neurological evaluations, developmental scores, and classifications of disability, including cerebral palsy and auditory and visual impairment | | | | | |
| Synbiotics supplementation | Included neonates regardless of | Neonatal oral probiotics/synbiotics supplementation | No probiotic supplementation/ | Primary outcomes: -All-cause neonatal mortality (death between 0–28 days | Studies selected for inclusion in this review were | | | | |
| – as-is review from Imdad 2020 [8] | health status, including low birth weight and preterm infants | | placebo | of life) -All-cause infant mortality at 6 months (death between 0 days to 6 months of life) | either experimental or quasi- | | | | |
| | | | | -All-cause infant mortality at 12 months (death between 0 days to 12 months life). | experimental studies that were designed as RCTs. Other study | | | | |
| | | | | In the event that the outcomes were not reported in the follow-up periods mentioned (e.g., 28 days, | designs were considered, such | | | | |
| | | | | 6 months, and 12 months), we first contacted the authors to obtain this data. If that data were not available from the authors, the following actions were taken: Mortality within the first six weeks of life was included as neonatal mortality at day 28, between 3–6 | as before-after studies, regression discontinuity designs, ITS but none of these | | | | |

| Prevention and Tr | eatment of Neon | atal Infections in LMICs | | | |
|--------------------------|---|--|---|--|--|
| Prevention and Tr | eatment of Neon | atal Infections in LMICs | | months were included as 6 months, and between 9–12 months were included as 12 months. If there was not a clear follow-up, the mortality data from the longest follow-up was included. Secondary outcomes: -Sepsis specific mortality measured between 0–28 days, 0 days to 6 months and 0 days to 12 months of life -Neonatal sepsis (as defined by authors) in the first six weeks of life -NEC (as defined by the authors) -Vitamin A Deficiency -Prevention of Hypoglycemia (as defined by authors) during the neonatal period -Treatment of Hypoglycemia (recurrence of hypoglycemia after the episode treated) -Any adverse reactions during the intervention period -Serious adverse events -Neurodevelopmental outcomes at 12 and 24 months and the longest follow-up A neurodevelopment outcome is an event that involves any cognitive, neurologic, and/or | studies were included. |
| | | | | sensory outcomes. | |
| Prophylactic systemic | Very preterm or VLBW infants, | Systemic antifungal prophylaxis, given by intravenous or enteral | Placebo or no drug, oral or topical | Primary outcomes:1. Confirmed invasive fungal infection as determined by | Randomized controlled trials |
| antifungal agents | with or without evidence of fungal colonisation but without | route | antifungal prophylaxis, or another systemic | culture of fungus from a normally sterile site e.g. cerebrospinal fluid, blood, urine, bone or joint, peritoneum, pleural space; | or quasi- randomized controlled trials |

| | eatment of Neonatal Infections in LMICs | | Conditions and analysis of the condition |
|------------------|---|---------------------|--|
| - updated review | evidence of | antifungal agent or | findings on autopsy examination consistent with |
| from Cleminson | invasive fungal | dose regimen | invasive fungal |
| 2015 [10] | infection at study entry | | infection; |
| | | | • findings on ophthalmological examination consistent with fungal ophthalmitis or retinitis; |
| | | | pathognomonic findings on renal ultrasound |
| | | | examination such as 'renal fungal balls'. |
| | | | 2. Death prior to hospital discharge. |
| | | | 3. Development: (i) neurodevelopmental outcomes assessed using validated tools at 12 months or more corrected age, and classifications of disability including non-ambulant cerebral palsy, developmental delay, auditory and visual impairment; (ii) cognitive and educational outcomes at 5 years or more e.g. intelligence quotient or indices of educational achievement measured using a validated tool (including school examination results). |
| | | | Secondary outcomes: |
| | | | 1. Bronchopulmonary dysplasia (oxygen |
| | | | supplementation at 36 weeks postmenstrual age). |
| | | | 2. Necrotising enterocolitis (Bell stage 2 or 3). |
| | | | 3. Retinopathy of prematurity: a) any stage; b) requiring treatment. |
| | | | 4. Duration of intensive care unit or hospital admission (days). |
| | | | 5. Emergence of organisms resistant to antifungal agents, as detected in individual infants enrolled in the study or, in the case of cluster randomized studies, on |

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|--|
|--|

| | | | | surveillance of other infants in the same unit in the study centre (including infants who were admitted to the unit following completion of the study). 6. Adverse drug reactions attributed to the antifungal agent, such as rash, gastrointestinal disturbance, abnormal hepatic or renal function, cardiac arrhythmias, thrombophlebitis, seizures, and anaphylaxis or toxicity sufficient to cease drug administration. | |
|--|--|---|--|--|--|
| Mixed setting & community-based antibiotic delivery for possible serious bacterial infections (PSBIs) - updated review from Duby 2019 [11] | Neonates born at any gestational age enrolled at any time between 0 to 27 completed days of life with possible serious bacterial infection (PSBI), as defined by the World Health Organization (WHO; WHO 2015). Confirmation of a bacterial infection with a positive culture from a sterile body site, can be contributory, but is not necessary for inclusion. | Comparison 1: Community-based programmes of newborn care that include the initiation of antibiotics in the community for PSBI in LMICs Comparison 2: Community-based delivery of simplified injectable antibiotics or oral antibiotics, or both for PSBI in neonates | Comparison 1: Community-based programmes of newborn care that do not include the provision of community-based antibiotics for PSBI in LMICs (i.e., standard hospital referral) Comparison 2: Community-based delivery of seven to 10 days of injectable penicillin/ampicillin and an injectable aminoglycoside for PBSI in neonates | 1. Neonatal mortality - the number of neonatal deaths from any cause among all neonates. For individually-randomized and quasi-randomized trials, neonatal morality was calculated as the number of neonatal deaths divided by the total number of neonates enrolled in the trial. For cluster-randomized trials, neonatal mortality was calculated as the number of neonatal deaths divided by the total number of live births within each cluster during the trial period. a. Early neonatal mortality: from birth through six completed days of life b. Late neonatal mortality: between 7 and 27 completed days of life 2. Sepsis-specific neonatal mortality - the number of neonatal deaths secondary to PSBI among all neonates during the trial period. Similar calculation considerations applied to sepsis- specific mortality as neonatal mortality. a. Early neonatal sepsis-specific mortality: from birth through six completed days of life | Individually- randomized, cluster- randomized and quasi- randomized trials |

b. Late neonatal sepsis-specific mortality: between 7 and 27 completed days of life

Secondary outcomes:

- Treatment failure defined as any one of the following: 1) death within seven days after enrolment;
 hospital admission within seven days after enrolment due to clinical deterioration;
 change of antibiotic regimen due to lack of improvement/ clinical deterioration within seven days after enrolment
- 2. Neonatal antibiotic-associated adverse events defined as occurrence of haematoma, bleeding or infection at an injection site, inability to pass urine for 12 hours, dehydration-associated severe diarrhoea, anaphylaxis, or development of rash within seven days of enrolment
- 3. Total cost (in USD) to manage all neonates with PSBI in the community during the trial period (including training, drug cost and delivery, and equipment)
- 4. Cost of intervention (in USD) per neonate life saved among all neonates with PSBI managed in the community during the trial period
- 5. Acceptability of antibiotics defined as the number of mothers who accept community-based antibiotic treatment for their neonates among all mothers of neonates with PSBI identified during the trial period
- 6. Antibiotic resistance defined as the number of cases in which there was isolation of bacteria resistant to penicillin/ampicillin and an aminoglycoside within 30 days after enrolment

BPD, Bronchopulmonary dysplasia; CBK, clean birth kit; CHW, community health worker; EOS, early-onset sepsis; ELBW, extremely low birth weight; ITS, interrupted time series; KMC, kangaroo mother care; LHW, lady health worker; LMICs, low- and middle-income countries; LOS, late-onset sepsis; MDRO, multidrug-resistant organism; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; RCTs, randomized controlled trials; TBA, trained birth attendant/traditional birth attendant; USD, United States dollar; UTI, urinary tract infection; VLBW, very low birth weight; WHO, World Health Organization

Appendix 3: Classification of Antimicrobial Stewardship Interventions

Table 3 Regulation, education, and restriction definitions

| Regulation | Regulation interventions were defined as non-education and non-restriction structural or organizational actions which attempt to prevent or |
|-------------|--|
| | control the development and spread of infections and antimicrobial resistance (AMR), such as surveillance and audit, health-care worker |
| | vaccination, sterilization of the built environment and multi-patient use equipment, institution of patient isolation measures, and the |
| | implementation of protocols and policies for infection and AMR management. |
| Education | Education interventions were defined as efforts to educate and inform healthcare workers of the appropriate policies and procedures for |
| | infection and antimicrobial resistance prevention and control, including but not limited to training sessions, journal clubs, ward round |
| | discussions, and reminders in the form of wall posters with algorithms for improved decision-making. |
| Restriction | Restriction interventions were defined as prescribing- and dispensing-related actions intended to control or restrict the use of broad- |
| | spectrum antibiotics in favour of narrow-spectrum antibiotics, and reduce initiation or shorten duration of antimicrobials, in the treatment |
| | of newborns. This included using antimicrobial susceptibility testing for guided therapy, introducing antibiotic justification forms, and |
| | instituting hard stops or drug dispensing pre-authorization policies. |

Appendix 4: Forest Plots

4.1 Facility Level Forest Plots

4.1.1. Strategies to Reduce Antimicrobial Resistance

Single-Component Intervention: <u>Regulation</u> **Outcome:** Neonatal sepsis/suspected sepsis

| After Intervention | | | Before Inter | vention | | Risk Ratio | | Risk Ratio | | | |
|---|--------|-------|----------------|-----------------|--------|--------------------|---------|----------------------------------|------------------|----|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% | S CI | | |
| Akintan 2024 (1) | 12 | 19 | 5 | 15 | 35.5% | 1.89 [0.86, 4.19] | | - | | | |
| Wang 2020 (2) | 356 | 4488 | 417 | 4743 | 64.5% | 0.90 [0.79, 1.03] | | = | | | |
| Total (95% CI) | | 4507 | | 4758 | 100.0% | 1.17 [0.59, 2.36] | | | - | | |
| Total events | 368 | | 422 | | | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect: | | | = 1 (P = 0.07) |); $I^2 = 69\%$ | Ś | | 0.1 0.2 | 2 0.5 1 2 Favours after Favou | t 5 rs before | 10 | |

<u>Footnotes</u>

- (1) Akintan 2024 reported sepsis among neonates prescribed antibiotics in the NICU
- (2) Wang 2020 reported sepsis/suspected sepsis among neonates admitted to the NICU

Outcome: Neonatal sepsis/suspected sepsis by study design

| | After Interv | ention | Before Inter | Before Intervention | | Risk Ratio | | Risk Ratio | | | | |
|---------------------------------------|-----------------------------|-----------------|------------------|---------------------|-----------------------|--------------------|--------------|------------|--------------------|---------------|-------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, | IV, Random, 95% CI | | | |
| 1.2.1 Cross-section | al study | | | | | | | | | | | |
| Akintan 2024 (1) Subtotal (95% CI) | 12 | 19 19 | 5 | 15 15 | 35.5% 35.5% | | | | | | — ► | |
| Total events | 12 | | 5 | | | | | | | | | |
| Heterogeneity: Not a | pplicable | | | | | | | | | | | |
| Test for overall effec | t: Z = 1.58 (P = | = 0.11) | | | | | | | | | | |
| 1.2.2 Cohort study | | | | | | | | | | | | |
| Wang 2020 (2) | 356 | 4488 | 417 | 4743 | 64.5% | 0.90 [0.79, 1.03] | | | | | | |
| Subtotal (95% CI) | | 4488 | | 4743 | 64.5% | 0.90 [0.79, 1.03] | | | • | | | |
| Total events | 356 | | 417 | | | | | | | | | |
| Heterogeneity: Not a | pplicable | | | | | | | | | | | |
| Test for overall effec | t: $Z = 1.49 (P =$ | = 0.14) | | | | | | | | | | |
| Total (95% CI) | | 4507 | | 4758 | 100.0% | 1.17 [0.59, 2.36] | | | | — | | |
| Total events | 368 | | 422 | | | | | | | | | |
| Heterogeneity: Tau ² | = 0.19; Chi ² = | 3.26, df | = 1 (P = 0.07) |); $I^2 = 69\%$ | ś | | | 0 2 (|) 5 1 | | | 10 |
| Test for overall effec | t: Z = 0.45 (P = | = 0.65) | | | | | 0.1 | ٠.ـ | rs after Fav | Z Vours bo | oforo | 10 |
| Test for subgroup di | fferences: Chi ² | = 3.26, | df = 1 (P = 0.0) | $(0.7), I^2 = 6$ | 9.3% | | | ravou | s aitel Fa | vouis be | iore | |
| | | | | | | | | | | | | |

Footnotes

- (1) Akintan 2024 reported sepsis among neonates prescribed antibiotics in the NICU
- (2) Wang 2020 reported sepsis/suspected sepsis among neonates admitted to the NICU

Outcome: Number of newborns receiving at least one antimicrobial

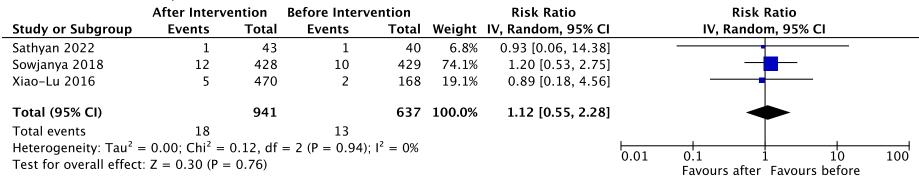
| | After Interv | Before Inter | vention | Risk Ratio | | | Risk Ratio | | |
|--|--------------|--------------|----------------|-----------------|--------|--------------------|------------|--------------------------------------|----------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| Akintan 2024 | 17 | 19 | 15 | 19 | 42.5% | 1.13 [0.86, 1.50] | | - | |
| Wang 2020 | 3328 | 4488 | 4478 | 4743 | 57.5% | 0.79 [0.77, 0.80] | | • | |
| Total (95% CI) | | 4507 | | 4762 | 100.0% | 0.92 [0.64, 1.31] | | | |
| Total events | 3345 | | 4493 | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect | | | = 1 (P = 0.01) |); $I^2 = 85\%$ | Ó | | 0.2 | 0.5 1 2 Favours after Favours before | 5 |

Outcome: Number of newborns receiving at least one antimicrobial by study design

| | After Interv | ention | Before Interv | ention | | Risk Ratio | Risk Ratio | | |
|---|---------------------|---------------------|---------------|---------------------|-----------------------|--------------------|---------------------------|---------------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Rando | m, 95% CI | |
| 1.4.1 Cross-sectiona | ıl study | | | | | | | | |
| Akintan 2024 Subtotal (95% CI) | 17 | 19 19 | 15 | 19 19 | 42.5% 42.5% | . , . | | | |
| Total events | 17 | | 15 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect | Z = 0.88 (P = | = 0.38) | | | | | | | |
| 1.4.2 Cohort study | | | | | | | | | |
| Wang 2020 Subtotal (95% CI) | 3328 | 4488 4488 | 4478 | 4743 4743 | 57.5% 57.5% | | • | | |
| Total events | 3328 | | 4478 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect | Z = 25.44 (P) | < 0.000 | 01) | | | | | | |
| Total (95% CI) | | 4507 | | 4762 | 100.0% | 0.92 [0.64, 1.31] | | | |
| Total events | 3345 | | 4493 | | | | | | |
| Heterogeneity: Tau² = Test for overall effect Test for subgroup dif | Z = 0.47 (P = 0.47) | = 0.64) | | _ | | - | 0.7 0.85 Favours after | 1 1.2 1 Favours before | |

Single-Component Intervention: *Restriction*

Outcome: Neonatal mortality



Outcome: Neonatal mortality by study design

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | Risk Ratio | |
|-----------------------------------|----------------------------|----------|------------------|---------------|--------|--------------------|------|----------------------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| 1.6.1 Cohort study | | | | | | | | | |
| Sathyan 2022 | 1 | 43 | 1 | 40 | 6.8% | 0.93 [0.06, 14.38] | | | |
| Subtotal (95% CI) | | 43 | | 40 | 6.8% | 0.93 [0.06, 14.38] | | | _ |
| Total events | 1 | | 1 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect | Z = 0.05 (P = 0.05) | = 0.96) | | | | | | | |
| 1.6.2 Quasi-experim | ental study | | | | | | | | |
| Sowjanya 2018 | 12 | 428 | 10 | 429 | 74.1% | 1.20 [0.53, 2.75] | | _ | |
| Xiao-Lu 2016 | 5 | 470 | 2 | 168 | 19.1% | 0.89 [0.18, 4.56] | | | |
| Subtotal (95% CI) | | 898 | | 597 | 93.2% | 1.13 [0.54, 2.37] | | * | |
| Total events | 17 | | 12 | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.10, df | = 1 (P = 0.75); | $I^2 = 0\%$ | | | | | |
| Test for overall effect | Z = 0.33 (P = 0.33) | = 0.74) | | | | | | | |
| Total (95% CI) | | 941 | | 637 | 100.0% | 1.12 [0.55, 2.28] | | • | |
| Total events | 18 | | 13 | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.12, df | = 2 (P = 0.94); | $I^2 = 0\%$ | | | 0.01 | | 10 16 |
| Test for overall effect | | | | | | | 0.01 | 0.1 İ Favours after Favours b | 10 10 |
| Test for subgroup dif | ferences: Chi ² | = 0.02, | df = 1 (P = 0.8) | 9), $I^2 = 0$ | % | | | ravours after ravours b | eioie |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Culture-positive sepsis

| After Intervention | | | Before Interv | ention | Risk Ratio | | | Risk Ratio | | | |
|-----------------------------------|----------------------------|----------|----------------|-------------|------------|--------------------|----------------------|-----------------|----------------------|-------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rando | m, 95% CI | | |
| Sowjanya 2018 | 14 | 428 | 18 | 429 | 8.8% | 0.78 [0.39, 1.55] | | | | | |
| Xiao-Lu 2016 | 144 | 470 | 77 | 168 | 91.2% | 0.67 [0.54, 0.83] | | - | | | |
| Total (95% CI) | | 898 | | 597 | 100.0% | 0.68 [0.55, 0.83] | | • | | | |
| Total events | 158 | | 95 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.18, df | = 1 (P = 0.67) | $I^2 = 0\%$ | | | $\frac{1}{\sqrt{2}}$ | 0 - | | | |
| Test for overall effect | Z = 3.74 (P = | = 0.0002 |) | | | | 0.2 | Favours [After] | L ∠ Favours [Befo | ore] | |

Outcome: Number of newborns on antibiotics

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | Risk Rat | tio | |
|-----------------------------------|----------------------------|----------|------------------|----------------|--------|--------------------|----------------|-------------|----------------|---------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, | 95% CI | |
| Jinka 2017 | 584 | 1276 | 681 | 1176 | 31.9% | 0.79 [0.73, 0.85] | | - | | |
| Sowjanya 2018 | 370 | 428 | 385 | 429 | 34.9% | 0.96 [0.92, 1.01] | | | | |
| Xiao-Lu 2016 | 372 | 470 | 154 | 168 | 33.3% | 0.86 [0.81, 0.92] | | - | | |
| Total (95% CI) | | 2174 | | 1773 | 100.0% | 0.87 [0.78, 0.98] | | | | |
| Total events | 1326 | | 1220 | | | | | | | |
| Heterogeneity: Tau ² = | = 0.01; Chi ² = | 19.71, d | f = 2 (P < 0.00) | $(001); I^2 =$ | 90% | | 1-0 | - | 1 5 | <u></u> |
| Test for overall effect | Z = 2.35 (P = 1.35) | = 0.02) | | | | | 0.5 0. Favo | - | vours [Before] | 2 |

Outcome: Number of newborns on amikacin

| | After Interv | ention | Before Interv | ention/ | | Risk Ratio | | Risk | Ratio | | |
|-----------------------------------|----------------------------|----------|------------------|----------------|--------|--------------------|---------------|-----------------|--|-------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rando | m, 95% CI | | |
| Jinka 2017 | 116 | 1276 | 301 | 1176 | 49.8% | 0.36 [0.29, 0.43] | | - | | | |
| Sowjanya 2018 | 160 | 428 | 190 | 429 | 50.2% | 0.84 [0.72, 0.99] | | - | \dashv | | |
| Total (95% CI) | | 1704 | | 1605 | 100.0% | 0.55 [0.23, 1.28] | | | | | |
| Total events | 276 | | 491 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.37; Chi ² = | 43.68, d | f = 1 (P < 0.00) | $(001); I^2 =$ | = 98% | | $\frac{1}{0}$ | 02 05 | | | 10 |
| Test for overall effect | Z = 1.39 (P = 1.39) | 0.17) | | | | | 0.1 | Favours [After] | Favours [Be | o efore] | 10 |

Outcome: Number of newborns on amikacin (of newborns on any antibiotic)

| | After Interv | ention | Before Interv | ention/ | | Risk Ratio | Risk I | Ratio | |
|-----------------------------------|----------------------------|----------|------------------|-------------------------|--------|--------------------|---------------|------------------|---------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Randor | m, 95% CI | |
| Jinka 2017 | 116 | 584 | 301 | 681 | 49.7% | 0.45 [0.37, 0.54] | - | | |
| Sowjanya 2018 | 160 | 370 | 190 | 385 | 50.3% | 0.88 [0.75, 1.02] | - | | |
| Total (95% CI) | | 954 | | 1066 | 100.0% | 0.63 [0.33, 1.21] | | _ | |
| Total events | 276 | | 491 | | | | | | |
| Heterogeneity: Tau ² = | = 0.22; Chi ² = | 29.78, d | f = 1 (P < 0.00) | 0001); I ² = | = 97% | | 0 1 0 2 0 5 1 | 1 | 5 10 |
| Test for overall effect | Z = 1.39 (P = 1.39) | 0.16) | | | | | 0.1 0.2 0.3 | Favours [Before] | |

Outcome: Number of newborns on piperacillin-tazobactam

| | After Interve | ention | Before Interv | ention | | Risk Ratio | | Risk Ratio | |
|-----------------------------------|---------------|--------|----------------|--------------|--------|--------------------|-----|----------------------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| Jinka 2017 | 81 | 1276 | 109 | 1176 | 40.8% | 0.68 [0.52, 0.90] | | | |
| Sowjanya 2018 | 155 | 428 | 175 | 429 | 59.2% | 0.89 [0.75, 1.05] | | | |
| Total (95% CI) | | 1704 | | 1605 | 100.0% | 0.80 [0.62, 1.03] | | • | |
| Total events | 236 | | 284 | | | | | | |
| Heterogeneity: Tau ² = | | | = 1 (P = 0.12) | $I^2 = 59\%$ | ó | | 0.2 | 0.5 1 2 | |
| Test for overall effect | Z = 1.76 (P = | (80.0 | | | | | | Favours [After] Favours [Before] | |

Outcome: Number of newborns on piperacillin-tazobactam (of newborns on any antibiotic)

| | After Interv | ention | Before Interv | ention/ | | Risk Ratio | | Ris | k Ratio | | |
|-----------------------------------|----------------------------|----------|----------------|-------------|--------|--------------------|-----|---------------|-----------|-------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rand | lom, 95% | CI | |
| Jinka 2017 | 81 | 584 | 109 | 681 | 27.2% | 0.87 [0.66, 1.13] | | | | | |
| Sowjanya 2018 | 155 | 370 | 175 | 385 | 72.8% | 0.92 [0.78, 1.08] | | | + | | |
| Total (95% CI) | | 954 | | 1066 | 100.0% | 0.91 [0.79, 1.04] | | | | | |
| Total events | 236 | | 284 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.15, df | = 1 (P = 0.70) | $I^2 = 0\%$ | | | 0.5 | 0.7 | + | 1 5 | |
| Test for overall effect | Z = 1.39 (P = 1.39) | = 0.16) | | | | | 0.5 | Favours [Afte | r] Favoui | rs [Before] | ۷ |

Outcome: AWaRe antibiotic usage

| 3 | After Interv | vention | Before Inter | vention | | Risk Ratio | Risk Ratio |
|--|------------------|-------------------|--------------|-------------------|----------------------|--|----------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 1.3.1 Access group | | | | | | | |
| Jinka 2017 - Amikacin | 116 | 584 | 301 | 681 | 7.1% | 0.45 [0.37, 0.54] | |
| Jinka 2017 - Ampicillin/Gentamicin | 491 | 584 | 449 | 681 | 7.3% | 1.28 [1.20, 1.36] | • |
| Sowjanya 2018 – Amikacin | 160 | 428 | 190 | 429 | 7.2% | 0.84 [0.72, 0.99] | |
| Sowjanya 2018 -Ampicillin | 40 | 428 | 45 | 429 | 6.2% | 0.89 [0.59, 1.33] | |
| Xiao-Lu 2016 - Penicillin | 346 | 470 | 156 | 168 | 7.3% | 0.79 [0.74, 0.85] | * |
| Subtotal (95% CI) | | 2494 | | 2388 | 35.2% | 0.81 [0.58, 1.13] | • |
| Total events | 1153 | | 1141 | | | | |
| Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 172.73$, $df = 4$ | (P < 0.00001) |); $I^2 = 98\%$ | : I | | | | |
| Test for overall effect: $Z = 1.25$ ($P = 0.21$) | | | | | | | |
| 1.3.2 Watch group | | | | | | | |
| Jinka 2017 – 3rd Gen. Cephalosporins | 39 | 584 | 281 | 681 | 6.6% | 0.16 [0.12, 0.22] | |
| Jinka 2017 – Ciprofloxacin | 45 | 584 | 5 | 681 | 3.7% | 10.49 [4.19, 26.26] | |
| Jinka 2017 – Meropenem | 58 | 584 | 58 | 681 | 6.5% | 1.17 [0.82, 1.65] | - |
| Jinka 2017 – Piperacillin–Tazobactam | 81 | 584 | 109 | 681 | 6.8% | 0.87 [0.66, 1.13] | |
| Sowjanya 2018 – Piperacillin–Tazobactam | 155 | 428 | 175 | 429 | 7.1% | 0.89 [0.75, 1.05] | |
| Xiao-Lu 2016 - 3rd and 4th Gen. Cephalosporins | 187 | 470 | 90 | 168 | 7.1% | 0.74 [0.62, 0.89] | - |
| Xiao-Lu 2016 - Carbapenems | 168 | 470 | 27 | 168 | 6.4% | 2.22 [1.54, 3.21] | |
| Xiao-Lu 2016 - Glycopeptides | 72 | 470 | 32 | 168 | 6.3% | 0.80 [0.55, 1.17] | - |
| Subtotal (95% CI) | | 4174 | | 3657 | 50.6% | 1.00 [0.61, 1.63] | • |
| Total events | 805 | | 777 | | | | |
| Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 165.33$, $df = 7$ Test for overall effect: $Z = 0.00$ ($P = 1.00$) | (P < 0.00001) |); $I^2 = 96\%$ | | | | | |
| | | | | | | | |
| 1.3.3 Mix of Access and Watch group | 175 | 420 | 105 | 420 | 7 20/ | 0.00[0.77.1.05] | |
| Sowjanya 2018 - Empirical 1st Line (1) | 175 | 428 | 195 | 429 | 7.2% | 0.90 [0.77, 1.05] | |
| Xiao-Lu 2016 - 1st and 2nd Gen. Cephalosporins Subtotal (95% CI) | 100 | 470 898 | 126 | 168 597 | 7.1% 14.3% | 0.28 [0.23, 0.34] 0.51 [0.16, 1.57] | |
| | 275 | 090 | 221 | 397 | 14.3/0 | 0.31 [0.10, 1.37] | |
| Total events | 275 | 12 000/ | 321 | | | | |
| Heterogeneity: $Tau^2 = 0.66$; $Chi^2 = 83.07$, $df = 1$ (I Test for overall effect: $Z = 1.18$ (P = 0.24) | P < 0.00001); | 1 = 99% | | | | | |
| Test for overall effect: $Z = 1.18$ (P = 0.24) | | | | | | | |
| Total (95% CI) | | 7566 | | 6642 | 100.0% | 0.82 [0.64, 1.06] | |
| Total events | 2233 | | 2239 | | | 0.02 [0.0 ., 2.00] | |
| Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 486.74$, $df = 14$ | | 1) $I^2 = 97^9$ | | | | | |
| Test for overall effect: $Z = 1.54$ (P = 0.12) | 1 (1 < 0.0000 | 1), 1 – 37 | 70 | | | | 0.05 0.2 1 5 20 |
| Test for subgroup differences: $Chi^2 = 1.32$, $Chi^2 = 1.32$ | $(P = 0.52) I^2$ | = 0% | | | | | Favours [After] Favours [Before] |
| Footnotes | (i - 0.52), i | 370 | | | | | |
| (1) Amikacin, Ampicillin, and Piperacillin-Tazobacta | am | | | | | | |
| (1) / tillikacili, Allipicilili, alia i iperacilili- razobaci | uiii | | | | | | |

Multi-Component Intervention: <u>Regulation & Restriction</u>

Outcome: Neonatal mortality due to nosocomial bloodstream infection

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | | Risk Ratio | | |
|---|---------------|--------|-----------------|-------------|--------|--------------------|------|------------|--------------|-------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, R | andom, 95% | 6 CI | |
| El-Baky 2020 | 59 | 617 | 65 | 462 | 98.6% | 0.68 [0.49, 0.95] | | | - | | |
| Landre-Peigne 2011 | 1 | 148 | 1 | 125 | 1.4% | 0.84 [0.05, 13.37] | | | - | | |
| Total (95% CI) | | 765 | | 587 | 100.0% | 0.68 [0.49, 0.95] | | | • | | |
| Total events | 60 | | 66 | | | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect: | • | | = 1 (P = 0.88); | $I^2 = 0\%$ | | | 0.02 | 0.1 | 1 | 10 | 50 |
| rest for overall effect. | 2 - 2.20 (1 - | 0.02) | | | | | | Favours [A | \fter] Favou | rs [Before] | |

Outcome: Neonatal mortality due to nosocomial bloodstream infection by level of care

| | After Interv | ention | Before Interv | ention | , | Risk Ratio | | Risk Ratio | |
|-----------------------------------|----------------------------|-------------------|-------------------|-------------------|-----------------------|---|------|---------------------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| 1.16.1 Tertiary or hig | gher | | | | | | | | |
| El-Baky 2020 Subtotal (95% CI) | 59 | 617 617 | 65 | 462 462 | 98.6% 98.6% | 0.68 [0.49, 0.95] 0.68 [0.49, 0.95] | | • | |
| Total events | 59 | | 65 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | Z = 2.29 (P = | 0.02) | | | | | | | |
| 1.16.2 Secondary | | | | | | | | | |
| Landre-Peigne 2011 | 1 | 148 | 1 | 125 | 1.4% | 0.84 [0.05, 13.37] | | | |
| Subtotal (95% CI) | | 148 | | 125 | 1.4% | 0.84 [0.05, 13.37] | | | |
| Total events | 1 | | 1 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | Z = 0.12 (P = | 0.90) | | | | | | | |
| Total (95% CI) | | 765 | | 587 | 100.0% | 0.68 [0.49, 0.95] | | • | |
| Total events | 60 | | 66 | | | | | | |
| Heterogeneity: Tau ² = | 0.00; Chi ² = 0 | 0.02, df = | = 1 (P = 0.88); | $I^2 = 0\%$ | | | 0.01 | 0.1 1 10 | 100 |
| Test for overall effect: | Z = 2.28 (P = | 0.02) | | | | | 0.01 | Favours [After] Favours [Before | |
| Test for subgroup diff | ferences: Chi ² | = 0.02, c | df = 1 (P = 0.88) | $(3), I^2 = 0$ | 6 | | | ravours pareir ravours (before | -1 |

Multi-Component Intervention: Regulation, Education & Restriction

Outcome: Neonatal mortality

| | After Interv | ention | Before Interv | ention/ | | Risk Ratio | | Risk Ratio | |
|-----------------------------------|----------------------------|----------|------------------|-------------------|--------|--------------------|------|--|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| Agarwal 2021 | 56 | 864 | 20 | 290 | 10.8% | 0.94 [0.57, 1.54] | | - | |
| Bassiouny 2020 | 31 | 150 | 20 | 60 | 11.2% | 0.62 [0.39, 1.00] | | | |
| Chu 2023 | 2 | 90 | 3 | 96 | 1.7% | 0.71 [0.12, 4.16] | | | |
| Feng 2022 | 0 | 2901 | 3 | 4804 | 0.7% | 0.24 [0.01, 4.58] | | · - | |
| Gill 2009 (1) | 144 | 1000 | 290 | 1000 | 17.6% | 0.50 [0.41, 0.59] | | + | |
| Gill 2009 (2) | 481 | 1000 | 598 | 1000 | 19.1% | 0.80 [0.74, 0.87] | | • | |
| Jain 2021 (3) | 16 | 1000 | 25 | 1000 | 8.6% | 0.64 [0.34, 1.19] | | | |
| Kommalur 2021 | 18 | 58 | 38 | 75 | 11.8% | 0.61 [0.39, 0.95] | | | |
| Lu 2019 | 388 | 5786 | 473 | 7754 | 18.5% | 1.10 [0.97, 1.25] | | • | |
| Total (95% CI) | | 12849 | | 16079 | 100.0% | 0.73 [0.57, 0.93] | | ♦ | |
| Total events | 1136 | | 1470 | | | | | | |
| Heterogeneity: Tau ² = | = 0.08; Chi ² = | 54.12, d | f = 8 (P < 0.00) | 0001); $I^2 =$ | = 85% | | 0.01 | | 100 |
| Test for overall effect | Z = 2.57 (P = 1.57) | = 0.01) | | | | | 0.01 | 0.1 1 10 Favours after Favours before | 100 |

Footnotes

- (1) Gill 2009 reported neonatal mortality in NICU 1 as deaths per 1000 admissions
- (2) Gill 2009 reported neonatal mortality in NICU 2 as deaths per 1000 admissions
- (3) Jain 2021 reported neonatal mortality per 1000 live births

Outcome: Neonatal mortality – sensitivity analysis (omitting studies with high risk of bias)

| | After Interve | ention | Before Inter | vention | | Risk Ratio | | Risk Ratio | | |
|-----------------------------------|----------------------------|----------|-----------------|----------------|--------|--------------------|------|-----------------------------|------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95 | % CI | |
| Agarwal 2021 | 56 | 864 | 20 | 290 | 12.0% | 0.94 [0.57, 1.54] | | | | |
| Bassiouny 2020 | 31 | 150 | 20 | 60 | 12.3% | 0.62 [0.39, 1.00] | | | | |
| Chu 2023 | 2 | 90 | 3 | 96 | 1.9% | 0.71 [0.12, 4.16] | | - | <u>—</u> | |
| Feng 2022 | 0 | 2901 | 3 | 4804 | 0.7% | 0.24 [0.01, 4.58] | | • | <u></u> - | |
| Gill 2009 (1) | 144 | 1000 | 290 | 1000 | 19.2% | 0.50 [0.41, 0.59] | | - | | |
| Gill 2009 (2) | 481 | 1000 | 598 | 1000 | 20.7% | 0.80 [0.74, 0.87] | | • | | |
| Kommalur 2021 | 18 | 58 | 38 | 75 | 13.0% | 0.61 [0.39, 0.95] | | | | |
| Lu 2019 | 388 | 5786 | 473 | 7754 | 20.1% | 1.10 [0.97, 1.25] | | † | | |
| Total (95% CI) | | 11849 | | 15079 | 100.0% | 0.73 [0.57, 0.95] | | • | | |
| Total events | 1120 | | 1445 | | | | | | | |
| Heterogeneity: Tau ² = | = 0.08; Chi ² = | 53.57, d | f = 7 (P < 0.0) | 0001); $I^2 =$ | = 87% | | 0.01 | | 10 | 100 |
| Test for overall effect | Z = 2.34 (P = 2.34) | 0.02) | | | | | 0.01 | 0.1 1 Favours after Favo | 10 urs before | 100 |

Footnotes

- (1) Gill 2009 reported neonatal mortality in NICU 1 as deaths per 1000 admissions
- (2) Gill 2009 reported neonatal mortality in NICU 2 as deaths per 1000 admissions

Outcome: Neonatal mortality by study design

| | After Interv | ention | Before Inter | vention | | | Risk Ratio | | |
|--------------------------------------|----------------------------|----------------------|-----------------|----------------------|-----------------------|---|------------|------------------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| 1.7.1 Cohort study | | | | | | | | | |
| Chu 2023 Subtotal (95% CI) | 2 | 90 90 | 3 | 96 96 | 1.7% 1.7% | | | | |
| Total events | 2 | | 3 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect | z = 0.38 (P = 0.38) | = 0.71) | | | | | | | |
| 1.7.2 Quasi-experim | nental study | | | | | | | | |
| Agarwal 2021 | 56 | 864 | 20 | 290 | 10.8% | 0.94 [0.57, 1.54] | | + | |
| Bassiouny 2020 | 31 | 150 | 20 | 60 | 11.2% | 0.62 [0.39, 1.00] | | | |
| Feng 2022 | 0 | 2901 | 3 | 4804 | 0.7% | 0.24 [0.01, 4.58] | | | |
| Gill 2009 (1) | 144 | 1000 | 290 | 1000 | 17.6% | 0.50 [0.41, 0.59] | | - | |
| Gill 2009 (2) | 481 | 1000 | 598 | 1000 | 19.1% | 0.80 [0.74, 0.87] | | • | |
| Jain 2021 (3) | 16 | 1000 | 25 | 1000 | 8.6% | 0.64 [0.34, 1.19] | | | |
| Kommalur 2021 | 18 | 58 | 38 | 75 | 11.8% | 0.61 [0.39, 0.95] | | | |
| Lu 2019 Subtotal (95% CI) | 388 | 5786 12759 | 473 | 7754 15983 | 18.5% 98.3% | 1.10 [0.97, 1.25] 0.73 [0.57, 0.93] | | <u>_</u> | |
| Total events | 1134 | 12739 | 1467 | 13963 | 30.3/6 | 0.73 [0.37, 0.33] | | Y | |
| Heterogeneity: Tau ² = | | 54.10. d | | 0001): $I^2 =$ | = 87% | | | | |
| Test for overall effect | | | | / , - | | | | | |
| Total (95% CI) | | 12849 | | 16079 | 100.0% | 0.73 [0.57, 0.93] | | • | |
| Total events | 1136 | | 1470 | | | | | | |
| Heterogeneity: Tau ² = | = 0.08; Chi ² = | 54.12, d | f = 8 (P < 0.0) | 0001); $I^2 =$ | = 85% | | 0.01 | 0.1 1 10 | 100 |
| Test for overall effect | | | | | | | 0.01 | Favours after Favours before | 100 |
| Test for subgroup dif | ferences: Chi ² | = 0.00, | df = 1 (P = 0. | 98), $I^2 = 0$ | % | | | Tavours after Tavours Defore | |

- $\underline{Footnotes}$
- (1) Gill 2009 reported neonatal mortality in NICU 1 as deaths per 1000 admissions
- (2) Gill 2009 reported neonatal mortality in NICU 2 as deaths per 1000 admissions
- (3) Jain 2021 reported neonatal mortality per 1000 live births

Outcome: Necrotizing enterocolitis (any Bell stage)

| | After Interv | ention | Before Interv | ention | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------|----------|----------------|-------------|--------|--------------------|------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Agarwal 2021 (1) | 49 | 864 | 21 | 290 | 8.8% | 0.78 [0.48, 1.28] | |
| Chu 2023 (2) | 8 | 90 | 7 | 96 | 2.3% | 1.22 [0.46, 3.22] | |
| Feng 2022 (3) | 30 | 2901 | 54 | 4804 | 10.9% | 0.92 [0.59, 1.43] | |
| Lu 2019 (4) | 249 | 5786 | 287 | 7754 | 77.9% | 1.16 [0.98, 1.37] | <u>=</u> |
| Total (95% CI) | | 9641 | | 12944 | 100.0% | 1.10 [0.95, 1.27] | • |
| Total events | 336 | | 369 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 2.91, df | = 3 (P = 0.41) | $I^2 = 0\%$ | | | 0.1 0.2 0.5 1 2 5 10 |
| Test for overall effect | Z = 1.22 (P = 1.22) | = 0.22) | | | | | Favours after Favours before |

Footnotes

- (1) Agarwal 2021 reported overall NEC
- (2) Chu 2023 reported NEC (Bell stage ≥ II)
- (3) Feng 2022 reported NEC (Bell stage ≥ II)
- (4) Lu 2019 reported NEC (Stage ≥ II)

Outcome: Necrotizing enterocolitis (any Bell stage) by study design

| | After Intervention | | Before Intervention | | | Risk Ratio | Risk Ratio |
|--------------------------------------|----------------------------|-----------------|----------------------------|-----------------|---------------------|---|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 1.9.1 Cohort study | | | | | | | |
| Chu 2023 Subtotal (95% CI) | 8 | 90 90 | 7 | 96 96 | 2.3% 2.3% | 1.22 [0.46, 3.22] 1.22 [0.46, 3.22] | |
| Total events | 8 | 30 | 7 | 30 | 2.370 | 1.22 [0.10, 5.22] | |
| Heterogeneity: Not an | _ | | | | | | |
| Test for overall effect | • | = 0.69) | | | | | |
| 1.9.2 Quasi-experim | ental study | | | | | | |
| Agarwal 2021 | 49 | 864 | 21 | 290 | 8.8% | 0.78 [0.48, 1.28] | · · · |
| Feng 2022 | 30 | 2901 | 54 | 4804 | 10.9% | 0.92 [0.59, 1.43] | |
| Lu 2019 | 249 | 5786 | 287 | 7754 | 77.9% | 1.16 [0.98, 1.37] | |
| Subtotal (95% CI) | | 9551 | | 12848 | 97.7% | 1.04 [0.82, 1.30] | ◆ |
| Total events | 328 | | 362 | | | | |
| Heterogeneity: Tau ² = | = 0.01; Chi ² = | 2.86, df | = 2 (P = 0.24) |); $I^2 = 30\%$ | ,) | | |
| Test for overall effect | Z = 0.30 (P = 0.30) | = 0.77) | | | | | |
| Total (95% CI) | | 9641 | | 12944 | 100.0% | 1.10 [0.95, 1.27] | • |
| Total events | 336 | | 369 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 2.91, df | = 3 (P = 0.41) |); $I^2 = 0\%$ | | | |
| Test for overall effect | | | | | | | 0.1 0.2 0.5 1 2 5 10 Favours after Favours before |
| Test for subgroup dif | ferences: Chi ² | = 0.10, | df = 1 (P = 0.7) | 75), $I^2 = 0$ | % | | ravours after Favours before |

Outcome: Necrotizing enterocolitis (Bell stage ≥ II)

| | After Interv | ention | Before Inter | vention | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------|----------|----------------|----------------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Chu 2023 | 8 | 90 | 7 | 96 | 2.5% | 1.22 [0.46, 3.22] | ·] - |
| Feng 2022 | 30 | 2901 | 54 | 4804 | 12.0% | 0.92 [0.59, 1.43] | ·] ——— |
| Lu 2019 | 249 | 5786 | 287 | 7754 | 85.5% | 1.16 [0.98, 1.37] | 'I <u>=</u> |
| Total (95% CI) | | 8777 | | 12654 | 100.0% | 1.13 [0.97, 1.32] | 1 |
| Total events | 287 | | 348 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.96, df | = 2 (P = 0.62) |); $I^2 = 0\%$ | | | 1 1 1 1 1 |
| Test for overall effect | Z = 1.58 (P = 1.58) | = 0.11) | | | | | 0.1 0.2 0.5 1 2 5 10 Favours after Favours before |

Outcome: Necrotizing enterocolitis (Bell stage ≥ II) by study design

| | After Interv | ention | Before Interv | ention | | Risk Ratio | Risk Ratio | |
|--------------------------------------|--------------------------|-----------------|----------------------|-----------------|---------------------|--------------------|---|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI | |
| 1.11.1 Cohort study | | | | | | | | |
| Chu 2023 Subtotal (95% CI) | 8 | 90 90 | 7 | 96 96 | 2.5% 2.5% | · / - | | |
| Total events | 8 | | 7 | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | |
| Test for overall effect: | Z = 0.40 (P = | 0.69) | | | | | | |
| 1.11.2 Quasi-experir | nental study | | | | | | | |
| Feng 2022 | 30 | 2901 | 54 | 4804 | 12.0% | 0.92 [0.59, 1.43] | | |
| Lu 2019 | 249 | 5786 | 287 | 7754 | 85.5% | - , <u>-</u> | | |
| Subtotal (95% CI) | | 8687 | | 12558 | 97.5% | 1.13 [0.97, 1.32] | ◆ | |
| Total events | 279 | | 341 | | | | | |
| Heterogeneity: Tau² = | 0.00; Chi ² = | 0.94, df | = 1 (P = 0.33); | $I^2 = 0\%$ | | | | |
| Test for overall effect: | Z = 1.53 (P = | 0.12) | | | | | | |
| Total (95% CI) | | 8777 | | 12654 | 100.0% | 1.13 [0.97, 1.32] | • | |
| Total events | 287 | | 348 | | | | | |
| Heterogeneity: Tau² = | 0.00; Chi ² = | 0.96, df | = 2 (P = 0.62); | $I^2 = 0\%$ | | | 0.1 	0.2 	0.5 	1 	2 	5 | 10 |
| Test for overall effect: | | | | | | | 0.1 0.2 0.5 1 2 5 Favours after Favours before | 1(|
| Test for subgroup diff | | | df = 1 (P = 0.8) | 8). $I^2 = 0$ | % | | ravours after ravours before | |

Outcome: Neonatal sepsis (any)

| | After Interv | Intervention Before Intervention | | | | Risk Ratio | | | Risk Ratio | | | |
|-----------------------------------|----------------------------|----------------------------------|------------------|----------------|--------|--------------------|-------------|------------------|-------------|-------------|-------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Ra | ndom, 95% | CI | | |
| Chu 2023 (1) | 10 | 90 | 23 | 96 | 23.7% | 0.46 [0.23, 0.92] | | | — | | | |
| Feng 2022 (2) | 10 | 2901 | 12 | 4804 | 22.0% | 1.38 [0.60, 3.19] | | | | _ | | |
| Lu 2019 (3) | 376 | 5786 | 884 | 7754 | 27.7% | 0.57 [0.51, 0.64] | | - | - | | | |
| Maalouf 2023 (4) | 39 | 532 | 77 | 153 | 26.7% | 0.15 [0.10, 0.20] | | - | | | | |
| Total (95% CI) | | 9309 | | 12807 | 100.0% | 0.46 [0.19, 1.09] | | | | | | |
| Total events | 435 | | 996 | | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.69; Chi ² = | 60.94, d | If = 3 (P < 0.0) | 0001); $I^2 =$ | = 95% | | | | | | | |
| Test for overall effect | Z = 1.77 (P = 1.77) | = 0.08) | | | | | 0.05 | 0.2 Favours a | ıfter Favou | s before | 20 | |

Footnotes

- (1) A positive blood or CSF fluid culture, or clinical deterioration and ≥2 abnormal blood indicators or changes in CSF consistent with meningitis
- (2) LOS defined as >72 hours of age and positive pathogenic results in blood, urine, or CSF fluid specimens
- (3) Late-onset defined as ≥72 hours after birth
- (4) EOS defined as ≤72 hours after birth

Outcome: Neonatal sepsis (any) by study design

| | After Interv | ention | Before Inter | vention | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------|----------|------------------|-------------------------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 1.13.1 Cohort study | | | | | | | |
| Chu 2023 | 10 | 90 | 23 | 96 | 23.7% | 0.46 [0.23, 0.92] | _ _ |
| Subtotal (95% CI) | | 90 | | 96 | 23.7% | 0.46 [0.23, 0.92] | |
| Total events | 10 | | 23 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 2.20 (P = | = 0.03) | | | | | |
| 1.13.2 Quasi-experi | mental study | | | | | | |
| Feng 2022 | 10 | 2901 | 12 | 4804 | 22.0% | 1.38 [0.60, 3.19] | • • |
| Lu 2019 | 376 | 5786 | 884 | 7754 | 27.7% | 0.57 [0.51, 0.64] | • |
| Maalouf 2023 | 39 | 532 | 77 | 153 | 26.7% | 0.15 [0.10, 0.20] | - |
| Subtotal (95% CI) | | 9219 | | 12711 | 76.3% | 0.46 [0.16, 1.36] | |
| Total events | 425 | | 973 | | | | |
| Heterogeneity: Tau2 = | = 0.85; Chi ² = | 60.89, d | f = 2 (P < 0.0) | 0001); I ² = | = 97% | | |
| Test for overall effect: | Z = 1.40 (P = 1.40) | = 0.16) | | | | | |
| Total (95% CI) | | 9309 | | 12807 | 100.0% | 0.46 [0.19, 1.09] | |
| Total events | 435 | | 996 | | | | |
| Heterogeneity: Tau ² = | = 0.69; Chi ² = | 60.94, d | f = 3 (P < 0.0) | $0001); I^2 =$ | = 95% | | |
| Test for overall effect: | | | | | | | 0.02 0.1 1 10 50 Favours after Favours before |
| Test for subgroup diff | ferences: Chi ² | = 0.00, | df = 1 (P = 0.1) | 99), $I^2 = 0$ | % | | ravours arter Favours before |

Outcome: Late-onset sepsis (>72 hours after birth)

| | After Interv | ention | Before Inter | vention | | Risk Ratio | Risk Ratio | | | | |
|-----------------------------------|----------------------------|----------|----------------|-----------------|--------|--------------------|------------|---------------|-----------------|----|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rando | m, 95% CI | | |
| Chu 2023 | 10 | 90 | 23 | 96 | 25.3% | 0.46 [0.23, 0.92] | | _ | | | |
| Feng 2022 (1) | 10 | 2901 | 12 | 4804 | 19.8% | 1.38 [0.60, 3.19] | | | _ | | |
| Lu 2019 (2) | 376 | 5786 | 884 | 7754 | 54.8% | 0.57 [0.51, 0.64] | | • | | | |
| Total (95% CI) | | 8777 | | 12654 | 100.0% | 0.64 [0.41, 1.02] | | • | | | |
| Total events | 396 | | 919 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.10; Chi ² = | 4.59, df | = 2 (P = 0.10) |); $I^2 = 56\%$ | Ś | | 0.02 | 01 | | 10 | |
| Test for overall effect | Z = 1.86 (P = 1.86) | = 0.06) | | | | | 0.02 | Favours after | ι Favours be | | 30 |

Footnotes

- (1) Feng 2022 reported LOS defined as >72 hours of age and positive pathogenic results in blood, urine, or cerebrospinal fluid specimens
- (2) Lu 2019 reported LOS and defined late-onset as ≥72 hours after birth

Outcome: Late-onset sepsis (>72 hours after birth) by study design

| | After Interve | Before Inter | vention | | Risk Ratio | Risk Ratio | |
|-----------------------------------|---------------------------|--------------|------------------|-----------------|------------|--------------------|------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 1.15.1 Cohort study | | | | | | | |
| Chu 2023 | 10 | 90 | 23 | 96 | 25.3% | | - |
| Subtotal (95% CI) | | 90 | | 96 | 25.3% | 0.46 [0.23, 0.92] | |
| Total events | 10 | | 23 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 2.20 (P = | 0.03) | | | | | |
| 1.15.2 Quasi-experir | nental study | | | | | | |
| Feng 2022 | 10 | 2901 | 12 | 4804 | 19.8% | 1.38 [0.60, 3.19] | - • |
| Lu 2019 | 376 | 5786 | 884 | 7754 | 54.8% | 0.57 [0.51, 0.64] | ■ |
| Subtotal (95% CI) | | 8687 | | 12558 | 74.7% | 0.80 [0.34, 1.86] | |
| Total events | 386 | | 896 | | | | |
| Heterogeneity: Tau ² = | 0.30; Chi ² = | 4.20, df | = 1 (P = 0.04) |); $I^2 = 76\%$ | ó | | |
| Test for overall effect: | Z = 0.51 (P = | 0.61) | | | | | |
| Total (95% CI) | | 8777 | | 12654 | 100.0% | 0.64 [0.41, 1.02] | • |
| Total events | 396 | | 919 | | | | |
| Heterogeneity: Tau ² = | 0.10; Chi ² = | 4.59, df | = 2 (P = 0.10) |); $I^2 = 56\%$ | Ś | | 0.05 0.2 1 5 20 |
| Test for overall effect: | Z = 1.86 (P = | 0.06) | | | | | Favours after Favours before |
| Test for subgroup diff | erences: Chi ² | = 0.97, | df = 1 (P = 0.1) | 32), $I^2 = 0$ | % | | ravours arter ravours before |

Outcome: Culture-negative sepsis

| | After Interv | ention | Before Inter | vention | | Risk Ratio | | Risk Ratio | |
|--|--------------|--------|----------------|----------------|--------|--------------------|-----|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| Feng 2022 (1) | 368 | 2901 | 663 | 4804 | 73.4% | 0.92 [0.82, 1.04] | | | |
| Lu 2019 (2) | 156 | 5786 | 248 | 7754 | 26.6% | 0.84 [0.69, 1.03] | | - | |
| Total (95% CI) | | 8687 | | 12558 | 100.0% | 0.90 [0.81, 0.99] | | | |
| Total events | 524 | | 911 | | | | | | |
| Heterogeneity: Tau² = Test for overall effect | | | = 1 (P = 0.46) |); $I^2 = 0\%$ | | | 0.5 | 0.7 1 1.5 Favours after Favours before | 2 |

Footnotes

- (1) Feng 2022 reported infants treated in ≤5 days for culture-negative sepsis
- (2) Lu 2019 reported all infants treated for culture-negative sepsis

Outcome: Pneumonia

| | After Interve | ention | Before Inter | vention | Risk Ratio | | | Risk Ratio | | |
|-----------------------------------|----------------------------|----------|-----------------|------------------|------------|--------------------|-----|------------------------------|-------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | | |
| Feng 2022 (1) | 128 | 2901 | 296 | 4804 | 47.9% | 0.72 [0.59, 0.88] | | - | | |
| Lu 2019 (2) | 434 | 5786 | 543 | 7754 | 52.1% | 1.07 [0.95, 1.21] | | • | | |
| Total (95% CI) | | 8687 | | 12558 | 100.0% | 0.88 [0.60, 1.31] | | | | |
| Total events | 562 | | 839 | | | | | | | |
| Heterogeneity: Tau ² = | = 0.07; Chi ² = | 11.19, d | f = 1 (P = 0.0) | 008); $I^2 =$ | 91% | | 0.2 | 0.5 1 2 | | |
| Test for overall effect | Z = 0.62 (P = 0.62) | 0.54) | | | | | 0.2 | Favours after Favours before | 5 | |

Footnotes

- (1) Feng 2022 reported infants treated in ≤5 days for pneumonia
- (2) Lu 2019 reported all infants treated for pneumonia

Outcome: Multidrug-resistant organism infection or colonization

| | After Interv | ention | Before Inter | vention | | Risk Ratio | | Risk Rat | tio | |
|--|--------------|--------|----------------|----------------|--------|--------------------|------|---------------------------|--------------------|---------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, | 95% CI | |
| Feng 2022 (1) | 3 | 2901 | 7 | 4804 | 5.2% | 0.71 [0.18, 2.74] | | | | |
| Lu 2019 (2) | 58 | 5786 | 109 | 7754 | 94.8% | 0.71 [0.52, 0.98] | | - | | |
| Total (95% CI) | | 8687 | | 12558 | 100.0% | 0.71 [0.52, 0.97] | | • | | |
| Total events | 61 | | 116 | | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect | | | = 1 (P = 0.99) |); $I^2 = 0\%$ | | | 0.05 | 0.2 1 Favours after Fa | 5 Ivours before | 20 e |

Footnotes

- (1) Feng 2022 reported multidrug-resistant organism infections
- (2) Lu 2019 reported multidrug-resistant organism colonizations

Outcome: Bloodstream isolates of methicillin-resistant Staphylococcus aureus (MRSA)

| | After Interv | ention | Before Interve | ention | Risk Ratio | | | Risk Ratio | | | |
|---------------------------------|--------------------|---------|-----------------|-------------|------------|--------------------|------|-------------|--------------|----------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Ran | dom, 95% | CI | |
| Bassiouny 2020 | 4 | 58 | 0 | 20 | 34.4% | 3.20 [0.18, 57.01] | | | - | | |
| Gill 2009 | 1 | 776 | 0 | 486 | 27.9% | 1.88 [0.08, 46.06] | | | - | | |
| Kommalur 2021 | 1 | 58 | 1 | 75 | 37.7% | 1.29 [0.08, 20.24] | | | - | | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 1.96 [0.36, 10.62] | | - | | | |
| Total events | 6 | | 1 | | | | | | | | |
| Heterogeneity: Tau ² | | | = 2 (P = 0.90); | $I^2 = 0\%$ | | | 0.01 | 0.1 | <u> </u> | 10 | 100 |
| Test for overall effect | t: $Z = 0.78 (P =$ | = 0.43) | | | | | | Favours aft | er Favour | s before | |

Outcome: Bloodstream isolates of Klebsiella spp.

| | After Intervention | | Before Intervention | | Risk Ratio | | | Risk Ratio | |
|-----------------------------------|----------------------------|----------|----------------------------|-------------|------------|--------------------|----------------|---------------------------|------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| Bassiouny 2020 | 12 | 58 | 8 | 20 | 12.6% | 0.52 [0.25, 1.08] | | | |
| Gill 2009 | 87 | 776 | 76 | 486 | 83.4% | 0.72 [0.54, 0.95] | | - | |
| Kommalur 2021 (1) | 3 | 58 | 7 | 75 | 4.0% | 0.55 [0.15, 2.05] | | - | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 0.68 [0.52, 0.88] | | • | |
| Total events | 102 | | 91 | | | | | | |
| Heterogeneity: Tau ² : | = 0.00; Chi ² = | 0.76, df | = 2 (P = 0.69) | $I^2 = 0\%$ | | | - | | 0 50 |
| Test for overall effect | t: $Z = 2.88 (P =$ | = 0.004) | | | | | 0.02 | Favours after Favours bef | |

Footnotes

(1) Kommalur 2021 reported Klebsiella pneumoniae organisms

Outcome: Bloodstream isolates of Acinetobacter spp.

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | Risk | Ratio | | |
|-----------------------------------|----------------------------|----------|----------------|----------------|--------|--------------------|------|--------------|------------------|--------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rando | om, 95% CI | | |
| Bassiouny 2020 | 8 | 58 | 1 | 20 | 26.0% | 2.76 [0.37, 20.71] | | | - | | |
| Gill 2009 (1) | 5 | 776 | 3 | 486 | 51.5% | 1.04 [0.25, 4.35] | | | • | | |
| Kommalur 2021 (2) | 1 | 58 | 4 | 75 | 22.6% | 0.32 [0.04, 2.82] | | - | | | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 1.03 [0.37, 2.89] | | • | | | |
| Total events | 14 | | 8 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.01; Chi ² = | 2.02, df | = 2 (P = 0.36) | $ I^2 = 1\% $ | | | 0.01 | 0 1 | 1 | 10 | 100 |
| Test for overall effect | z = 0.06 (P = 0.06) | = 0.95) | | | | | 0.01 | Favours afte | ı r Favours l | 10 pefore | 100 |

Footnotes

- (1) Gill 2009 reported Acinetobacter baumanii organisms
- (2) Kommalur 2021 reported Acinetobacter baumanii organisms

${\it Prevention \ and \ Treatment \ of \ Neonatal \ Infections \ in \ LMICs}$

Outcome: Bloodstream isolates of Escherichia coli (E. coli)

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | Risk Rat | io | |
|-----------------------------------|----------------------------|----------|----------------|--------------|--------|--------------------|------|------------------|--------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, | 95% CI | |
| Bassiouny 2020 | 4 | 58 | 0 | 20 | 24.6% | 3.20 [0.18, 57.01] | | | • | |
| Gill 2009 | 8 | 776 | 16 | 486 | 53.7% | 0.31 [0.14, 0.73] | | | | |
| Kommalur 2021 | 1 | 58 | 0 | 75 | 21.7% | 3.86 [0.16, 93.16] | | - | | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 0.96 [0.15, 6.11] | | | | |
| Total events | 13 | | 16 | | | | | | | |
| Heterogeneity: Tau ² = | = 1.48; Chi ² = | 4.24, df | = 2 (P = 0.12) | $I^2 = 53\%$ | ,) | | 0.01 | 01 1 | 10 | 100 |
| Test for overall effect | Z = 0.05 (P = 0.05) | = 0.96) | | | | | 0.01 | Favours after Fa | | 100 |

Outcome: Bloodstream isolates of Enterobacter spp.

| | After Interve | ention | Before Interve | ntion | | Risk Ratio | | Risk | (Ratio | | |
|-----------------------------------|----------------------------|----------|-----------------|--------------|--------|--------------------|------|---------------------|--------------|-------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rand | om, 95% CI | | |
| Bassiouny 2020 | 4 | 58 | 0 | 20 | 9.2% | 3.20 [0.18, 57.01] | | | - | | |
| Gill 2009 | 48 | 776 | 47 | 486 | 90.8% | 0.64 [0.43, 0.94] | | - | - | | |
| Kommalur 2021 | 0 | 58 | 0 | 75 | | Not estimable | | | | | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 0.74 [0.30, 1.85] | | ⋖ | | | |
| Total events | 52 | | 47 | | | | | | | | |
| Heterogeneity: Tau ² = | = 0.20; Chi ² = | 1.18, df | = 1 (P = 0.28); | $I^2 = 15\%$ | ,) | | 0.01 | 0 1 | 1 | + | 100 |
| Test for overall effect | Z = 0.64 (P = 0.64) | 0.52) | | | | | 0.01 | 0.1 Favours afte | - | 10 efore | 100 |

Outcome: Bloodstream isolates of coagulase-negative staphylococci (CoNS)

| | After Interv | ention | Before Interv | vention | | Risk Ratio | | Risk | Ratio | | |
|--|--------------|--------|----------------|----------------|--------|--------------------|------|---------------------|--------------|-------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rand | om, 95% CI | | |
| Bassiouny 2020 | 14 | 58 | 1 | 20 | 10.0% | 4.83 [0.68, 34.41] | | _ | - | | _ |
| Gill 2009 | 34 | 776 | 11 | 486 | 86.1% | 1.94 [0.99, 3.78] | | | | | |
| Kommalur 2021 | 0 | 58 | 1 | 75 | 3.8% | 0.43 [0.02, 10.35] | | • | | _ | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 2.00 [1.08, 3.73] | | | • | | |
| Total events | 48 | | 13 | | | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect | | | = 2 (P = 0.43) |); $I^2 = 0\%$ | | | 0.01 | 0.1 Favours afte | - | 10 efore | 100 |

Outcome: Bloodstream isolates of Pseudomonas spp.

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | Risk F | Ratio | |
|-----------------------------------|----------------------------|----------|----------------|-------------|--------|--------------------|------|------------------------|------------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Randor | n, 95% CI | |
| Bassiouny 2020 | 1 | 58 | 0 | 20 | 2.4% | 1.07 [0.05, 25.21] | | | | |
| Gill 2009 | 20 | 776 | 52 | 486 | 95.2% | 0.24 [0.15, 0.40] | | - | | |
| Kommalur 2021 (1) | 0 | 58 | 1 | 75 | 2.4% | 0.43 [0.02, 10.35] | | | | |
| Total (95% CI) | | 892 | | 581 | 100.0% | 0.25 [0.15, 0.41] | | • | | |
| Total events | 21 | | 53 | | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = | 0.94, df | = 2 (P = 0.63) | $I^2 = 0\%$ | | | 0.01 | | 10 | 100 |
| Test for overall effect | z = 5.49 (P < 1) | < 0.0000 | 1) | | | | 0.01 | 0.1 1 Favours after | . 10 Favours before | 100 |

Footnotes

(1) Kommalur 2021 reported *Pseudomonas aeruginosa* organisms

Outcome: Bloodstream isolates of Candida spp.

| | After Interv | ention | Before Interv | ention | | Risk Ratio | | R | isk Ratio | | |
|--|--------------|--------|-----------------|-------------|--------|--------------------|------|------------------|-----------------|------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Ra | ndom, 959 | % CI | |
| Bassiouny 2020 | 3 | 58 | 8 | 20 | 87.1% | 0.13 [0.04, 0.44] | | | | | |
| Kommalur 2021 | 0 | 58 | 1 | 75 | 12.9% | 0.43 [0.02, 10.35] | | | | | |
| Total (95% CI) | | 116 | | 95 | 100.0% | 0.15 [0.05, 0.47] | | | | | |
| Total events | 3 | | 9 | | | | | | | | |
| Heterogeneity: Tau ² : Test for overall effect | | | = 1 (P = 0.49); | $I^2 = 0\%$ | | | 0.01 | 0.1 Favours a | 1 fter Favou | 10 urs before | 100 |

Outcome: Mean length of hospital stay

| | After | Interver | ition | Before | Interver | ntion | | Mean Difference | Mean Difference |
|--|-------|----------|-------|-----------|----------|-----------------------|--------|------------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Bassiouny 2020 | 11.94 | 10.71 | 150 | 15.15 | 11.38 | 60 | 49.9% | -3.21 [-6.56, 0.14] | - |
| Maalouf 2023 | 41.6 | 31.8 | 563 | 23.6 | 5.5 | 153 | 50.1% | 18.00 [15.23, 20.77] | - |
| Total (95% CI) | | | 713 | | | 213 | 100.0% | 7.42 [-13.37, 28.20] | |
| Heterogeneity: Tau² = Test for overall effect | | | | df = 1 (P | < 0.000 | 01); I ² = | = 99% | - | -20 -10 0 10 20 Favours [After] Favours [Before] |

Outcome: Mean length of hospital stay (including Feng 2022 [13])

| | After | Interver | ition | Before | Interver | ntion | | Mean Difference | Mean Difference |
|--|-------|----------|-------|-----------|----------|-----------------------|--------|------------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Bassiouny 2020 | 11.94 | 10.71 | 150 | 15.15 | 11.38 | 60 | 32.9% | -3.21 [-6.56, 0.14] | - |
| Feng 2022 (1) | 7 | 2.96 | 2901 | 7 | 3.7 | 4804 | 33.9% | 0.00 [-0.15, 0.15] | • |
| Maalouf 2023 | 41.6 | 31.8 | 563 | 23.6 | 5.5 | 153 | 33.2% | 18.00 [15.23, 20.77] | - |
| Total (95% CI) | | | 3614 | | | 5017 | 100.0% | 4.92 [-6.34, 16.18] | |
| Heterogeneity: Tau ² = Test for overall effect | | | | df = 2 (P | < 0.000 | 01); I ² = | = 99% | | -20 -10 0 10 20 Favours after Favours before |

Footnotes

(1) Feng 2022 expressed length of hospital stay as median and IQR; assuming the distribution of data is symmetrical, we estimated mean and SD

Outcome: Number of newborns receiving antibiotics

| | After Interv | ention | Before Interv | ention | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------|----------|------------------|----------------|--------|--------------------|------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Agarwal 2021 (1) | 544 | 864 | 226 | 290 | 21.8% | 0.81 [0.75, 0.88] | |
| Chu 2023 (2) | 60 | 90 | 95 | 96 | 18.7% | 0.67 [0.58, 0.78] | |
| Feng 2022 (3) | 1341 | 2901 | 3153 | 4804 | 22.9% | 0.70 [0.67, 0.74] | * |
| Kommalur 2021 (4) | 44 | 58 | 63 | 75 | 17.2% | 0.90 [0.76, 1.08] | |
| Maalouf 2023 (5) | 208 | 532 | 118 | 153 | 19.3% | 0.51 [0.44, 0.58] | |
| Total (95% CI) | | 4445 | | 5418 | 100.0% | 0.71 [0.61, 0.81] | • |
| Total events | 2197 | | 3655 | | | | |
| Heterogeneity: Tau ² = | = 0.02; Chi ² = | 41.16, d | f = 4 (P < 0.00) | $(001); I^2 =$ | = 90% | • | |
| Test for overall effect | t: $Z = 4.84 (P - 4.84)$ | < 0.0000 | 1) | | | | Favours after Favours before |

Footnotes

- (1) Agarwal 2021 reported neonates unexposed to antibiotics (from which the neonates exposed to antibiotics was derived)
- (2) Chu 2023 reported proportion of early antibiotic usage
- (3) Feng 2022 reported proportion of antibiotic exposure
- (4) Kommalur 2021 reported percentage of neonates with no antibiotics (from which neonates receiving antibiotics was derived)
- (5) Maalouf 2023 reported proportion of neonates treated for early-onset sepsis

Outcome: Number of newborns receiving antibiotics by study design

| | After Interv | ention | Before Interv | vention | | Risk Ratio | | Risk Ratio | |
|-----------------------------------|----------------------------|-----------|------------------|----------------|--------|--------------------|-----|------------------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| 1.29.1 Cohort study | | | | | | | | | |
| Chu 2023 | 60 | 90 | 95 | 96 | 18.7% | | | - | |
| Subtotal (95% CI) | | 90 | | 96 | 18.7% | 0.67 [0.58, 0.78] | | • | |
| Total events | 60 | | 95 | | | | | | |
| Heterogeneity: Not ap | oplicable | | | | | | | | |
| Test for overall effect | Z = 5.25 (P < 1.00) | < 0.0000 | 1) | | | | | | |
| 1.29.2 Quasi-experi | mental study | | | | | | | | |
| Agarwal 2021 | 544 | 864 | 226 | 290 | 21.8% | 0.81 [0.75, 0.88] | | | |
| Feng 2022 | 1341 | 2901 | 3153 | 4804 | 22.9% | 0.70 [0.67, 0.74] | | • | |
| Kommalur 2021 | 44 | 58 | 63 | 75 | 17.2% | 0.90 [0.76, 1.08] | | | |
| Maalouf 2023 | 208 | 532 | 118 | 153 | 19.3% | - , - | | | |
| Subtotal (95% CI) | | 4355 | | 5322 | 81.3% | 0.71 [0.60, 0.84] | | • | |
| Total events | 2137 | | 3560 | | | | | | |
| Heterogeneity: Tau ² = | = 0.03; Chi ² = | 40.55, d | f = 3 (P < 0.00) | $0001); I^2 =$ | = 93% | | | | |
| Test for overall effect | Z = 3.91 (P < 1.00) | < 0.0001) | | | | | | | |
| Total (95% CI) | | 4445 | | 5418 | 100.0% | 0.71 [0.61, 0.81] | | • | |
| Total events | 2197 | | 3655 | | | | | | |
| Heterogeneity: Tau ² = | = 0.02; Chi ² = | 41.16, d | f = 4 (P < 0.00) | $0001); I^2 =$ | = 90% | | 0.2 | 0.5 1 2 | |
| Test for overall effect | Z = 4.84 (P < 1.84) | < 0.0000 | 1) | | | | 0.2 | Favours after Favours before | 5 |
| Test for subgroup dif | ferences: Chi ² | = 0.24, | df = 1 (P = 0.6 | 52), $I^2 = 0$ | % | | | ravours areer ravours before | |

Outcome: *Duration of antibiotic therapy >5 days*

| | After Intervention | | | vention | | Risk Ratio | | Risk Ratio | | | |
|--|--------------------|-------|-----------------|-------------------------|--------|--------------------|------|----------------------|-----------------------|----|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Rando | om, 95% CI | | |
| Chu 2023 (1) | 19 | 90 | 92 | 96 | 47.8% | 0.22 [0.15, 0.33] | | _ | | | |
| Feng 2022 (2) | 654 | 2901 | 1882 | 4804 | 52.2% | 0.58 [0.53, 0.62] | | | | | |
| Total (95% CI) | | 2991 | | 4900 | 100.0% | 0.36 [0.14, 0.93] | | | | | |
| Total events | 673 | | 1974 | | | | | | | | |
| Heterogeneity: Tau ² : Test for overall effect | | | f = 1 (P < 0.0) | 0001); I ² = | = 95% | | 0.05 | 0.2 Favours after | 1 5 Favours before | 20 | |

<u>Footnotes</u>

- (1) Chu 2023 reported the proportion of neonates treated with an initial antibiotic course >7 days
- (2) Feng 2022 reported the proportion of neonates treated with a duration of therapy >5 days

Outcome: Duration of antibiotic therapy >5 days by study design

| | After Interv | ention | Before Interv | ention/ | | Risk Ratio | | Risk Ratio | |
|--------------------------------------|---------------------------|-----------------|------------------|-----------------|-----------------------|---|------|------------------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | |
| 1.31.1 Cohort study | | | | | | | | | |
| Chu 2023 Subtotal (95% CI) | 19 | 90 90 | 92 | 96 96 | 47.8% 47.8% | 0.22 [0.15, 0.33] 0.22 [0.15, 0.33] | | • | |
| Total events | 19 | | 92 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | Z = 7.38 (P < | < 0.0000 | 1) | | | | | | |
| 1.31.2 Quasi-experir | nental study | | | | | | | | |
| Feng 2022 | 654 | 2901 | 1882 | 4804 | 52.2% | 0.58 [0.53, 0.62] | | = | |
| Subtotal (95% CI) | | 2901 | | 4804 | 52.2% | 0.58 [0.53, 0.62] | | ♦ | |
| Total events | 654 | | 1882 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | Z = 14.23 (P | < 0.000 | 01) | | | | | | |
| Total (95% CI) | | 2991 | | 4900 | 100.0% | 0.36 [0.14, 0.93] | | | |
| Total events | 673 | | 1974 | | | | | | |
| Heterogeneity: Tau ² = | 0.44; Chi ² = | 21.21, d | f = 1 (P < 0.00) | $0001); I^2 =$ | = 95% | | 0.02 | 0.1 1 10 | |
| Test for overall effect: | Z = 2.11 (P = | = 0.03) | | | | | 0.02 | Favours after Favours before | |
| Test for subgroup diff | erences: Chi ² | = 21.21, | df = 1 (P < 0) | .00001), I | $^{2} = 95.3\%$ |) | | ravours arter ravours below | Ξ |

Outcome: Neonates with antibiotics discontinued after 48 hours

| | After Intervention | | Before Interv | ention | | Risk Ratio | | Risk Ratio | | | |
|--|--------------------|-------|----------------|--------------|--------|----------------------|-------|---------------------------------------|-----|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Random, 95% CI | | IV, Random, 95% CI | | | |
| Kommalur 2021 | 11 | 58 | 0 | 75 | 30.6% | 29.63 [1.78, 492.56] | | - | | | |
| Lu 2019 | 5497 | 5786 | 2481 | 7754 | 69.4% | 2.97 [2.87, 3.07] | | | | | |
| Total (95% CI) | | 5844 | | 7829 | 100.0% | 6.00 [0.75, 47.88] | | | | | |
| Total events | 5508 | | 2481 | | | | | | | | |
| Heterogeneity: Tau ² = Test for overall effect | | | = 1 (P = 0.11) | $I^2 = 61\%$ | Ó | | 0.002 | 0.1 1 10 Favours after Favours before | 500 | | |

4.1.2. Chlorhexidine Cleansing

Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

Outcome: Neonatal mortality

| | 3 , | | | d care | | Risk Ratio | Risk Ratio |
|--|--------|-------|--------|--------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Gathwala 2013 | 0 | 70 | 4 | 70 | 100.0% | 0.11 [0.01, 2.03] | <u> </u> |
| Total (95% CI) | | 70 | | 70 | 100.0% | 0.11 [0.01, 2.03] | |
| Total events | 0 | | 4 | | | | |
| Heterogeneity: Not ap Test for overall effect | - |) | | | | | 0.01 0.1 1 10 100 Favours [Chlorhexidine] Favours [Dry cord care] |

Outcome: Omphalitis

| | Chlorhexidine cle | ansing | Dry core | d care | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------------|-----------|------------|-------------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Gathwala 2013 | 13 | 70 | 24 | 70 | 31.2% | 0.54 [0.30, 0.98] | |
| Ishaq 2023 | 2 | 32 | 7 | 32 | 4.8% | 0.29 [0.06, 1.27] | |
| Kinanu 2022 | 26 | 165 | 44 | 163 | 57.4% | 0.58 [0.38, 0.90] | - |
| Riaz 2019 | 5 | 100 | 4 | 100 | 6.5% | 1.25 [0.35, 4.52] | |
| Total (95% CI) | | 367 | | 365 | 100.0% | 0.58 [0.42, 0.80] | • |
| Total events | 46 | | 79 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = 2.29, | df = 3 (P | = 0.51); I | $ ^2 = 0\%$ | | - | |
| Test for overall effect | | | ,, | | | | 0.1 0.2 0.5 1 2 5 10 Favours [Chlorhexidine] Favours [Dry cord care] |

Outcome: Omphalitis by cleansing frequency

| | Chlorhexidine cle | eansing | Dry cord | d care | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------------|------------|---------------|--------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| 1.7.1 Single cleansin | ıg | | | | | | |
| Ishaq 2023 | 2 | 32 | 7 | 32 | 4.7% | 0.29 [0.06, 1.27] | |
| Ozdemir 2017 | 1 | 86 | 3 | 86 | 2.1% | 0.33 [0.04, 3.14] | · · · · · · · · · · · · · · · · · · · |
| Subtotal (95% CI) | | 118 | | 118 | 6.8% | 0.30 [0.09, 1.04] | |
| Total events | 3 | | 10 | | | | |
| Heterogeneity: Tau2 = | = 0.00; Chi ² = 0.01, | df = 1 (P | = 0.91); I | $^{2} = 0\%$ | | | |
| Test for overall effect | Z = 1.90 (P = 0.06) | 5) | | | | | |
| 1.7.2 Multiple cleans | sing | | | | | | |
| Gathwala 2013 | 13 | 70 | 24 | 70 | 30.2% | 0.54 [0.30, 0.98] | |
| Kinanu 2022 | 26 | 165 | 44 | 163 | 55.5% | 0.58 [0.38, 0.90] | |
| Ozdemir 2017 | 0 | 86 | 3 | 86 | 1.2% | 0.14 [0.01, 2.72] | - |
| Riaz 2019 | 5 | 100 | 4 | 100 | 6.3% | 1.25 [0.35, 4.52] | |
| Subtotal (95% CI) | | 421 | | 419 | 93.2% | 0.59 [0.42, 0.82] | • |
| Total events | 44 | | 75 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = 2.28, | df = 3 (P | = 0.52); I | $^{2} = 0\%$ | | | |
| Test for overall effect | Z = 3.10 (P = 0.00) |)2) | | | | | |
| Total (95% CI) | | 539 | | 537 | 100.0% | 0.56 [0.41, 0.78] | • |
| Total events | 47 | | 85 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² = 3.37, | df = 5 (P) | = 0.64); I | $^{2} = 0\%$ | | | |
| Test for overall effect | | | | | | | 0.01 0.1 1 10 1 Favours [Chlorhexidine] Favours [Dry cord care] |
| Test for subgroup dif | | | (P = 0.30) | $1.1^2 = 5$ | 7% | | ravours [Chiornexiume] ravours [Dry cord care] |

Comparison: Chlorhexidine for whole-body cleansing versus water/saline

Outcome: Neonatal mortality

| | Chlorhexidine clea | insing | Water/s | aline | | Risk Ratio | | Risk Ratio | | | |
|--|--------------------|--------|---------------|-------|--------|---------------------|-----------|----------------------|---------------------------|---------------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | | М | -H, Random, 95% C | CI . | |
| Anitha 2022 | 6 | 59 | 10 | 61 | 100.0% | 0.62 [0.24, 1.60] | | _ | | | |
| Total (95% CI) | | 59 | | 61 | 100.0% | 0.62 [0.24, 1.60] | | - | | | |
| Total events | 6 | | 10 | | | | | | | | |
| Heterogeneity: Not ap Test for overall effect | | | | | | | 0.02 F | 0.1 avours [Chlor | 1 hexidine] Favours [\ | 10 Water/Saline] | 50 |

Outcome: Bloodstream infection/sepsis

| | Chlorhexidine clea | | Water/saline | | | Risk Ratio | Risk Ratio |
|---|--------------------|-------|---------------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Anitha 2022 | 6 | 59 | 12 | 61 | 100.0% | 0.52 [0.21, 1.29] | - |
| Total (95% CI) | | 59 | | 61 | 100.0% | 0.52 [0.21, 1.29] | |
| Total events | 6 | | 12 | | | | |
| Heterogeneity: Not a Test for overall effect | • • |) | | | | F (| 0.01 0.1 1 10 100 Favours [Chlorhexidine] Favours [Water/Saline] |

4.1.3. Topical Emollients

Comparison: Topical ointment/cream versus routine skin care in preterm neonates

Outcome: *Invasive infection (any organism)*

| | Topical ointment, | Routine ski | n care | | Risk Ratio | | Risk Ratio | | | | | | |
|--|-------------------|-------------|--------|-------|------------|--------------------|------------|----------------|--------------------|---------------|------------------|----------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | | M-H, | Fixed, 95 | % CI | | |
| Darmstadt 2005 | 27 | 157 | 40 | 181 | 65.8% | 0.78 [0.50, 1.21] | | | | | | | |
| Erdemir 2014 | 23 | 100 | 19 | 97 | 34.2% | 1.17 [0.68, 2.01] | | | _ | | | | |
| Total (95% CI) | | 257 | | 278 | 100.0% | 0.91 [0.65, 1.28] | | | • | | | | |
| Total events | 50 | | 59 | | | | | | | | | | |
| Heterogeneity: Chi² = Test for overall effect | · | | 26% | | | | 0.1 | 0.2 Favours | 0.5 ointment/cr | 1 eam Favo | 2 urs routine | 5 skin care | 10 |

Outcome: Invasive infection (coagulase negative staphylococci)

| To | Topical ointment/cream | | Routine skin care | | Risk Ratio | | | | | | |
|---|-------------------------------|-------|-------------------|-----|--------------------------|-------------------|------|--------------------|------------------|-------------------|-------------|
| Study or Subgroup | Events | Total | Events Total | | Weight M-H, Fixed, 95% C | | | M-H, Fixed, 95% CI | | | |
| Darmstadt 2005 | 0 | 157 | 0 | 181 | | Not estimable | | | | | |
| Erdemir 2014 | 22 | 100 | 17 | 97 | 100.0% | 1.26 [0.71, 2.22] | | | | | |
| Total (95% CI) | | 257 | | 278 | 100.0% | 1.26 [0.71, 2.22] | | | | | |
| Total events | 22 | | 17 | | | | | | | | |
| Heterogeneity: Not applic Test for overall effect: Z = | | 3) | | | | | 0.02 | 0.1 | 1 | 10 | |
| rest for overall effect. Z - | = 0.70 (I = 0. 1 . | ٠, | | | | | | Favours ointmen | it/cream Favours | routine skin care | |

${\it Prevention \ and \ Treatment \ of \ Neonatal \ Infections \ in \ LMICs}$

Outcome: *Invasive infection (other bacteria)*

| | Topical ointment, | cream | Routine ski | n care | | Risk Ratio | | Risk Ratio | | |
|--|-------------------|-------|-------------|--------|--------|--------------------|------|---|---|----------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | | |
| Darmstadt 2005 | 23 | 157 | 34 | 181 | 92.6% | 0.78 [0.48, 1.27] | | | | |
| Erdemir 2014 | 0 | 100 | 2 | 97 | 7.4% | 0.19 [0.01, 3.99] | • | - | | |
| Total (95% CI) | | 257 | | 278 | 100.0% | 0.74 [0.46, 1.18] | | | | |
| Total events | 23 | | 36 | | | | | | | |
| Heterogeneity: Chi ² = Test for overall effect | | | 0% | | | | 0.01 | 0.1 1 Favours ointment/cream Favours ro | 10 utine skin care | 100 e |

Outcome: *Invasive infection (fungi)*

| | Topical ointment, | /cream | Routine ski | n care | | Risk Ratio | | Risk Ratio | | | | |
|--|-------------------|--------|-------------|--------|--------|--------------------|--------------------------|----------------------------|------------------------|-----|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | | | | |
| Darmstadt 2005 | 4 | 157 | 3 | 181 | 84.6% | 1.54 [0.35, 6.76] | | | _ | | | |
| Erdemir 2014 | 1 | 100 | 0 | 97 | 15.4% | 2.91 [0.12, 70.60] | _ | - | | | | |
| Total (95% CI) | | 257 | | 278 | 100.0% | 1.75 [0.46, 6.65] | | | - | | | |
| Total events | 5 | | 3 | | | | | | | | | |
| Heterogeneity: Chi ² = Test for overall effect | | | 0% | | | | 0.01 0.1 Favours oint | 1 ment/cream Favours ro | 10 outine skin care | 100 | | |

Outcome: All-cause neonatal mortality

| | Topical ointment | /cream | Routine ski | n care | | Risk Ratio | Risk Ratio |
|---|------------------|--------|-------------|--------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Darmstadt 2005 | 85 | 157 | 128 | 181 | 96.7% | 0.77 [0.64, 0.91] | - |
| Erdemir 2014 | 10 | 100 | 4 | 97 | 3.3% | 2.42 [0.79, 7.47] | |
| Total (95% CI) | | 257 | | 278 | 100.0% | 0.82 [0.69, 0.98] | • |
| Total events | 95 | | 132 | | | | |
| Heterogeneity: Chi ² = Test for overall effect | | | 76% | | | | 0.2 0.5 1 2 5 Favours ointment/cream Favours routine skin care |

Outcome: Necrotizing enterocolitis

| | Topical ointment/crea | | | | | Risk Ratio | | Risk Ratio | |
|-------------------------|-----------------------|-------|--------|-------|--------|--------------------|------|--|-------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | |
| Erdemir 2014 | 3 | 100 | 2 | 97 | 100.0% | 1.46 [0.25, 8.52] | | | |
| Total (95% CI) | | 100 | | 97 | 100.0% | 1.46 [0.25, 8.52] | | | |
| Total events | 3 | | 2 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | 0.01 | 0.1 1 1 | 0 100 |
| Test for overall effect | Z = 0.42 (P = 0.68) | 3) | | | | | 0.01 | Favours ointment/cream Favours routine | |

Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: *Invasive infection (any organism)*

| | l oil | Routine skin | care | | Risk Ratio | | Risk Ratio | | | | |
|------------------------------|------------|--------------|-------------------|-------|------------|--------------------|------------|---|--|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | | | |
| Arora 2005 | 4 | 23 | 1 | 46 | 0.8% | 8.00 [0.95, 67.55] | | • | | | |
| Darmstadt 2004 | 12 | 51 | 26 | 52 | 31.2% | 0.47 [0.27, 0.83] | | | | | |
| Darmstadt 2005 | 22 | 159 | 43 | 181 | 48.7% | 0.58 [0.36, 0.93] | | - | | | |
| Kukreja 2018 | 2 | 39 | 2 | 39 | 2.4% | 1.00 [0.15, 6.75] | | | | | |
| Salam 2015 | 4 | 126 | 14 | 128 | 16.8% | 0.29 [0.10, 0.86] | | | | | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 31 | | Not estimable | | | | | |
| Soriano 2000 | 0 | 29 | 0 | 31 | | Not estimable | | | | | |
| Total (95% CI) | | 459 | | 508 | 100.0% | 0.57 [0.41, 0.78] | | • | | | |
| Total events | 44 | | 86 | | | | | | | | |
| Heterogeneity: $Chi^2 = 8.1$ | 16, df = 4 | (P = 0. | 09); $I^2 = 51\%$ | | | | 0.01 | | | | |
| Test for overall effect: Z = | = 3.44 (P | = 0.000 | 06) | | | | 0.01 | 0.1 1 10 100 Favours topical oil Favours routine skin care | | | |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Invasive infection (coagulase negative staphylococci)

| | Topica | Topical oil Routine skin care | | | | Risk Ratio | | | |
|--------------------------------|---------|-------------------------------|--------|-------|--------|--------------------|------|----------------------------------|--------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | |
| Darmstadt 2005 | 0 | 159 | 0 | 181 | | Not estimable | | | |
| Kukreja 2018 | 0 | 39 | 0 | 39 | | Not estimable | | | |
| Salam 2015 | 1 | 128 | 7 | 130 | 100.0% | 0.15 [0.02, 1.16] | | | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 31 | | Not estimable | | | |
| Soriano 2000 | 0 | 29 | 0 | 31 | | Not estimable | | | |
| Total (95% CI) | | 387 | | 412 | 100.0% | 0.15 [0.02, 1.16] | - | | |
| Total events | 1 | | 7 | | | | | | |
| Heterogeneity: Not application | able | | | | | | 0.01 | 0.1 | 10 100 |
| Test for overall effect: Z = | 1.82 (P | = 0.07 |) | | | | 0.01 | Favours topical oil Favours rout | |

Outcome: *Invasive infection (other bacteria)*

| | Topical oil | | | ı care | | Risk Ratio | Risk Ratio | | | |
|--|-------------|-------|--------|--------|--------|--------------------|-------------------|-----------------------------|------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% C | il . | |
| Darmstadt 2005 | 26 | 159 | 34 | 181 | 61.6% | 0.87 [0.55, 1.38] | | - | | |
| Kukreja 2018 | 2 | 39 | 2 | 39 | 3.9% | 1.00 [0.15, 6.75] | | | | |
| Salam 2015 | 7 | 128 | 18 | 130 | 34.6% | 0.39 [0.17, 0.91] | | | | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 31 | | Not estimable | | | | |
| Soriano 2000 | 0 | 29 | 0 | 31 | | Not estimable | | | | |
| Total (95% CI) | | 387 | | 412 | 100.0% | 0.71 [0.48, 1.05] | | • | | |
| Total events | 35 | | 54 | | | | | | | |
| Heterogeneity: $Chi^2 = 2.7$ Test for overall effect: Z = | | | | | | | 0.01 0.1 Favou | 1 rs topical oil Favours | 10 | 100 |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Invasive infection (fungi)

| | Topical oil | | | care | | Risk Ratio | | Risk Ratio | | |
|------------------------------|-------------|---------|-------------------|-------|--------|---------------------|------|---|----------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | | |
| 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 | | | | |
| Total (95% CI) | | 387 | | 412 | 100.0% | 1.93 [0.42, 8.78] | | | | |
| Total events | 4 | | 2 | | | | | | | |
| Heterogeneity: $Chi^2 = 2.0$ | 8, df = 1 | (P = 0. | 15); $I^2 = 52\%$ | | | | 0.01 | 0.1 1 10 | 100 | |
| Test for overall effect: Z = | = 0.85 (P | = 0.39) |) | | | | 0.01 | 0.1 1 10 Favours topical oil Favours routine sk | 100 in care | |

Outcome: All-cause neonatal mortality

| | Topical oil | | | n care | | Risk Ratio | Risk Ratio |
|--|-------------|--------|--------|--------|--------|--------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Arora 2005 | 3 | 23 | 1 | 46 | 1.3% | 6.00 [0.66, 54.54] | · · · · · · · · · · · · · · · · · · · |
| Darmstadt 2004 | 12 | 51 | 18 | 52 | 15.9% | 0.68 [0.37, 1.26] | - • |
| Darmstadt 2005 | 46 | 151 | 75 | 181 | 69.6% | 0.74 [0.55, 0.99] | - ■- |
| Fallah 2013 | 1 | 30 | 0 | 30 | 0.6% | 3.00 [0.13, 70.83] | · · |
| Kukreja 2018 | 8 | 38 | 6 | 39 | 6.7% | 1.37 [0.52, 3.57] | • |
| Kumar 2013 | 1 | 26 | 0 | 23 | 0.6% | 2.67 [0.11, 62.42] | · · |
| Salam 2015 | 4 | 128 | 7 | 126 | 4.2% | 0.56 [0.17, 1.87] | · · |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 31 | | Not estimable | 2 |
| Soriano 2000 | 1 | 29 | 2 | 31 | 1.1% | 0.53 [0.05, 5.58] | • |
| Total (95% CI) | | 508 | | 559 | 100.0% | 0.78 [0.61, 1.00] | • |
| Total events Heterogeneity: Chi ² = 6.6 | | | | | | | 0.01 0.1 1 10 100 |
| Test for overall effect: Z = | = 1.99 (P | = 0.05 |) | | | | Favours topical oil Favours routine skin care |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Rate of weight gain (g/kg/day)

| | Тор | • | | | Routine skin care | | | Mean Difference | Mean Difference |
|--|------|-----|-------|------|-------------------|-------|--------|------------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Fallah 2013 | 10.9 | 5.6 | 28 | 6.6 | 5.5 | 27 | 18.2% | 4.30 [1.37, 7.23] | |
| Farhat 2010 | 8 | 5.6 | 30 | 7.8 | 5.5 | 29 | 19.5% | 0.20 [-2.63, 3.03] | |
| Jabraeille 2016 | 16 | 7.7 | 42 | 6.8 | 10.1 | 44 | 10.9% | 9.20 [5.41, 12.99] | |
| Soriano 2000 | 18 | 3.3 | 29 | 14.9 | 3.6 | 31 | 51.4% | 3.10 [1.35, 4.85] | - ■- |
| Total (95% CI) | | | 129 | | | 131 | 100.0% | 3.42 [2.17, 4.67] | • |
| Heterogeneity: $Chi^2 = 14.40$, $df = 3$ ($P = 0.002$); $I^2 = 79\%$ Test for overall effect: $Z = 5.36$ ($P < 0.00001$) | | | | | | | | | -10 -5 0 5 10 Favours routine skin care Favours topical oil |

Outcome: Change in crown-heel length (mm/week)

| | Topical oil Routine skin care | | | | | | | Mean Difference | Mean Difference | | | |
|--|-------------------------------|------|-------|------|-----|-------|--------|--------------------|---|--|--|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI | | | |
| Fallah 2013 | 8 | 2.5 | 28 | 6 | 6.1 | 27 | 42.8% | 2.00 [-0.48, 4.48] | | | | |
| Jabraeille 2016 | 10.3 | 10.1 | 33 | 7.7 | 8.4 | 37 | 13.7% | 2.60 [-1.78, 6.98] | - • | | | |
| Soriano 2000 | 8.4 | 2.5 | 29 | 7 | 6.5 | 31 | 43.5% | 1.40 [-1.06, 3.86] | | | | |
| Total (95% CI) | | | 90 | | | 95 | 100.0% | 1.82 [0.20, 3.44] | | | | |
| Heterogeneity: $Chi^2 = 0.25$, $df = 2$ (P = 0.88); $I^2 = 0\%$ Test for overall effect: $Z = 2.20$ (P = 0.03) | | | | | | | | | -10 -5 0 5 10 Favours routine skin care Favours topical oil | | | |

Outcome: Change in circumference (mm/week)

| | Тор | Topical oil Routine skin | | | | care | | Mean Difference | Mean Difference |
|--|------|--------------------------|-------|------|------|-------|--------|--------------------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Fallah 2013 | 5.5 | 7.4 | 28 | 4 | 7.3 | 27 | 20.7% | 1.50 [-2.39, 5.39] | - • |
| Jabraeille 2016 | 5.7 | 5.2 | 33 | 4.6 | 4.6 | 37 | 58.5% | 1.10 [-1.21, 3.41] | - • |
| Soriano 2000 | 7.7 | 7.5 | 29 | 7.2 | 7.8 | 31 | 20.8% | 0.50 [-3.37, 4.37] | |
| Total (95% CI) | | | 90 | | | 95 | 100.0% | 1.06 [-0.71, 2.83] | |
| Heterogeneity: Chi ² = Test for overall effect | | | | | : 0% | | | | -10 -5 0 5 10 Favours routine skin care Favours topical oil |

Outcome: Change in triceps skinfold thickness (mm/week)

| Topical oil | | | | Routin | e skin | care | | Mean Difference | Mean Difference | | | | |
|--|------|------|---------|--------|--------|-------|--------|--------------------|-----------------|---------------------------|--------------------|--------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | | IV, | Fixed, 95% C | | |
| Soriano 2000 | 0.16 | 0.27 | 29 | 0.14 | 0.28 | 31 | 100.0% | 0.02 [-0.12, 0.16] | | | - | | _ |
| Total (95% CI) | | | 29 | | | 31 | 100.0% | 0.02 [-0.12, 0.16] | | | * | | |
| Heterogeneity: Not ap Test for overall effect | | | = 0.78) | | | | | | + -2 F | -1 avours routine skir | 0 1 care Favour | 1 s topical oil | 2 |

Comparison: Topical ointment/cream versus topical oil in preterm neonates

Outcome: *Invasive infection (any organism)*

| | Topical ointment/o | ream | Topica | ıl oil | | Risk Ratio | Risk Ratio |
|--|--------------------|-------|--------|--------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | 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 ap Test for overall effect | • | | | | | | 0.05 0.2 1 5 20 Favours topical ointment Favours topical oil |

Outcome: Invasive infection (coagulase negative staphylococci)

| | Topical ointment | :/cream | Topica | l oil | | Risk Ratio | | | Risk Ratio | | |
|--|------------------|---------|--------|-------|--------|--------------------|--------------|-------------------------|-------------------|----------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-I | H, Fixed, 95% | S CI | |
| Darmstadt 2005 | 0 | 157 | 0 | 159 | | Not estimable | | | | | |
| Total (95% CI) | | 157 | | 159 | | Not estimable | | | | | |
| Total events | 0 | | 0 | | | | | | | | |
| Heterogeneity: Not ap Test for overall effect | • | | | | | | 0.01 Favo | 0.1 ours topical oin | 1 Itment Favou | 10 rs topical oil | 100 |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Invasive infection (other bacteria)

| | Topical ointment, | /cream | Topica | l oil | | Risk Ratio | Risk Ratio |
|--|-------------------|--------|---------------|-------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | 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 ap Test for overall effect | - |) | | | | _ | 0.05 0.2 1 5 20 Favours topical ointment Favours topical oil |

Outcome: Invasive infection (fungi)

| | Topical ointment/ | cream | Topica | ıl oil | | Risk Ratio | | | Risk Ratio | | |
|-------------------------|-----------------------|-------|--------|--------|--------|--------------------|------|------------------|------------------|------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-I | 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 a | · • | | | | | | 0.01 | 0.1 | 1 | 10 | 100 |
| Test for overall effect | (2 = 0.40) (P = 0.69) | | | | | | Favo | ours topical oir | ntment Favours t | opical oil | |

Outcome: All-cause neonatal mortality

| | Topical ointment/ | cream | Topica | l oil | | Risk Ratio | | Ri | sk Ratio | | |
|--|-------------------|-------|---------------|-------|--------|--------------------|---------------|------------------------|-----------------|----------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, F | ixed, 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 ap Test for overall effect | • | | | | | _ | 0.5 Favour | 0.7 s topical ointm | 1 ent Favour | 1.5 s topical oil | 2 |

Comparison: One topical oil (or combination) versus another oil (or combination)

Outcome: *Invasive infection*

| | Coconu | ıt oil | Minera | ıl oil | | Risk Ratio | | Ris | k Ratio | | |
|--|--------|--------|--------|--------|--------|--------------------|------|------------------------|------------------|-------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fi | xed, 95% C | <u> </u> | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 32 | | Not estimable | | | | | |
| Total (95% CI) | | 32 | | 32 | | Not estimable | | | | | |
| Total events | 0 | | 0 | | | | | | | | |
| Heterogeneity: Not applic Test for overall effect: No | | ole | | | | | 0.01 | 0.1 Favours coconut | 1 oil Favours | 10 mineral oil | 100 |

Outcome: All-cause mortality

| | Coconu | t oil | Minera | ıl oil | | Risk Ratio | | Ris | k Ratio | |
|--|--------|-------|---------------|--------|--------|--------------------|------|--------------------------|------------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fi | xed, 95% CI | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 32 | | Not estimable | | | | |
| Total (95% CI) | | 32 | | 32 | | Not estimable | | | | |
| Total events | 0 | | 0 | | | | | | | |
| Heterogeneity: Not applic Test for overall effect: No | | le | | | | | 0.01 | 0.1 Favours coconut o | 1 10 1 Tavours mine | 100 ral oil |

Comparison: Combined topical ointment/cream or oil versus routine skin care in preterm newborns

Outcome: All-cause neonatal mortality

| | Topical ointment | /cream | Routine ski | n care | | Risk Ratio | Risk Ratio |
|--|--|----------------------|-------------------------|--------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.5.1 Topical oil | | | | | | | |
| Arora 2005 | 3 | 23 | 1 | 46 | 0.3% | 6.00 [0.66, 54.54] | + |
| Darmstadt 2004 | 12 | 51 | 18 | 52 | 7.9% | 0.68 [0.37, 1.26] | |
| Darmstadt 2005 (2) | 46 | 151 | 75 | 181 | 30.2% | 0.74 [0.55, 0.99] | |
| Fallah 2013 | 1 | 30 | 0 | 30 | 0.2% | 3.00 [0.13, 70.83] | - |
| Kukreja 2018 | 8 | 38 | 6 | 39 | 2.6% | 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 | 126 | 3.1% | 0.56 [0.17, 1.87] | |
| Sankaranarayanan 2005 | 0 | 32 | 0 | 31 | | Not estimable | |
| Soriano 2000 | 1 | 29 | 2 | 31 | 0.9% | 0.53 [0.05, 5.58] | |
| Subtotal (95% CI) | | 508 | | 559 | 45.5% | 0.80 [0.63, 1.02] | • |
| Total events | 76 | | 109 | | | | |
| Heterogeneity: Chi ² = 6.66 | $6, df = 7 (P = 0.46); I^2$ | 2 = 0% | | | | | |
| Test for overall effect: Z = | 1.77 (P = 0.08) | | | | | | |
| 1.5.2 Topical ointment o | r cream | | | | | | |
| Darmstadt 2005 (1) | 85 | 157 | 128 | 181 | 52.7% | 0.77 [0.64, 0.91] | = |
| Erdemir 2014 | 10 | 100 | 4 | 97 | 1.8% | 2.42 [0.79, 7.47] | + - |
| Subtotal (95% CI) | | 257 | | 278 | 54.5% | 0.82 [0.69, 0.98] | ◆ |
| Total events | 95 | | 132 | | | | |
| Heterogeneity: Chi ² = 4.19 | θ , df = 1 (P = 0.04); θ | ² = 76% | | | | | |
| Test for overall effect: Z = | 2.25 (P = 0.02) | | | | | | |
| Total (95% CI) | | 765 | | 837 | 100.0% | 0.81 [0.70, 0.94] | ♦ |
| Total events | 171 | | 241 | | | _ | |
| Heterogeneity: Chi ² = 10.8 | 30, df = 9 (P = 0.29): | l ² = 17% | | | | | <u> </u> |
| Test for overall effect: Z = | · · · · · · · · · · · · · · · · · · · | - | | | | | 0.01 0.1 1 10 100 |
| Test for subgroup differen | ` ' | = 1 (P = 0.9 | 38) I ² = 0% | | | | Favours ointment/cream Favours routine skin care |

4.1.4. Probiotics Supplementation

Comparison: Probiotics versus control in preterm newborns by probiotic type

Outcome: *Necrotizing enterocolitis*

| Study or Subgroup | Probio: | tics Total | Cont | rol Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|--------------------------------|---------------------|---------------------------|--------------|-------------------------|---|------------------------------------|
| 1.1.1 Bifidobacterium spp. | Events | · Otai | | rotal | reigilt | , 11xeu, 53% Cl | M-11, 11ACU, 33/0 CI |
| Dilli 2015 | 2 | 100 | 18 | 100 | 7.6% | 0.11 [0.03, 0.47] | , |
| Huang 2009 Hussain 2016 | 0 | 95 150 | 3 3 7 | 88 150 | 1.5% | 0.13 [0.01, 2.53] 0.19 [0.09, 0.41] | |
| Subtotal (95% CI) | , | 345 | ,, | 338 | 24.6% | 0.16 [0.08, 0.31] | • |
| Total events | 9 | | 58 | | | | |
| Heterogeneity: Chi ² = 0.44, d Test for overall effect: Z = 5.3 | if = 2 (P = 38 (P < 0 | = 0.80); .00001) | I* = 0% | | | | |
| 1.1.2 Lactobacillus spp. Cui 2019 | 1 | 45 | 5 | 48 | 2.0% | 0.21 [0.03, 1.76] | |
| Hernandez-Enriquez 2016 | 1 | 24 | 5 | 20 | 2.3% | 0.17 [0.02, 1.31] | |
| Kaban 2019 | 0 | 47 26 | 3 | 47 26 | 1.5% | 0.14 [0.01, 2.69] | · · · · · · |
| Matin 2022 Oncel 2014 | 0 | 200 | 10 | 200 | 4.2% | Not estimable 0.80 [0.32, 1.99] | |
| Rojas 2012 | 9 | 372 | 15 | 378 | 6.3% | 0.61 [0.27, 1.38] | |
| Shadkam 2015 | 2 6 | 30 37 | 11 10 | 30 35 | 4.6% 4.3% | 0.18 [0.04, 0.75] | _ |
| Singh 2017 Subtotal (95% CI) | ь | 781 | 10 | 784 | 25.2% | 0.57 [0.23, 1.40] 0.46 [0.30, 0.70] | • |
| Total events | 27 | | 59 | | | | - |
| Heterogeneity: Chi ² = 5.81, d Test for overall effect: Z = 3.5 | if = 6 (P = 56 (P = 0 | = 0.44); .0004) | I ² = 0% | | | | |
| 1.1.3 Saccharomyces spp. | | | | | | | |
| Demirel 2013 Serce 2013 | 6 | 135 104 | 7 | 136 104 | 2.9% | 0.86 [0.30, 2.50] 1.00 [0.36, 2.75] | |
| Subtotal (95% CI) | | 239 | | 240 | 5.9% | 0.93 [0.45, 1.94] | * |
| Total events | 13 | 0.00 | 14 | | | | |
| Heterogeneity: $Chi^2 = 0.04$, d Test for overall effect: $Z = 0$. | 11 = 1 (P = 19 (P = 0 | = 0.84); .85) | I ² = 0% | | | | |
| 1.1.4 Bacillus spp. Sari 2011 | 6 | 110 | 10 | 111 | 4.2% | 0.61 [0.23, 1.61] | |
| Tewari 2015 | 0 | 123 | 0 | 121 | | Not estimable | - |
| Subtotal (95% CI) | | 233 | | 232 | 4.2% | 0.61 [0.23, 1.61] | - |
| Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.0 | | .31) | 10 | | | | |
| 1.1.5 Bacillus subtilis plus E | | | | | | | |
| Lin 2013 | 2 | 65 | 8 | 55 | 3.6% | 0.21 [0.05, 0.96] | |
| Subtotal (95% CI) Total events | 2 | 65 | 8 | 55 | 3.6% | 0.21 [0.05, 0.96] | |
| Heterogeneity: Not applicable Test for overall effect: Z = 2.0 | | .04) | | | | | |
| 1.1.6 Bifidobacterium spp. p | | | | | | | |
| Braga 2011 | 0 | 119 60 | 4 | 112 59 | 1.9% 2.5% | 0.10 [0.01, 1.92] | |
| Chowdhury 2016 Roy 2014 | 2 | 56 | 2 | 56 | 0.8% | 0.16 [0.02, 1.32] 1.00 [0.15, 6.85] | |
| Saengtawesin 2014 | 1 | 31 | 1 | 29 | 0.4% | 0.94 [0.06, 14.27] | |
| Samanta 2009 Sowden 2022 | 5 | 91 100 | 15 1 | 95 100 | 6.2% | 0.35 [0.13, 0.92] 0.33 [0.01, 8.09] | |
| Van Niekerk 2014 | 0 | 91 | 4 | 93 | 1.9% | 0.11 [0.01, 2.08] | • • • |
| Zahed Pasha 2016 | 1 | 30 | 1 | 30 574 | 0.4% 14.9% | 1.00 [0.07, 15.26] 0.33 [0.17, 0.63] | |
| Subtotal (95% CI) Total events | 10 | 578 | 34 | 574 | 14.9% | 0.33 [0.17, 0.63] | • |
| Heterogeneity: Chi ² = 4.05, d Test for overall effect: Z = 3.3 | if = 7 (P = | = 0.77); .0007) | | | | | |
| 1.1.7 Bifidobacterium spp. p | | | s spp. | plus Sa | ccharomy | ces spp. | |
| Chandrashekar 2018 | 0 | 70 | 3 | 70 | 1.5% | 0.14 [0.01, 2.72] | |
| Duta 2015 Hariharan 2016 | 6 | 114 93 | 0 | 35 103 | 0.3% | 4.07 [0.23, 70.49] | |
| Shashidhar 2017 | 2 | 49 | 6 | 49 | 2.5% | 1.11 [0.23, 5.35] 0.33 [0.07, 1.57] 0.67 [0.28, 1.58] | |
| Subtotal (95% CI) | | 326 | | 257 | 5.5% | 0.67 [0.28, 1.58] | - |
| Total events Heterogeneity: Chi ² = 3.76, d Test for overall effect: Z = 0.9 | 11 if = 3 (P = | = 0.29); | 12 I ² = 20 | % | | | |
| 1.1.8 Bifidobacterium spp. p | | | s spp. | plus St | reptococo | us spp. | |
| Dashti 2014 | 2 | 69 | 1 | 67 | 0.4% | 1.94 [0.18, 20.92] | |
| Fernández-Carrocera 2014 | 6 | 75 73 | 12 | 75 73 | 5.0% | 0.50 [0.20, 1.26] | |
| Rehman 2018 Ren 2010 | 2 | /3 80 | 8 | 73 70 | 3.4% 2.2% | 0.25 [0.05, 1.14] | |
| Subtotal (95% CI) | | 297 | | 285 | 11.1% | 0.53 [0.13, 2.12] 0.48 [0.25, 0.92] | • |
| Total events Heterogeneity: Chi ² = 2.06, d Test for overall effect: Z = 2.3 | 13 if = 3 (P = 21 (P = 0 | = 0.56); | 26 I ² = 0% | | | | |
| 1.1.9 Bifidobacterium spp. p | | obacillu | s spp. | | | ıs | |
| Wu 2020 | 2 | 250 | 12 | 250 | 5.0% | 0.17 [0.04, 0.74] | |
| Subtotal (95% CI) Total events | 2 | 250 | 12 | 250 | 5.0% | 0.17 [0.04, 0.74] | _ |
| Heterogeneity: Not applicable | | 03) | 12 | | | | |
| Test for overall effect: Z = 2.: Total (95% CI) | ου (P = 0. | .02) | | 3015 | 100.0% | 0.39 [0.31, 0.49] | |
| Total (95% CI) | 93 | 3114 | 233 | 2012 | 100.0% | 0.33 [0.31, 0.49] | • |
| Heterogeneity: Chi2 = 32.98, | df = 30 (| P = 0.32 | | 9% | | | 0.01 0.1 1 10 100 |
| Test for overall effect: Z = 7.9 Test for subgroup differences | 94 (P < 0 s: Chi² = | .00001) 17.30, d | f = 8 (I | P = 0.0 | 3), I ² = 53 | .8% | Favours probiotics Favours control |
| | | | | | | | |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause neonatal mortality

| Study or Subgroup | Probio Events | | Conti Events | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|--|------------------------------------|------------------|-----------------------------|-------------------|----------------------|--|------------------------------------|
| 1.2.1 Bifidobacterium spp. | - | 100 | 10 | 100 | 6 10/ | 0.35 (0.07.0.00) | |
| Dilli 2015 Subtotal (95% CI) | 3 | 100 100 | 12 | 100 100 | 6.1% 6.1% | 0.25 [0.07, 0.86] 0.25 [0.07, 0.86] | |
| Total events | 3 | 100 | 12 | 100 | 0.1/0 | 5.23 [0.07, 0.00] | |
| rotal events Heterogeneity: Not applicable | | | 12 | | | | |
| Test for overall effect: $Z = 2$. | | .03) | | | | | |
| 1.2.2 Lactobacillus spp. | | | | | | | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.3% | 4.20 [0.21, 82.72] | |
| Kaban 2019 | 1 | 47 | 4 | 47 | 2.0% | 0.25 [0.03, 2.15] | - |
| Matin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.2% | 0.75 [0.40, 1.42] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | - |
| Singh 2017 Subtotal (95% CI) | 3 | 37 736 | 3 | 35 736 | 1.6% 29.4% | 0.95 [0.20, 4.38] 0.77 [0.53, 1.13] | |
| | | /50 | | /30 | 29.4% | 0.77 [0.55, 1.15] | — |
| Fotal events Heterogeneity: Chi ² = 2.52, o | | | 57 ; $I^2 = 0\%$ | | | | |
| Fest for overall effect: $Z = 1$. | .33 (P = 0 | .18) | | | | | |
| 1.2.3 Saccharomyces spp. | - | 125 | _ | 120 | 9 50 | 1.01.50.20.2 | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.5% | 1.01 [0.30, 3.40] | |
| Serce 2013 Subtotal (95% CI) | 5 | 104 239 | 4 | 104 240 | 2.0% 4.6% | 1.25 [0.35, 4.52] | |
| | 10 | 239 | 9 | 240 | 4.0% | 1.12 [0.46, 2.70] | |
| Fotal events Heterogeneity: Chi² = 0.06, o | | - 0.01 | | | | | |
| Heterogeneity: Chi ² = 0.06, o Fest for overall effect: Z = 0. | | | , i = U% | | | | |
| L.2.4 Bacillus spp. | | | | | | | |
| Sari 2011 | 3 | 110 | 3 | 111 | 1.5% | 1.01 [0.21, 4.89] | |
| Tewari 2015 | 12 | 123 | 14 | 121 | 7.2% | 0.84 [0.41, 1.75] | |
| Subtotal (95% CI) | 12 | 233 | 1.4 | 232 | 8.7% | 0.87 [0.45, 1.69] | • |
| Total events | 15 | | 17 | | | | Ŧ |
| Heterogeneity: Chi ² = 0.04, of Fest for overall effect: Z = 0. | | | $I^2 = 0\%$ | | | | |
| I.2.5 Bifidobacterium spp. | plus Lact | obacill | us spp. | | | | |
| Braga 2011 | 26 | 119 | 27 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| i 2019 | ő | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | |
| Roy 2014 | 7 | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | | Not estimable | |
| Samanta 2009 | 4 | 91 | 14 | 95 | 7.0% | 0.30 [0.10, 0.87] | |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.33 [0.01, 8.09] | |
| Van Niekerk 2014 | 5 | 91 | 6 | 93 | 3.0% | 0.85 [0.27, 2.69] | |
| Zahed Pasha 2016 | 2 | 30 | 0 | 30 | 0.3% | 5.00 [0.25, 99.95] | |
| Subtotal (95% CI) | | 594 | | 588 | 33.8% | 0.75 [0.54, 1.06] | • |
| Fotal events Heterogeneity: Chi² = 5.74, o | 49 df = 7 (P : | = 0.57) | 64 : I ² = 0% | | | | |
| Test for overall effect: $Z = 1$. | 64 (P = 0 | .10) | , | | | | |
| 1.2.6 Bifidobacterium spp. | plus Lact | | | | | | |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 2.0% | 0.25 [0.03, 2.18] | |
| Outa 2015 | 8 | 114 | 2 | 35 | 1.6% | 1.23 [0.27, 5.52] | |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| hashidhar 2017 | 1 | 49 | 3 | 49 | 1.5% | 0.33 [0.04, 3.09] | |
| Subtotal (95% CI) | | 326 | _ | 257 | 7.6% | 0.67 [0.30, 1.49] | |
| Fotal events | 14 | | 14 | | | | |
| Heterogeneity: Chi² = 1.98, o Fest for overall effect: Z = 0. | | | ; 1' = 0% | | | | |
| L.2.7 Bifidobacterium spp. | | | us spp. i | plus St | reptococc | us spp. | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | + |
| Fernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | |
| Rehman 2018 | 4 | 73 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Sinha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | |
| Subtotal (95% CI) | | 885 | - | 887 | 9.7% | 0.73 [0.37, 1.43] | - |
| Fotal events | 14 | | 19 | | | | |
| Heterogeneity: Chi² = 5.27, o Fest for overall effect: Z = 0. | df = 3 (P = 0 | = 0.15) .36) | | % | | | |
| L.2.8 Bifidobacterium spp. | | | iis snn | nlus Fr | terococci | ıs | |
| Nu 2020 | pius Lace 0 | 250 | us spp. 0 | 250 | | Not estimable | |
| Subtotal (95% CI) | U | 250 | U | 250 | | Not estimable | |
| Total events | 0 | _55 | 0 | _55 | | 2541114016 | |
| Heterogeneity: Not applicable Fest for overall effect: Not ap | e | | U | | | | |
| | piicabie | 2262 | | 2205 | 100.05 | 0.75 (0.61 6.55) | |
| Fotal (95% CI) Fotal events | 149 | 3363 | 192 | 3290 | 100.0% | 0.75 [0.61, 0.92] | • |
| Heterogeneity: Chi ² = 19.62, | | P = 0.9 | | 0% | | | |
| | | | /, - | | | | 0.01 0.1 1 10 |
| est for overall effect: Z = 2. est for subgroup difference | 80 (P = 0 s: Chi ² = | .005) 4.12, d | f = 6 (P | = 0.66) | $I^2 = 0\%$ | | Favours probiotics Favours control |

Outcome: *Invasive infection*

| Study or Subgroup | Probio Events | | Contr Events | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|--|--|--|---|---|---|--|--|
| 1.3.1 Bifidobacterium spp. | | | | | | | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Subtotal (95% CI) | | 100 | | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Total events | 8 | | 13 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: $Z = 1.1$ | L4 (P = 0 | .26) | | | | | |
| 1.3.2 Lactobacillus spp. | | | | | | | |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | |
| Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | 5.00 [0.66, 38.15] | • |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | |
| Matin 2022 | 0 | 26 | 3 | 26 | 0.8% | 0.14 [0.01, 2.63] | |
| Oncel 2014 | 13 | 200 | 25 | 200 | 5.4% | 0.52 [0.27, 0.99] | |
| Shadkam 2015 | 0 | 30 | 0 | 30 | | Not estimable | |
| Subtotal (95% CI) | | 372 | | 371 | 7.9% | 0.60 [0.36, 1.01] | • |
| Total events | 22 | | 36 | | | | - |
| Heterogeneity: $Chi^2 = 5.60$, d Test for overall effect: $Z = 1.9$ | | | $ I^2 = 299$ | 6 | | | |
| 1.3.3 Saccharomyces spp. | | | | | | | |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | |
| Xu 2016 | 4 | 65 | 6 | 60 | 1.4% | 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) | 4 | 304 | 0 | 300 | 11.3% | 0.82 [0.18, 2.08] | ~ |
| Total events | 43 | ' | 52 | | | ,, | 7 |
| Heterogeneity: $Chi^2 = 0.59$, d Test for overall effect: $Z = 1.0$ | f = 2 (P = | | | | | | |
| 1.3.4 Bacillus spp. | | | | | | | |
| | 20 | 110 | 20 | 111 | F C01 | 1 12 [0 71 1 70] | <u> </u> |
| Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | |
| Tewari 2015 Subtotal (95% CI) | 8 | 123 233 | 11 | 121 232 | 2.4% 8.0% | 0.72 [0.30, 1.72] | |
| | | 233 | | 232 | 8.0% | 1.00 [0.67, 1.51] | — |
| Total events | 37 | | 37 | | | | |
| Heterogeneity: $Chi^2 = 0.81$, d Test for overall effect: $Z = 0.0$ | | | $; 1^2 = 0\%$ | | | | |
| | | | | | | | |
| 1.3.5 Bifidobacterium spp. p | | | | | | | |
| Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | + |
| Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Samanta 2009 | 13 | 91 | 28 | 95 | 5.9% | 0.48 [0.27, 0.88] | |
| Van Niekerk 2014 | 15 | 91 | 10 | 93 | 2.1% | 1.53 [0.73, 3.23] | |
| | | 388 | | 376 | 26.8% | 0.81 [0.66, 0.99] | ◆ |
| Subtotal (95% CI) | | | | | | | |
| Total events | 101 | | 123 | | | | |
| Total events Heterogeneity: Chi² = 6.59, d | f = 4 (P : | | | 6 | | | |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 | f = 4 (P = 05 (P = 0 | .04) | $I^2 = 399$ | | ccharomy | ces spp. | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p | f = 4 (P = 05 (P = 0 | .04) | ; I ² = 399 us spp. p | | ccharomy 2.8% | | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 | f = 4 (P : 05 (P = 0 olus Lactor | .04) obacill 70 | ; I ² = 399 us spp. r 13 | olus Sa 70 | 2.8% | 1.15 [0.59, 2.24] | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 | f = 4 (P = 0)5 (P = 0) lus Lacter 15 | .04) obacill 70 114 | ; I ² = 399 us spp. r 13 6 | olus Sa 70 35 | 2.8% 2.0% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.6 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 | f = 4 (P = 0)5 (P = 0) lus Lacte 15 10 9 | .04) obacill 70 114 93 | ; I ² = 399 us spp. r 13 6 16 | 70 35 103 | 2.8% 2.0% 3.3% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 | f = 4 (P = 0)5 (P = 0) lus Lacter 15 | .04) obacill 70 114 93 49 | ; I ² = 399 us spp. r 13 6 | 70 35 103 49 | 2.8% 2.0% 3.3% 1.5% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] | |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (05% CI) | f = 4 (P = 0)5 (P = 0) lus Lacte 15 10 9 6 | .04) obacill 70 114 93 | ; I ² = 399 us spp. p 13 6 16 7 | 70 35 103 | 2.8% 2.0% 3.3% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] | - |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d | f = 4 (P = 0)5 (P = 0) lus Lacte 15 10 9 6 40 f = 3 (P = 0) | .04) 70 114 93 49 326 | ; I ² = 399 us spp. p 13 6 16 7 | 70 35 103 49 | 2.8% 2.0% 3.3% 1.5% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 | f = 4 (P = 0) | .04) bbacill 70 114 93 49 326 = 0.48) | ; ² = 399; us spp. r 13 6 16 7 42 ; ² = 0% | 70 35 103 49 257 | 2.8% 2.0% 3.3% 1.5% 9.6% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p | f = 4 (P = 0) | .04) pbacill 70 114 93 49 326 = 0.48) .26) | us spp. p 13 6 16 7 42 ; l ² = 0% us spp. p | 70 35 103 49 257 | 2.8% 2.0% 3.3% 1.5% 9.6% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 | f = 4 (P = 0) | .04) bbacill 70 114 93 49 326 = 0.48) | ; ² = 399; us spp. r 13 6 16 7 42 ; ² = 0% | 70 35 103 49 257 | 2.8% 2.0% 3.3% 1.5% 9.6% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández–Carrocera 2014 Sinha 2015 | f = 4 (P = 0) | .04) bbacill 70 114 93 49 326 = 0.48) .26) bbacill | us spp. p 13 6 16 7 42 ; 2 = 0% us spp. p 44 | 70 35 103 49 257 blus St | 2.8% 2.0% 3.3% 1.5% 9.6% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.C 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) | f = 4 (P = 0)5 (P = 0)6 (P = 0)6 (P = 0)7 (P = 0 | .04) 70 114 93 49 326 = 0.48) .26) bbacill 75 668 | us spp. r 13 6 16 7 42 ; 1 ² = 0% us spp. r 44 107 | 70 35 103 49 257 blus Str 75 672 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events | f = 4 (P = 0) | .04) 70 114 93 49 326 = 0.48) .26) bbacill 75 668 743 | us spp. r 13 6 16 7 42 ; l ² = 0% us spp. r 44 107 | 70 35 103 49 257 blus Str 75 672 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% Cl) Total events Heterogeneity: Chi² = 1.05, d | f = 4 (P = 0) f = 7 (P = 0) f = 8 (P = 0) f = 15 f = 10 f | .04) pbacill 70 114 93 49 326 = 0.48) .26) pbacill 75 668 743 = 0.31) | us spp. r 13 6 16 7 42 ; l ² = 0% us spp. r 44 107 | 70 35 103 49 257 blus Str 75 672 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p, p | f = 4 (P = 0) | .04) 70 114 93 326 = 0.48) .26) bbacill 75 668 743 = 0.31) | ; 2 = 399; us spp. p 13 6 16 7 42 ; | 70 35 103 49 257 blus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p | f = 4 (P = 0) | .04) pbacill 70 114 93 49 326 = 0.48) .26) pbacill 75 6688 743 = 0.31) .09) pbacill 250 | ; 2 = 399; us spp. p 13 6 16 7 42 ; | olus Sa 70 35 103 49 257 olus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 134] 0.62 [0.21, 134] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.05, d Test for overall effect: Z = 1.7 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.05, d Test for overall effect: Z = 1.7 | f = 4 (P = 0) f = 7 (P = 0) f = 8 (P = 0) f = 15 f = 10 f = 3 (P = 0) f = 3 (P = 0) f = 3 (P = 0) f = 10 (P = 0 | .04) 70 114 93 49 326 = 0.48) .26) bbacill 75 668 743 = 0.31) | us spp. r 13 6 16 7 42 ; l ² = 0% us spp. r 44 107 151 ; l ² = 4% us spp. r | olus Sa 70 35 103 49 257 olus Sti 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.31] 0.62 [0.29, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p William 2015 Las Bifidobacterium spp. p 1.3.8 Bifidobacterium spp. p | f = 4 (P = 0) f = 7 (P = 0) f = 8 (P = 0) f = 15 f = 10 f = 3 (P = 0) f = 3 (P = 0) f = 3 (P = 0) f = 10 (P = 0 | .04) pbacill 70 114 93 49 326 = 0.48) .26) pbacill 75 6688 743 = 0.31) .09) pbacill 250 | us spp. r 13 6 16 7 42 ; l ² = 0% us spp. r 44 107 151 ; l ² = 4% us spp. r | olus Sa 70 35 103 49 257 olus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 134] 0.62 [0.21, 134] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi ² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wu 2020 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wu 2020 Subtotal (95% CI) Total events | f = 4 (P : 05 (P = 0 olus Laction 15 | .04) bbacill 70 114 93 49 326 = 0.48) .26) bbacill 75 668 743 = 0.31) .09) | us spp. r 13 6 16 7 ; l ² = 0% us spp. r 44 107 151 ; l ² = 4% us spp. r 4 | olus Sa 70 35 103 49 257 olus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 134] 0.62 [0.21, 134] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wu 2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Total events Heterogeneity: Chi² = 1.7 1.3.8 Bifidobacterium spp. p Wu 2020 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.3 | f = 4 (P : 05 (P = 0 olus Laction 15 | .04) bbacill 70 114 93 326 = 0.48) .26) bbacill 75 668 743 = 0.31) .09) bbacill 250 250 | us spp. r 13 6 16 7 ; l ² = 0% us spp. r 44 107 151 ; l ² = 4% us spp. r 4 | 70 35 103 257 257 5672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.34] 0.62 [0.21, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] 15 0.75 [0.17, 3.32] 0.75 [0.17, 3.32] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Usal Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wa 2020 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.3 Total (95% CI) | f = 4 (P : 5) (P = 0 to 5) (P : 10 to 5) (P : 1 | .04) bbacill 70 114 93 49 326 = 0.48) .26) bbacill 75 668 743 = 0.31) .09) | us spp. ; 1 ² = 39 ² us spp. ; 1 ³ = 6 16 7 42 42 107 151 151 151 151 17 4 4 4 4 | 70 35 103 257 257 5672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 134] 0.62 [0.21, 134] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wu 2020 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.3 Total (95% CI) Total (95% CI) | f = 4 (P : 5 (P = 0 to 5) (P = | .04) bbacill 70 114 93 49 326 cobbacill 75 668 743 cobbacill 250 250 .70) | us spp. ; | 70 35 103 49 257 5672 747 0lus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.34] 0.62 [0.21, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] 15 0.75 [0.17, 3.32] 0.75 [0.17, 3.32] | • |
| Total events Heterogeneity: Chi² = 6.59, d Test for overall effect: Z = 2.0 1.3.6 Bifidobacterium spp. p Chandrashekar 2018 Duta 2015 Hariharan 2016 Shashidhar 2017 Subtotal (95% CI) Total events Heterogeneity: Chi² = 2.46, d Test for overall effect: Z = 1.1 1.3.7 Bifidobacterium spp. p Fernández-Carrocera 2014 Sinha 2015 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Usal Subtotal (95% CI) Total events Heterogeneity: Chi² = 1.05, d Test for overall effect: Z = 1.7 1.3.8 Bifidobacterium spp. p Wa 2020 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.3 Total (95% CI) | f = 4 (P + (P | .04) bbacill 70 114 93 49 326 = 0.48) .26) bbacill 75 668 743 = 0.31) .09) .70) .70) .70) .716 P = 0.5 | us spp. ; | 70 35 103 49 257 5672 747 0lus Str 75 672 747 | 2.8% 2.0% 3.3% 1.5% 9.6% reptococc 9.5% 23.1% 32.7% | 1.15 [0.59, 2.24] 0.51 [0.20, 1.34] 0.62 [0.21, 1.34] 0.86 [0.31, 2.37] 0.79 [0.53, 1.18] us spp. 0.95 [0.72, 1.26] 0.79 [0.61, 1.03] 0.84 [0.69, 1.02] 15 0.75 [0.17, 3.32] 0.75 [0.17, 3.32] | 0.01 0.1 10 1 Favours problotics Favours control |

Comparison: Probiotics versus control in preterm newborns by probiotic strain type

Outcome: Necrotizing enterocolitis

Probiotics Control Risk Ratio Risk Ratio

| | Probio | tics | Conti | rol | | Risk Ratio | Risk Ratio |
|--|-----------------------|---------|------------|--------|-------------|--------------------|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 2.1.1 Single strain | | | | | | | |
| Cui 2019 | 1 | 45 | 5 | 48 | 2.0% | 0.21 [0.03, 1.76] | |
| Demirel 2013 | 6 | 135 | 7 | 136 | 2.9% | 0.86 [0.30, 2.50] | |
| Dilli 2015 | 2 | 100 | 18 | 100 | 7.6% | 0.11 [0.03, 0.47] | |
| Hernandez-Enriquez 2016 | 1 | 24 | 5 | 20 | 2.3% | 0.17 [0.02, 1.31] | <u> </u> |
| Huang 2009 | 0 | 95 | 3 | 88 | 1.5% | 0.13 [0.01, 2.53] | • |
| Hussain 2016 | 7 | 150 | 37 | 150 | 15.5% | 0.19 [0.09, 0.41] | |
| Kaban 2019 | 0 | 47 | 3 | 47 | 1.5% | 0.14 [0.01, 2.69] | • |
| Matin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| Oncel 2014 | 8 | 200 | 10 | 200 | 4.2% | 0.80 [0.32, 1.99] | |
| Rojas 2012 | 9 | 372 | 15 | 378 | 6.3% | 0.61 [0.27, 1.38] | |
| Sari 2011 | 6 | 110 | 10 | 111 | 4.2% | 0.61 [0.23, 1.61] | |
| Serce 2013 | 7 | 104 | 7 | 104 | 2.9% | 1.00 [0.36, 2.75] | |
| Shadkam 2015 | 2 | 30 | 11 | 30 | 4.6% | 0.18 [0.04, 0.75] | |
| Singh 2017 | 6 | 37 | 10 | 35 | 4.3% | 0.57 [0.23, 1.40] | |
| Tewari 2015 | 0 | 123 | 0 | 121 | 4.3/0 | Not estimable | |
| Subtotal (95% CI) | U | 1598 | U | 1594 | 59.9% | 0.39 [0.29, 0.53] | A |
| Total events | 55 | 1330 | 141 | 133. | 331370 | 0.55 [0.25, 0.55] | ~ |
| Heterogeneity: Chi ² = 19.75. | | (D = 0 | | 2.00/ | | | |
| Test for overall effect: Z = 6. | | | | 39% | | | |
| Test for overall effect. $Z = 6$. | 10 (P < U | .00001 | L) | | | | |
| 2.1.2 Multiple strains | | | | | | | |
| Braga 2011 | 0 | 119 | 4 | 112 | 1.9% | 0.10 [0.01, 1.92] | |
| Chandrashekar 2018 | 0 | 70 | 3 | 70 | 1.5% | 0.14 [0.01, 2.72] | |
| Chowdhury 2016 | 1 | 60 | 6 | 59 | 2.5% | 0.16 [0.02, 1.32] | |
| Dashti 2014 | 2 | 69 | 1 | 67 | 0.4% | 1.94 [0.18, 20.92] | |
| Duta 2015 | 6 | 114 | 0 | 35 | 0.3% | 4.07 [0.23, 70.49] | |
| Fernández-Carrocera 2014 | 6 | 75 | 12 | 75 | 5.0% | 0.50 [0.20, 1.26] | |
| Hariharan 2016 | 3 | 93 | 3 | 103 | 1.2% | 1.11 [0.23, 5.35] | |
| Lin 2013 | 2 | 65 | 8 | 55 | 3.6% | 0.21 [0.05, 0.96] | |
| Rehman 2018 | 2 | 73 | 8 | 73 | 3.4% | 0.25 [0.05, 1.14] | |
| Ren 2010 | 3 | 80 | 5 | 70 | 2.2% | 0.53 [0.13, 2.12] | |
| Roy 2014 | 2 | 56 | 2 | 56 | 0.8% | 1.00 [0.15, 6.85] | |
| Saengtawesin 2014 | 1 | 31 | 1 | 29 | 0.4% | 0.94 [0.06, 14.27] | |
| Samanta 2009 | 5 | 91 | 15 | 95 | 6.2% | 0.35 [0.13, 0.92] | |
| Shashidhar 2017 | 2 | 49 | 6 | 49 | 2.5% | 0.33 [0.07, 1.57] | |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.6% | 0.33 [0.01, 8.09] | |
| Van Niekerk 2014 | 0 | 91 | 4 | 93 | 1.9% | 0.11 [0.01, 2.08] | |
| Wu 2020 | 2 | 250 | 12 | 250 | 5.0% | 0.17 [0.04, 0.74] | |
| Zahed Pasha 2016 | 1 | 30 | 1 | 30 | 0.4% | 1.00 [0.07, 15.26] | |
| Subtotal (95% CI) | 1 | 1516 | 1 | 1421 | 40.1% | 0.39 [0.27, 0.56] | _ |
| Total events | 38 | 1310 | 92 | 1 | 10.170 | 0.55 [0.27, 0.50] | ~ |
| Heterogeneity: Chi ² = 13.19. | | (D 0 | | 00/ | | | |
| Test for overall effect: Z = 5. | | • | | U% | | | |
| | , | | | 201- | 100.007 | 0.20 [0.24 6 :0] | _ |
| Total (95% CI) | | 3114 | | 3015 | 100.0% | 0.39 [0.31, 0.49] | • |
| Total events | 93 | | 233 | | | | |
| Heterogeneity: $Chi^2 = 32.98$ | | • | | 9% | | | 0.01 0.1 1 10 1 |
| Test for overall effect: $Z = 7$. | | | | | | | Favours probiotics Favours control |
| Test for subgroup difference | s: Chi ² = | 0.00, 0 | df = 1 (P) | = 0.95 | $1^2 = 0\%$ | | and production in a control |

Outcome: All-cause neonatal mortality

| Study or Subgroup | Probio Events | | Conti Events | | Wejaht | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M–H, Fixed, 95% CI |
|--|------------------|-------------------|-----------------|-------------------|----------------------|--|----------------------------------|
| 2.2.1 Single strain | | · Jui | | · · · · · · · | | 11, 1 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1 | , |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.6% | 1.01 [0.30, 3.40] | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.2% | 0.25 [0.07, 0.86] | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.3% | 4.20 [0.21, 82.72] | |
| Kaban 2019 | 1 | 47 | 4 | 47 | 2.1% | 0.25 [0.03, 2.15] | |
| Matin 2022 | 0 | 26 | 0 | 26 | 2.1/0 | Not estimable | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.3% | 0.75 [0.40, 1.42] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.3% | 0.80 [0.47, 1.37] | |
| Sari 2011 | 3 | 110 | 3 | 111 | 1.5% | 1.01 [0.21, 4.89] | |
| Serce 2013 | 5 | 104 | 4 | 104 | 2.1% | 1.25 [0.35, 4.52] | |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.6% | 0.95 [0.20, 4.38] | |
| Tewari 2015 | 12 | 123 | 14 | 121 | 7.3% | 0.84 [0.41, 1.75] | |
| Subtotal (95% CI) | 12 | 1308 | 17 | 1308 | 49.2% | 0.76 [0.56, 1.02] | • |
| Total events | 72 | -500 | 95 | -500 | | 0 0 [0.00, 1.01] | • |
| Heterogeneity: Chi ² = 6.63, a | | P = 0.76 | | % | | | |
| Test for overall effect: $Z = 1$. | | | 5), 1 — 0 | 70 | | | |
| 2.2.2 Multiple studing | | | | | | | |
| 2.2.2 Multiple strains | 26 | 119 | 27 | 112 | 14 20/ | 0.01 [0.56 1.45] | |
| Braga 2011 | | | 27 | 112 | 14.3% | 0.91 [0.56, 1.45] | |
| Chandrashekar 2018 | 1 5 | 70 | 4 | 70 | 2.1% | 0.25 [0.03, 2.18] | · |
| Chowdhury 2016 | 8 | 60 69 | 7 4 | 59 67 | 3.6% | 0.70 [0.24, 2.09] | <u> </u> |
| Dashti 2014 | _ | | | | 2.1% | 1.94 [0.61, 6.15] | |
| Duta 2015 | 8 | 114 | 2 | 35 | 1.6% | 1.23 [0.27, 5.52] | |
| Fernández-Carrocera 2014 | 1 | 75 03 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | • |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Li 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | <u> </u> |
| Rehman 2018 | 4 7 | 73 5.0 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Roy 2014 | - | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Saengtawesin 2014 | 0 | 31 91 | 0 | 29 95 | 7 10/ | Not estimable | |
| Samanta 2009 | 4 | | 14 | | 7.1% | 0.30 [0.10, 0.87] | |
| Shashidhar 2017 | 1 | 49 | 3 | 49 672 | 1.5% | 0.33 [0.04, 3.09] | <u> </u> |
| Sinha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | • |
| Sowden 2022 | 0 | 100 | 0 | 100 | 2 10/ | Not estimable | |
| Van Niekerk 2014 | 5 | 91 | 6 | 93 | 3.1% | 0.85 [0.27, 2.69] | • |
| Wu 2020 Zahad Basha 2016 | 0 | 250 | 0 | 250 | 0.20/ | Not estimable | |
| Zahed Pasha 2016 Subtotal (95% CI) | 2 | 30 2055 | 0 | 30 1982 | 0.3% 50.8% | 5.00 [0.25, 99.95] 0.74 [0.56, 0.99] | <u> </u> |
| Total events | 77 | _055 | 96 | 1502 | 33.070 | o [0.50, 0.55] | ~ |
| Heterogeneity: Chi ² = 12.74, | | (P = 0.1) | | 0% | | | |
| Test for overall effect: $Z = 2$. | 05 (P = 0) | .04) | | | | | |
| Total (95% CI) | | 3363 | | 3290 | 100.0% | 0.75 [0.61, 0.92] | ♦ |
| Total events | 149 | | 191 | | | | |
| Heterogeneity: $Chi^2 = 19.35$, | | | 78); $I^2 =$ | 0% | | | 0.01 0.1 1 10 1 |
| Test for overall effect: $Z = 2$. | | | | | | | U.U.1 U.1 1 1U ! |

Outcome: *Invasive infection*

| Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl State St | , | Probio | tics | Conti | ol | | Risk Ratio | Risk Ratio |
|---|----------------------------------|---------|---------|-----------------|---------|----------------|--------------------|---------------------------------------|
| Cui 2019 | Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Demirel 2013 | 2.3.1 Single strain | | | | | | | |
| Dilli 2015 | Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | |
| Hernandez-Enriquez 2016 6 24 1 20 0.2% 5.00 [0.66, 38.15] Kaban 2019 1 47 3 47 0.7% 0.33 [0.04, 3.09] Matin 2022 0 26 3 26 0.8% 0.14 [0.01, 2.63] Matin 2022 0 26 3 26 0.8% 0.52 [0.27, 0.99] Matin 2022 0 25 200 5.4% 0.52 [0.27, 0.99] Matin 2021 13 200 25 200 5.4% 0.52 [0.27, 0.99] Matin 2021 2 9110 26 1111 5.6% 11.13 [0.71, 1.78] Matin 2015 0 30 0 30 Not estimable Tewari 2015 8 123 11 121 2.4% 0.76 [0.45, 1.29] Matin 2015 8 123 11 121 2.4% 0.72 [0.30, 1.72] Mu 2016 4 65 6 60 1.4% 0.62 [0.18, 2.08] Matin 2015 0 1009 1003 30.0% 0.79 [0.63, 1.00] Matin 2015 Mutatil [95% CI) 1009 1003 30.0% 0.79 [0.63, 1.00] Matin 2015 Mutatil 2 10.09 0.42); I² = 2% Subtotal [95% CI] Mutatil 2 10.09 0.42); I² = 2% Mutatil 2 10.09 0.42); I² = 0% 0.42); I² | Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Hernandez-Enriquez 2016 6 24 1 20 0.2% 5.00 [0.66, 38.15] Kaban 2019 1 47 3 47 0.7% 0.33 [0.04, 3.09] Matin 2022 0 26 3 26 0.8% 0.14 [0.01, 2.63] Matin 2022 0 26 3 26 0.8% 0.52 [0.27, 0.99] Matin 2022 0 25 200 5.4% 0.52 [0.27, 0.99] Matin 2021 13 200 25 200 5.4% 0.52 [0.27, 0.99] Matin 2021 2 9110 26 1111 5.6% 11.13 [0.71, 1.78] Matin 2015 0 30 0 30 Not estimable Tewari 2015 8 123 11 121 2.4% 0.76 [0.45, 1.29] Matin 2015 8 123 11 121 2.4% 0.72 [0.30, 1.72] Mu 2016 4 65 6 60 1.4% 0.62 [0.18, 2.08] Matin 2015 0 1009 1003 30.0% 0.79 [0.63, 1.00] Matin 2015 Mutatil [95% CI) 1009 1003 30.0% 0.79 [0.63, 1.00] Matin 2015 Mutatil 2 10.09 0.42); I² = 2% Subtotal [95% CI] Mutatil 2 10.09 0.42); I² = 2% Mutatil 2 10.09 0.42); I² = 0% 0.42); I² | Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | | |
| Kaban 2019 1 47 3 47 0.7% 0.33 [0.04, 3.09] Matin 2022 0 26 3 26 0.8% 0.14 [0.1, 2.63] 4 Concel 2014 13 200 25 200 5.4% 0.52 [0.27, 0.99] Sar 2011 29 110 26 111 5.6% 1.13 [0.71, 1.78] Serce 2013 19 104 25 104 5.4% 0.75 [0.45, 1.29] Shadkam 2015 0 30 0 30 Not estimable Tewari 2015 8 123 11 121 2.4% 0.72 [0.30, 1.72] 2.7 Standam 2016 4 465 6 6 6 6 6.14% 0.62 [0.18, 2.08] 1.72] Total events 110 138 Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); l² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.32 Multiple strains Braga 2011 40 119 42 112 9.4% 0.90 [0.63, 1.27] 0.94 | Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | | |
| Matin 2022 | | 1 | 47 | 3 | 47 | 0.7% | | · · · · · · · · · · · · · · · · · · · |
| Sari 2011 29 110 26 111 5.6% 1.13 [0.71, 1.78] Serce 2013 19 104 25 104 5.4% 0.76 [0.45, 1.29] Shadkam 2015 0 30 0 30 Not estimable Tewari 2015 8 123 11 121 2.4% 0.72 [0.30, 1.72] Xu 2016 4 65 6 60 1.4% 0.62 [0.18, 2.08] Subtotal (95% Cl) 1009 1003 30.0% 0.79 [0.63, 1.00] Total events 110 138 Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); i² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.3.2 Multiple strains Braga 2011 40 119 42 112 9.4% 0.90 [0.63, 1.27] Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Sangtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Viekerk 2014 15 90 10 0.9% 0.75 [0.17, 0.94] Total (95% Cl) 2716 263 100.0% 0.81 [0.72, 0.91] Fotal events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); i² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Feyeurus probibities Favours control | Matin 2022 | 0 | 26 | 3 | 26 | | | • |
| Sari 2011 | Oncel 2014 | 13 | 200 | 25 | 200 | 5.4% | 0.52 [0.27, 0.99] | |
| Serice 2013 19 104 25 104 5.4% 0.76 [0.45, 1.29] Shadkam 2015 0 30 0 30 Not estimable Tewari 2015 8 123 11 121 2.4% 0.72 [0.30, 1.72] Xu 2016 4 65 6 60 1.4% 0.62 [0.18, 2.08] Subtotal (95% CI) 1009 1003 30.0% 0.79 [0.63, 1.00] Total events 110 138 Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); l² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.3.2 Multiple strains Praga 2011 40 119 42 112 9.4% 0.90 [0.63, 1.27] Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 1.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Van Niekerk 2014 15 91 10 91 10 100 100 100 100 100 100 100 | Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | | |
| Shadkam 2015 | Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | | |
| Tewari 2015 | Shadkam 2015 | 0 | 30 | 0 | 30 | | | |
| Xu 2016 4 65 6 60 1.4% 0.62 [0.18, 2.08] Subtotal (95% Cl) 1009 1003 30.0% 0.79 [0.63, 1.00] Total events 110 138 Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); l² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.3.2 Multiple strains Braga 2011 40 119 42 112 9.4% 0.90 [0.63, 1.27] Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] ———————————————————————————————————— | Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | | |
| Total events 110 138 Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); l² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.3.2 Multiple strains Braga 2011 40 119 42 112 9.4% 0.90 [0.63, 1.27] Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% Cl) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | | 4 | | 6 | | 1.4% | | |
| Heterogeneity: Chi² = 10.22, df = 10 (P = 0.42); l² = 2% Test for overall effect: Z = 1.96 (P = 0.05) 2.3.2 Multiple strains Braga 2011 | Subtotal (95% CI) | | | | 1003 | | | |
| 2.3.2 Multiple strains Braga 2011 | Total events | 110 | | 138 | | | | |
| 2.3.2 Multiple strains Braga 2011 | Heterogeneity: $Chi^2 = 10.22$, | df = 10 | (P = 0. | 42); $I^2 =$ | 2% | | | |
| 2.3.2 Multiple strains Braga 2011 | | | | ,, | | | | |
| Braga 2011 | | · | | | | | | |
| Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | 2.3.2 Multiple strains | | | | | | | |
| Chandrashekar 2018 15 70 13 70 2.8% 1.15 [0.59, 2.24] Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | - |
| Duta 2015 10 114 6 35 2.0% 0.51 [0.20, 1.31] Fernández-Carrocera 2014 42 75 44 75 9.5% 0.95 [0.72, 1.26] Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | _ | | | | | | | |
| Fernández-Carrocera 2014 | Duta 2015 | 10 | 114 | 6 | 35 | | | |
| Hariharan 2016 9 93 16 103 3.3% 0.62 [0.29, 1.34] Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | Fernández-Carrocera 2014 | 42 | 75 | 44 | 75 | 9.5% | 0.95 [0.72, 1.26] | + |
| Roy 2014 31 56 42 56 9.1% 0.74 [0.56, 0.98] Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | | |
| Saengtawesin 2014 2 31 1 20 0.3% 1.29 [0.13, 13.31] Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | | |
| Samanta 2009 13 91 28 95 5.9% 0.48 [0.27, 0.88] Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | | 2 | 31 | 1 | 20 | | | |
| Shashidhar 2017 6 49 7 49 1.5% 0.86 [0.31, 2.37] Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); I² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); I² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | Samanta 2009 | 13 | 91 | 28 | 95 | | | |
| Sinha 2015 84 668 107 672 23.1% 0.79 [0.61, 1.03] Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); I² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); I² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | Shashidhar 2017 | 6 | 49 | | | | | |
| Van Niekerk 2014 15 91 10 93 2.1% 1.53 [0.73, 3.23] Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | | 84 | 668 | 107 | 672 | 23.1% | | |
| Wu 2020 3 250 4 250 0.9% 0.75 [0.17, 3.32] Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] Total events 270 320 Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); I² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total (95% CI) 2716 2633 100.0% 0.81 [0.72, 0.91] Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); I² = 0% 0.01 0.1 100 Test for overall effect: Z = 3.49 (P = 0.0005) Eavours probiotics Eavours control | | 15 | 91 | 10 | 93 | | | l l |
| Subtotal (95% CI) 1707 1630 70.0% 0.82 [0.71, 0.94] | | | | | | | | |
| Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total (95% CI) | Subtotal (95% CI) | | 1707 | | 1630 | | | |
| Heterogeneity: Chi² = 10.42, df = 11 (P = 0.49); l² = 0% Test for overall effect: Z = 2.89 (P = 0.004) Total (95% CI) | Total events | 270 | | 320 | | | | |
| Test for overall effect: Z = 2.89 (P = 0.004) Total (95% CI) Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | | df = 11 | (P = 0. | 49); $I^2 =$ | 0% | | | |
| Total (95% CI) 2716 2633 100.0% 0.81 [0.72, 0.91] Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) | | | | | | | | |
| Total events 380 458 Heterogeneity: Chi² = 20.67, df = 22 (P = 0.54); l² = 0% Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | | • | • | | | | | |
| Heterogeneity: $Chi^2 = 20.67$, $df = 22$ (P = 0.54); $I^2 = 0\%$ Test for overall effect: Z = 3.49 (P = 0.0005) Test for overall effect: Z = 3.49 (P = 0.0005) | Total (95% CI) | | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | ♦ |
| Test for overall effect: $Z = 3.49$ (P = 0.0005) Test for overall effect: $Z = 3.49$ (P = 0.0005) | Total events | 380 | | 458 | | | | |
| Test for overall effect: $Z = 3.49$ (P = 0.0005) Test for overall effect: $Z = 3.49$ (P = 0.0005) | Heterogeneity: $Chi^2 = 20.67$, | | (P = 0. | 54); $I^2 =$ | 0% | | | |
| | | | | | | | | |
| | | | | | = 0.82) |), $I^2 = 0\%$ | | ravours probletics ravours control |

Comparison: Probiotics versus control in preterm newborns by feeding type

Outcome: Necrotizing enterocolitis

Probiotics Control Risk Ratio Risk Ratio

| | Probio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|---|-----------------|-------------------|----------------------------|-------------------|----------------------|--|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.1.1 Human milk only | | | | | | | |
| Matin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| Roy 2014 | 2 | 56 | 2 | 56 | 0.8% | 1.00 [0.15, 6.85] | |
| Samanta 2009 | 5 | 91 | 15 | 95 | 6.2% | 0.35 [0.13, 0.92] | |
| Shadkam 2015 | 2 | 30 | 11 | 30 | 4.6% | 0.18 [0.04, 0.75] | |
| Shashidhar 2017 | 2 | 49 | 6 | 49 | 2.5% | 0.33 [0.07, 1.57] | |
| Singh 2017 | 6 | 37 | 10 | 35 | 4.3% | 0.57 [0.23, 1.40] | |
| Tewari 2015 | 0 | 123 | 0 | 121 | | Not estimable | |
| Van Niekerk 2014 | 0 | 91 | 4 | 93 | 1.9% | 0.11 [0.01, 2.08] | • |
| Zahed Pasha 2016 | 1 | 30 | 1 | 30 | 0.4% | 1.00 [0.07, 15.26] | |
| Subtotal (95% CI) | | 533 | | 535 | 20.8% | 0.37 [0.23, 0.62] | ◆ |
| Total events | 18 | | 49 | | | | |
| Heterogeneity: $Chi^2 = 4.01$, of | df = 6 (P = | = 0.68 | $I^2 = 0\%$ | | | | |
| Test for overall effect: $Z = 3$. | 81 (P = 0) | .0001) | | | | | |
| | | | | | | | |
| 3.1.2 Mixed-human milk or | formula | or bot | h | | | | |
| Braga 2011 | 0 | 119 | 4 | 112 | 1.9% | 0.10 [0.01, 1.92] | - |
| Chandrashekar 2018 | 0 | 70 | 3 | 70 | 1.5% | 0.14 [0.01, 2.72] | • |
| Chowdhury 2016 | 1 | 60 | 6 | 59 | 2.5% | 0.16 [0.02, 1.32] | |
| Dashti 2014 | 2 | 69 | 1 | 67 | 0.4% | 1.94 [0.18, 20.92] | |
| Demirel 2013 | 6 | 135 | 7 | 136 | 2.9% | 0.86 [0.30, 2.50] | |
| Dilli 2015 | 2 | 100 | 18 | 100 | 7.6% | 0.11 [0.03, 0.47] | |
| Duta 2015 | 6 | 114 | 0 | 35 | 0.3% | 4.07 [0.23, 70.49] | |
| Fernández-Carrocera 2014 | 6 | 75 | 12 | 75 | 5.0% | 0.50 [0.20, 1.26] | |
| Hariharan 2016 | 3 | 93 | 3 | 103 | 1.2% | 1.11 [0.23, 5.35] | |
| Hernandez-Enriquez 2016 | 1 | 24 | 5 | 20 | 2.3% | 0.17 [0.02, 1.31] | <u> </u> |
| Huang 2009 | 0 | 95 | 3 | 88 | 1.5% | 0.13 [0.01, 2.53] | |
| Kaban 2019 | 0 | 47 | 3 | 47 | 1.5% | 0.14 [0.01, 2.69] | - |
| Lin 2013 | 2 | 65 | 8 | 55 | 3.6% | 0.21 [0.05, 0.96] | |
| Oncel 2014 | 8 | 200 | 10 | 200 | 4.2% | 0.80 [0.32, 1.99] | |
| Rehman 2018 | 2 | 73 | 8 | 73 | 3.4% | 0.25 [0.05, 1.14] | |
| Ren 2010 | 3 | 80 | 5 | 70 | 2.2% | 0.53 [0.13, 2.12] | |
| Rojas 2012 | 9 | 372 | 15 | 378 | 6.3% | 0.61 [0.27, 1.38] | |
| Saengtawesin 2014 | 1 | 31 | 1 | 29 | 0.4% | 0.94 [0.06, 14.27] | |
| Sari 2011 | 6 | 110 | 10 | 111 | 4.2% | 0.61 [0.23, 1.61] | |
| Serce 2013 | 7 | 104 | 7 | 104 | 2.9% | 1.00 [0.36, 2.75] | |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.6% | 0.33 [0.01, 8.09] | |
| Subtotal (95% CI) | U | 2136 | 1 | 2032 | 56.6% | 0.48 [0.36, 0.64] | ▲ |
| Total events | 65 | | 130 | | 30.070 | 0.10 [0.50, 0.01] | ~ |
| Heterogeneity: $Chi^2 = 20.83$, | | (P = 0 . | | 19/ | | | |
| Test for overall effect: $Z = 5$. | | | | 4/0 | | | |
| rest for overall effect. Z = 3. | 00 (1 < 0 | .00001 | .) | | | | |
| 3.1.3 Formula only | | | | | | | |
| Cui 2019 | 1 | 45 | 5 | 48 | 2.0% | 0.21 [0.02 1.76] | |
| Hussain 2016 | 7 | 150 | 37 | 150 | 15.5% | 0.21 [0.03, 1.76] 0.19 [0.09, 0.41] | |
| Wu 2020 | 2 | | 12 | | | | |
| Subtotal (95% CI) | 2 | 250 445 | 12 | 250 448 | 5.0% 22.6% | 0.17 [0.04, 0.74] 0.19 [0.10, 0.36] | |
| · | 10 | 773 | E 4 | 770 | 22.0/0 | 0.19 [0.10, 0.30] | |
| Total events | 10 st = 2 (B | 0.00 | 54 1 ² – 09/ | | | | |
| Heterogeneity: $Chi^2 = 0.04$, or Test for overall effect: $Z = 5$. | | | | | | | |
| Total (95% CI) | | 3114 | | 3015 | 100.0% | 0.39 [0.31, 0.49] | • |
| Total events | 93 | | 233 | | | ,, | * |
| Heterogeneity: $Chi^2 = 32.98$, | | (P = 0) | | 9% | | | |
| Test for overall effect: $Z = 7$. | | | | J/0 | | | 0.01 0.1 1 10 100 |
| | | | | | | | Favours probiotics Favours control |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause neonatal mortality

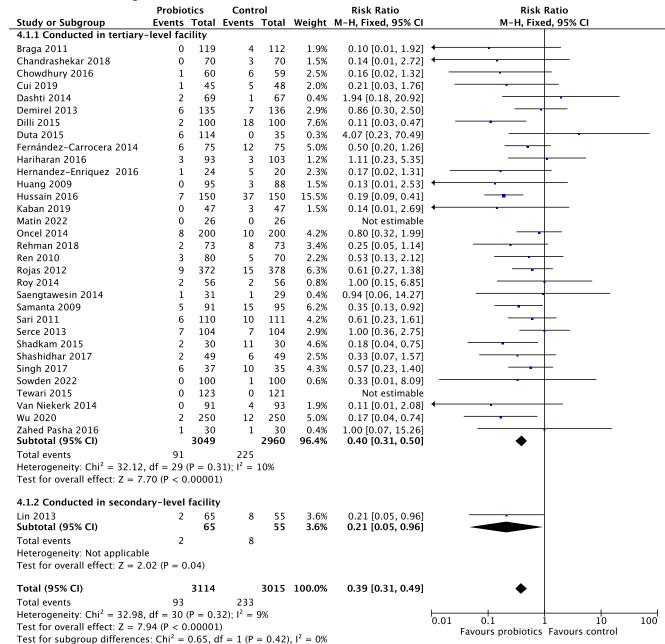
| | Probio | | Contr | | | Risk Ratio | Risk Ratio |
|--|----------------------|-------------------|----------------|-------------------|----------------------|--|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.2.1 Human milk only | | | | | | | |
| Matin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| Roy 2014 | 7 | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Samanta 2009 | 4 | 91 | 14 | 95 | 7.0% | 0.30 [0.10, 0.87] | - |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | • |
| Shashidhar 2017 | 1 | 49 | 3 | 49 | 1.5% | 0.33 [0.04, 3.09] | |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.6% | 0.95 [0.20, 4.38] | |
| Sinha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | |
| Tewari 2015 | 12 | 123 | 14 | 121 | 7.2% | 0.84 [0.41, 1.75] | |
| Van Niekerk 2014 | 5 | 91 | 6 | 93 | 3.0% | 0.85 [0.27, 2.69] | |
| Zahed Pasha 2016 Subtotal (95% CI) | 2 | 30 1201 | 0 | 30 1207 | 0.3% 26.8% | 5.00 [0.25, 99.95] 0.70 [0.46, 1.04] | • |
| Total events | 36 | | 52 | | | | |
| Heterogeneity: $Chi^2 = 5.39$, of | df = 8 (P = | = 0.72 |); $I^2 = 0\%$ | | | | |
| Test for overall effect: $Z = 1$. | | | | | | | |
| | | | | | | | |
| 3.2.2 Mixed-human milk or | formula | or bot | :h | | | | |
| Braga 2011 | 26 | 119 | 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | - |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 2.0% | 0.25 [0.03, 2.18] | · · |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.5% | 1.01 [0.30, 3.40] | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Duta 2015 | 8 | 114 | 2 | 35 | 1.6% | 1.23 [0.27, 5.52] | |
| Fernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.3% | 4.20 [0.21, 82.72] | |
| Kaban 2019 | 1 | 47 | 4 | 47 | 2.0% | 0.25 [0.03, 2.15] | <u> </u> |
| Li 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.2% | 0.75 [0.40, 1.42] | |
| Rehman 2018 | 4 | 73 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | 17.270 | Not estimable | |
| Sari 2011 | 3 | 110 | 3 | 111 | 1.5% | 1.01 [0.21, 4.89] | |
| Serce 2013 | 5 | 104 | 4 | 104 | 2.0% | 1.25 [0.35, 4.52] | |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.33 [0.01, 8.09] | |
| Subtotal (95% CI) | U | 1912 | | 1833 | 73.2% | 0.76 [0.60, 0.97] | • |
| Total events | 113 | | 140 | | . 5.27 | o o [o.oo, o.o., | • |
| Heterogeneity: Chi ² = 14.02, | | D - 0 | | 1 0⁄ | | | |
| Test for overall effect: $Z = 2$. | | | 07), 1 = 1 | 070 | | | |
| 3.2.3 Formula only | | | | | | | |
| Wu 2020 | 0 | 250 | 0 | 250 | | Not estimable | |
| Subtotal (95% CI) | | 250 | | 250 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not applicabl Test for overall effect: Not ap | | | | | | | |
| Total (95% CI) | | 3363 | | 3290 | 100.0% | 0.75 [0.61, 0.92] | • |
| Total events | 149 | | 192 | | | | |
| Heterogeneity: $Chi^2 = 19.62$, Test for overall effect: $Z = 2$. Test for subgroup difference | df = 26 80 (P = 0 | .005) | 81); $I^2 = 0$ | | 12 - 004 | | 0.01 0.1 1 10 Favours probiotics Favours control |

Outcome: *Invasive infection*

| Sander on Colombia | Probio | | Conti | | 14/a : la 4 | Risk Ratio | Risk Ratio |
|---|-------------|-------------|----------------|-------|--------------|--|--------------------|
| Study or Subgroup | Events | Total | Events | Total | weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.3.1 Human milk only | | | | | | | |
| Matin 2022 | 0 | 26 | 3 | 26 | 0.8% | 0.14 [0.01, 2.63] | - |
| Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | <u></u> |
| Samanta 2009 | 13 | 91 | 28 | 95 | 5.9% | 0.48 [0.27, 0.88] | |
| Shadkam 2015 | 0 | 30 | 0 | 30 | | Not estimable | |
| Shashidhar 2017 | 6 | 49 | 7 | 49 | 1.5% | 0.86 [0.31, 2.37] | |
| Sinha 2015 | 84 | 668 | 107 | 672 | 23.1% | 0.79 [0.61, 1.03] | |
| Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | 0.72 [0.30, 1.72] | • |
| Van Niekerk 2014 | 15 | 91 | 10 | 93 | 2.1% | 1.53 [0.73, 3.23] | <u> </u> |
| Subtotal (95% CI) | 1.53 | 1134 | 200 | 1142 | 45.0% | 0.76 [0.64, 0.91] | ▼ |
| Total events | 157 | 0.24\ | 208 | 2.4 | | | |
| Heterogeneity: Chi² = 7.08, c Test for overall effect: Z = 2. | • | | ; 1 = 15 | % | | | |
| 3.3.2 Mixed-human milk or | formula | or bot | h | | | | |
| Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | - |
| Chandrashekar 2018 | 15 | 70 | 13 | 70 | 2.8% | 1.15 [0.59, 2.24] | - - - |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Duta 2015 | 10 | 114 | 6 | 35 | 2.0% | 0.51 [0.20, 1.31] | |
| Fernández-Carrocera 2014 | 42 | 75 | 44 | 75 | 9.5% | 0.95 [0.72, 1.26] | + |
| Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | 0.62 [0.29, 1.34] | |
| Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | 5.00 [0.66, 38.15] | |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | |
| Oncel 2014 | 13 | 200 | 25 | 200 | 5.4% | 0.52 [0.27, 0.99] | |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | |
| Subtotal (95% CI) | | 1222 | | 1133 | 52.0% | 0.86 [0.74, 1.01] | ♦ |
| Total events | 214 | | 236 | | | | |
| Heterogeneity: Chi² = 11.52, Test for overall effect: Z = 1. | | | $18); I^2 =$ | 0% | | | |
| 3.3.3 Formula only | o_ (, | , | | | | | |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0 52 [0 10 2 77] | |
| Wu 2020 | 3 | 250 | | 250 | | 0.53 [0.10, 2.77] | |
| wu 2020 Xu 2016 | 3 4 | 65 | 4 6 | 60 | 0.9% 1.4% | 0.75 [0.17, 3.32] 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) | 4 | 3 60 | б | 358 | 3.1% | 0.62 [0.18, 2.08] 0.63 [0.28, 1.43] | |
| Total events | 9 | | 14 | | , | [| |
| Heterogeneity: $Chi^2 = 0.09$, c Test for overall effect: $Z = 1$. | lf = 2 (P = | | | | | | |
| Total (95% CI) | | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | • |
| Total events | 380 | | 458 | | | | |
| Heterogeneity: $Chi^2 = 20.67$, | df = 22 (| P = 0.5 | $(54); I^2 = $ | 0% | | | 0.01 0.1 1 10 1 |
| Test for overall effect: $Z = 3$. | 40 /B 0 | 0005) | | | | | O.O1 O.1 I IO J |

Comparison: Probiotics versus control in preterm newborns by facility level

Outcome: Necrotizing enterocolitis



Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause neonatal mortality

| | Probio | | Conti | | | Risk Ratio | Risk Ratio |
|---|---------|-----------|------------------------------|-------|--------|--------------------|--------------------|
| Study or Subgroup | | | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 4.2.1 Conducted in tertiary- | | • | | | | | |
| Braga 2011 | 26 | 119 | 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | _ - |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 2.0% | 0.25 [0.03, 2.18] | • |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.5% | 1.01 [0.30, 3.40] | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Duta 2015 | 8 | 114 | 2 | 35 | 1.6% | 1.23 [0.27, 5.52] | |
| Fernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.3% | 4.20 [0.21, 82.72] | |
| Kaban 2019 | 1 | 47 | 4 | 47 | 2.0% | 0.25 [0.03, 2.15] | |
| Matin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.2% | 0.75 [0.40, 1.42] | |
| Rehman 2018 | 4 | 73 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | |
| Roy 2014 | 7 | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | | Not estimable | |
| Samanta 2009 | 4 | 91 | 14 | 95 | 7.0% | 0.30 [0.10, 0.87] | |
| Sari 2011 | 3 | 110 | 3 | 111 | 1.5% | 1.01 [0.21, 4.89] | |
| Serce 2013 | 5 | 104 | 4 | 104 | 2.0% | 1.25 [0.35, 4.52] | |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | · · · |
| Shashidhar 2017 | 1 | 49 | 3 | 49 | 1.5% | 0.33 [0.04, 3.09] | |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.6% | 0.95 [0.20, 4.38] | |
| Sinha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | - |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.33 [0.01, 8.09] | |
| Tewari 2015 | 12 | 123 | 14 | 121 | 7.2% | 0.84 [0.41, 1.75] | |
| Van Niekerk 2014 | 5 | 91 | 6 | 93 | 3.0% | 0.85 [0.27, 2.69] | |
| Wu 2020 | 0 | 250 | 0 | 250 | 3.070 | Not estimable | |
| Zahed Pasha 2016 | 2 | 30 | 0 | 30 | 0.3% | 5.00 [0.25, 99.95] | |
| Subtotal (95% CI) | _ | 3347 | ŭ | 3276 | 99.2% | 0.75 [0.61, 0.92] | ♦ |
| Total events | 149 | | 191 | | | | · |
| Heterogeneity: Chi ² = 19.25, Test for overall effect: Z = 2. | | | 79); I ² = | 0% | | | |
| 4.2.2 Conducted in seconda | - | facility | | | | | |
| Li 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | • |
| Subtotal (95% CI) | | 16 | | 14 | 0.8% | 0.29 [0.01, 6.69] | |
| Total events | 0 | | 1 | | | | |
| Heterogeneity: Not applicable Test for overall effect: Z = 0. | | .44) | | | | | |
| Total (95% CI) | | 3363 | | 3290 | 100.0% | 0.75 [0.61, 0.92] | • |
| Total events | 149 | | 192 | | | | |
| Heterogeneity: $Chi^2 = 19.62$, | df = 26 | (P = 0.8) | (31) : $I^2 = \frac{1}{2}$ | 0% | | | |
| Test for overall effect: $Z = 2$. | | | | | | | 0.01 0.1 1 10 1 |

Outcome: *Invasive infection*

| | Probio | tics | Cont | ol | | Risk Ratio | Risk Ratio |
|------------------------------------|------------------------|------------|-----------------|-------|---------|--------------------|------------------------------------|
| Study or Subgroup | | | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 4.3.1 Conducted in tertiary- | -level fac | ility | | | | | |
| Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | |
| Chandrashekar 2018 | 15 | 70 | 13 | 70 | 2.8% | 1.15 [0.59, 2.24] | - |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Duta 2015 | 10 | 114 | 6 | 35 | 2.0% | 0.51 [0.20, 1.31] | |
| Fernández-Carrocera 2014 | 42 | 75 | 44 | 75 | 9.5% | 0.95 [0.72, 1.26] | + |
| Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | 0.62 [0.29, 1.34] | |
| Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | 5.00 [0.66, 38.15] | |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | |
| Matin 2022 | 0 | 26 | 3 | 26 | 0.8% | 0.14 [0.01, 2.63] | • |
| Oncel 2014 | 13 | 200 | 25 | 200 | 5.4% | 0.52 [0.27, 0.99] | |
| Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Samanta 2009 | 13 | 91 | 28 | 95 | 5.9% | 0.48 [0.27, 0.88] | |
| Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | - |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | |
| Shadkam 2015 | 0 | 30 | 0 | 30 | | Not estimable | |
| Shashidhar 2017 | 6 | 49 | 7 | 49 | 1.5% | 0.86 [0.31, 2.37] | |
| Sinha 2015 | 84 | 668 | 107 | 672 | 23.1% | 0.79 [0.61, 1.03] | |
| Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | 0.72 [0.30, 1.72] | |
| Van Niekerk 2014 | 15 | 91 | 10 | 93 | 2.1% | 1.53 [0.73, 3.23] | • • |
| Wu 2020 | 3 | 250 | 4 | 250 | 0.9% | 0.75 [0.17, 3.32] | |
| Xu 2016 | 4 | 65 | 6 | 60 | 1.4% | 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) | | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | ♦ |
| Total events | 380 | | 458 | | | | |
| Heterogeneity: $Chi^2 = 20.67$, | df = 22 | (P = 0.1) | 54); $I^2 =$ | 0% | | | |
| Test for overall effect: $Z = 3$. | | | | | | | |
| | | , | | | | | |
| 4.3.2 Conducted in seconda | ry-level | facility | y | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not ap | | | | | | | |
| T - 1 (05% CI) | | 2716 | | 2622 | 100.00/ | 0.01 [0.72 0.01] | |
| Total (95% CI) | | 2716 | = | 2633 | 100.0% | 0.81 [0.72, 0.91] | • |
| Total events | 380 | , <u> </u> | 458 | | | | |
| Heterogeneity: $Chi^2 = 20.67$, | | | | 0% | | | 0.01 0.1 1 10 10 |
| Test for overall effect: $Z = 3$. | | | | | | | Favours probiotics Favours control |
| Test for subgroup difference | s: Not ap _l | plicable | 2 | | | | , |

Comparison: Probiotics versus control in preterm newborns by duration of intervention

Outcome: Necrotizing enterocolitis

| tudy or Subgroup | Probiot Events | | Contr Events | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|--|--|---|--|--|--|---|---------------------------------------|
| i.1.1 For 1 week | _ | | - | | 1.50 | 0.13 (0.01. 3.55) | |
| uang 2009 en 2010 | 0 | 95 80 | 3 5 | 88 70 | 1.5% 2.2% | 0.13 [0.01, 2.53] | • |
| ubtotal (95% CI) | 3 | 175 | 3 | 158 | 3.8% | 0.53 [0.13, 2.12] 0.37 [0.11, 1.25] | |
| otal events | 3 | 173 | 8 | 130 | 3.070 | 0.57 [0.11, 1.25] | |
| leterogeneity: Chi² = 0.71, c | | 0.40) | | | | | |
| est for overall effect: $Z = 1$. | | | 1 - 0/0 | | | | |
| .1.2 For 10-14 days | | | | | | | |
| handrashekar 2018 | 0 | 70 | 3 | 70 | 1.5% | 0.14 [0.01, 2.72] | |
| in 2013 | 2 | 65 | 8 | 55 | 3.6% | 0.21 [0.05, 0.96] | |
| hadkam 2015 | 2 | 30 | 11 | 30 | 4.6% | 0.18 [0.04, 0.75] | |
| Subtotal (95% CI) | | 165 | | 155 | 9.7% | 0.19 [0.07, 0.50] | • |
| otal events | 4 | | 22 | | | | |
| Heterogeneity: Chi² = 0.06, o Test for overall effect: Z = 3. | df = 2 (P = .37 (P = 0. | : 0.97); 0008) | I ² = 0% | | | | |
| i.1.3 For 3 weeks | | | | | | | |
| Outa 2015 | 6 | 114 | 0 | 35 | 0.3% | 4.07 [0.23, 70.49] | |
| Hernandez-Enriquez 2016 | 1 | 24 | 5 | 20 | 2.3% | 0.17 [0.02, 1.31] | |
| iubtotal (95% CI) | | 138 | | 55 | 2.6% | 0.64 [0.18, 2.30] | - |
| otal events | 7 | | 5 | | | | |
| Heterogeneity: Chi ² = 3.25, o | | | $I^2 = 699$ | 6 | | | |
| est for overall effect: Z = 0. | | oU) | | | | | |
| .1.4 For 4 weeks or till dis raga 2011 | charge 0 | 119 | 4 | 112 | 1.9% | 0.10 [0.01, 1.92] | |
| Matin 2022 | 0 | 26 | 0 | 26 | 2.3/0 | Not estimable | |
| iowden 2022 | 0 | 100 | 1 | 100 | 0.6% | 0.33 [0.01, 8.09] | |
| an Niekerk 2014 | o | 91 | 4 | 93 | 1.9% | 0.11 [0.01, 2.08] | + |
| ubtotal (95% CI) | | 336 | | 331 | 4.4% | 0.14 [0.03, 0.77] | |
| otal events | 0 | | 9 | | | | |
| Heterogeneity: Chi ² = 0.34, o Test for overall effect: Z = 2. | df = 2 (P = | 0.84); | $I^2 = 0\%$ | | | | |
| 5.1.5 For 6 weeks or till dis | | / | | | | | |
| 1.1.5 For 6 weeks or till dis Hariharan 2016 | scnarge 3 | 93 | 3 | 103 | 1.2% | 1.11 [0.23, 5.35] | |
| Rov 2014 | 2 | 56 | 2 | 56 | 0.8% | 1.00 [0.15, 6.85] | |
| iaengtawesin 2014 | 1 | 31 | 1 | 29 | 0.4% | 0.94 [0.06, 14.27] | |
| ewari 2015 | ō | 123 | ō | 121 | | Not estimable | |
| iubtotal (95% CI) | | 303 | | 309 | 2.5% | 1.04 [0.34, 3.17] | - |
| | | | | | | | |
| otal events Heterogeneity: Chi² = 0.01, o Test for overall effect: Z = 0. | 6 df = 2 (P = .07 (P = 0. | 0.99); 94) | $I^2 = 0\%$ | | | | |
| Heterogeneity: $Chi^2 = 0.01$, of Test for overall effect: $Z = 0$. | df = 2 (P = .07 (P = 0. | 0.99); 94) | | | | | |
| Heterogeneity: Chi ² = 0.01, of Test for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis | df = 2 (P = .07 (P = 0. scharge | 94) | I ² = 0% | 100 | 7.6V | 0.11 [0.02 0.47] | |
| Heterogeneity: $Chi^2 = 0.01$, of est for overall effect: $Z = 0$. 5.1.6 For 8 weeks or till displication of the contraction | df = 2 (P = .07 (P = 0. | 0.99); 94) 100 100 | | 100 100 | 7.6% 7.6 % | 0.11 [0.03, 0.47] 0.11 [0.03, 0.47] | _ |
| deterogeneity: Chi ² = 0.01, of cest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 billi 2015 bibtotal (95% CI) | df = 2 (P = 0.07 (P = 0.05) | 94) | I ² = 0% | | | 0.11 [0.03, 0.47] 0.11 [0.03, 0.47] | - |
| leterogeneity: Chi ² = 0.01, c Test for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 subtotal (95% CI) Total events leterogeneity: Not applicable | df = 2 (P = .07 (P = 0. scharge 2 | 94) 100 100 | I ² = 0% | | | 0.11 [0.03, 0.47] 0.11 [0.03, 0.47] | - |
| leterogeneity: Chi ² = 0.01, c Test for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 subtotal (95% CI) Total events leterogeneity: Not applicable Test for overall effect: Z = 3. | df = 2 (P = .07 (P = 0. scharge 2 | 94) 100 100 | I ² = 0% | | | 0.11 [0.03, 0.47] 0.11 [0.03, 0.47] | - |
| deterogeneity: Chi ² = 0.01, of est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 bibtotal (95% CI) Total events deterogeneity: Not applicable est for overall effect: Z = 3. 5.1.7 Till discharge | df = 2 (P = 0.07 (P = 0.07 (P = 0.000 | 100 100 003) | 18 18 | 100 | 7.6% | 0.11 [0.03, 0.47] | |
| eterogeneity: Chi ² = 0.01, c Fest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 bibtotal (95% Cl) fotal events eterogeneity: Not applicable Fest for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 | df = 2 (P = 0.07 (P = 0.07 (P = 0.000 | 100 100 003) | 18 18 | 1 00 | 7.6% 2.5% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] | |
| eleterogeneity: Chi ² = 0.01, c rest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis pilli 2015 ubtotal (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 cui 2019 | df = 2 (P = 0.07 (P = 0.07 (P = 0.000 (P = 0 | 100 100 003) | 18 18 18 | 100 59 48 | 7.6% 2.5% 2.0% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] | |
| eleterogeneity: Chi ² = 0.01, c Fest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 bibtotal (95% Ch) Total events eleterogeneity: Not applicabli- rest for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 bi 2019 asshti 2014 | df = 2 (P = 0.07 (P = 0.07 (P = 0.000)) scharge | 100 100 003) 60 45 69 | 18 18 18 | 59 48 67 | 7.6% 2.5% 2.0% 0.4% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] | |
| eleterogeneity: Chi ² = 0.01, c rest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 total events: teterogeneity: Not applicable rest for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 Lui 2019 Dashti 2014 Demirel 2013 | df = 2 (P = 0.07 (P = 0.00 | 100 100 003) | 18 18 18 | 100 59 48 | 7.6% 2.5% 2.0% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] | |
| eleterogeneity: Chi ² = 0.01, c Fest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 bibtotal (95% Ch) Total events eleterogeneity: Not applicabli- rest for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 bi 2019 asshti 2014 | df = 2 (P = 0.07 (P = 0.07 (P = 0.000)) scharge | 100 100 100 003) 60 45 69 135 | 18 18 18 7 | 59 48 67 136 | 2.5% 2.0% 0.4% 2.9% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] | |
| eleterogeneity: Chi² = 0.01, c rest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015. billi 2015. fotal events: teterogeneity: Not applicable rest for overall effect: Z = 3. 5.1.7 Till discharge chowdhury 2016 buil 2019 pashti 2014 permirel 2013 saban 2019 nocel 2014 | df = 2 (P = 0.07 | 100 100 100 003) 60 45 69 135 47 | 18 18 18 6 5 1 7 | 59 48 67 136 47 | 2.5% 2.0% 0.4% 2.9% 1.5% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] 0.80 [0.32, 1.99] | |
| eleterogeneity: Chi² = 0.01, crest for overall effect: Z = 0.5.1.6 For 8 weeks or till dis illili 2015 (biblio 2015) (biblio 2015) (biblio 2015) (biblio 2016) (biblio 201 | df = 2 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 | 18 18 18 6 5 1 7 3 | 59 48 67 136 47 200 | 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] | |
| eleterogeneity: Chi² = 0.01, crest for overall effect: Z = 0.5.1.6 For 8 weeks or till dis illil 2015 (2016) (2016 | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 94) 100 100 003) 60 45 69 135 47 200 73 372 91 | 18 18 18 6 5 1 7 3 10 8 15 | 59 48 67 136 47 200 73 378 95 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.92] | |
| eleterogeneity: Chi² = 0.01, crest for overall effect: Z = 0.5.1.6 For 8 weeks or till dis illil 2015 (2016) (2016 | df = 2 (P = 0.07 (P = 0.00 | 94) 100 100 003) 60 45 69 135 47 200 73 372 | 18 18 18 6 5 1 7 3 10 8 15 | 59 48 67 136 47 200 73 378 | 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 4.2% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] | |
| eleterogeneity: Chi² = 0.01, crest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 6.1.3 For 8 weeks or till dis 6.1.4 For 8 weeks or till dis 6.1.5 For 8 weeks or till dis | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 94) 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 | 18 18 18 6 5 1 7 3 10 8 15 10 7 | 59 48 67 136 47 200 73 378 95 111 104 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 4.2% 2.9% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.92] 0.61 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| eleterogeneity: Chi² = 0.01, c rest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 billi 2015 billi 2015 control of the control of the control control of the control control of the control con | df = 2 (P = 0.07 | 94) 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 | 18 18 18 6 5 1 7 3 10 8 15 15 | 59 48 67 136 47 200 73 378 95 111 104 49 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 4.2% 4.2% 2.5% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.50] 0.80 [0.32, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.16 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 6.1.2 For 8 weeks or till dis | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 94) 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 | 18 18 18 6 5 1 7 3 10 8 15 10 7 6 | 59 48 67 136 47 200 73 378 95 111 104 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 4.2% 2.9% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.92] 0.61 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| eleterogeneity: Chi ² = 0.01, c fest for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis billi 2015 bibtotal (95% Ch) fotal events feterogeneity: Not applicable feterogeneity: Not applicable fest for overall effect: Z = 3. 5.1.7 Till discharge Chowdhury 2016 billi 2019 chashti 2014 bemirel 2013 ckaban 2019 briel 2014 behman 2018 bojas 2012 amanta 2009 ari 2011 erce 2013 hashidar 2017 bibtotal (95% Ch) fotal events | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 | 18 18 18 6 5 1 7 3 10 0 8 15 15 10 7 6 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 4.2% 4.2% 2.5% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.50] 0.80 [0.32, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.16 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| leterogeneity. Chi² = 0.01, cest for overall effect: Z = 0. 3.1.6 For 8 weeks or till disolilli 2015 ubtotal (95% CI) otal events icterogeneity: Not applicable sets for overall effect: Z = 3. 3.1.7 Till discharge chowdhury 2016 tui 2019 basht 2014 bemirel 2013 aban 2019 breel 2014 behman 2018 tojas 2012 amanta 2009 ari 2011 erce 2013 hashidhar 2017 ubtotal (95% CI) otal events feterogeneity: Chi² = 9.11, cest for overall effect: Z = 0.11, cest for overall effect: Z = 0.01, cest for overall effect: Z = 0.11, cest for overall effect: Z = 0.11, cest for overall effect: Z = 0.11, cest for overall effect: Z = 0.01, cest for | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 = 0.61 | 18 18 18 6 5 1 7 3 10 0 8 15 15 10 7 6 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 4.2% 4.2% 2.5% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.50] 0.80 [0.32, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.16 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| leterogeneity: Chi² = 0.01, cest for overall effect: Z = 0. 1.1.6 For 8 weeks or till diswill 2015 withotal (95% CI) otal events otal events leterogeneity: Not applicable sets for overall effect: Z = 3. 1.1.7 Till discharge howdhury 2016 win 2019 sasht 2014 bemirel 2013 aban 2019 shoel 2014 ehman 2018 ojaan tata 2009 ari 2011 erce 2013 hashidhar 2017 ubtotal (95% CI) otal events leterogeneity: Chi² = 9.11, cest for overall effect: Z = 3. | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 = 0.61 | 18 18 18 6 5 1 7 3 10 0 8 15 15 10 7 6 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 4.2% 4.2% 2.5% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.50] 0.80 [0.32, 2.50] 0.14 [0.01, 2.69] 0.25 [0.05, 1.14] 0.16 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] | |
| ideterogeneity: Chi² = 0.01, ciest for overall effect: Z = 0. 2.1.6 For 8 weeks or till dis 3.1.1 For 8 weeks or till dis 3.1.1 For 8 weeks or till dis 3.1.1 For 10 F | df = 2 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 = 0.61 | 18 18 18 6 5 1 7 3 10 0 7 6 9 9 3 9 3 10 10 11 11 11 11 11 11 11 11 11 11 11 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 | 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 3.4% 6.3% 4.2% 2.9% 3.5% 3.9.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.27] 0.61 [0.23, 1.61] 1.00 [0.36, 2.75] 0.33 [0.07, 1.57] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 5.1.3 For 8 weeks or till dis 5.1.4 Till discharge 6.5.1 Till discharge 6.5.1 Till discharge 6.5.1 Till discharge 6.5.2 For 9 weeks 6.5.3 For 9 weeks 6.5.3 For 9 weeks 6.5.4 Till discharge 6.5.4 Till discharge 6.5.5 For 9 weeks 6.5.5 For 9 weeks 6.5.6 For 9 weeks 6.5.7 Till discharge 6.5.6 For 9 weeks 6.5.7 Till discharge 6.5.7 Till dis | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 21 110 104 49 1355 = 0.61 | 18 18 18 6 5 1 7 7 3 3 100 8 8 15 5 15 10 7 7 6 6 93 93 93 12 | 599 488 675 675 675 675 675 675 675 675 675 675 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 3.4% 6.2% 4.29% 2.5% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.50] 0.80 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.15 [0.05, 1.14] 0.16 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] 0.36 [0.75] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 6.1.2 For 8 weeks or till dis | df = 2 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 = 0.61 0003) | 18 18 18 6 5 1 7 3 10 0 7 6 9 9 3 9 3 10 10 11 11 11 11 11 11 11 11 11 11 11 | 59 48 67 1366 47 200 73 378 95 111 104 49 1367 | 2.5% 2.0% 0.4% 2.9% 1.5% 4.2% 3.4% 6.3% 4.2% 2.9% 3.5% 3.9.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.27] 0.61 [0.23, 1.61] 1.00 [0.36, 2.75] 0.33 [0.07, 1.57] | |
| eleterogeneity: Chi² = 0.01, crest for overall effect: Z = 0.5.1.6 For 8 weeks or till dis illili 2015 subtotal (95% Cl) cital events to total events teterogeneity: Not applicable est for overall effect: Z = 3.5.1.7 Till discharge chowdhury 2016 illililililililililililililililililili | df = 2 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 372 201 110 104 49 1355 = 0.61 0003) | 18 18 18 6 5 1 7 7 3 3 10 10 8 8 15 15 10 7 6 6 93 37 12 37 37 37 12 37 37 37 37 37 37 37 37 37 37 37 37 37 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 1.5% 6.3% 4.2% 4.2% 2.5% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.092] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.27] 0.31 [0.23, 1.61] 1.00 [0.36, 2.75] 0.33 [0.07, 1.57] 0.54 [0.38, 0.75] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis jilli 2013; bubtotal (95% CI) total events leterogeneity: Not applicable 'est for overall effect: Z = 3. 5.1.7 Till discharge Chowdhury 2016 'Lui 2019 Jashti 2014 Joemirel 2013 (aban 2019 Joed! 2014 Joedle 2014 Joedle 2014 Joedle 2014 Joedle 2014 Joedle 2015 Joedle 2014 Joedle 2015 Joedle 2016 Joedle 2017 Joedle 2017 Joedle 2018 Joedle 2018 Joedle 2018 Joedle 2019 J | df = 2 (P = 0.07 (P = 0.00 | 100 100 003) 60 45 69 135 47 200 73 377 291 110 104 49 1355 = 0.61 0003) | 18 18 18 6 6 5 1 7 3 3 10 0 8 15 10 7 6 6 2 3 7 10 12 2 3 7 10 10 | 599 488 677 1366 477 2000 733 3788 95 111 1044 49 1367 6 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 2.9% 2.55% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.15 [0.05, 1.14] 0.15 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] 0.54 [0.38, 0.75] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 5.1.3 For 8 weeks or till dis 5.1.4 For 8 weeks or till dis 6.1.5 For 8 weeks or till dis 6.1.5 For 8 weeks or till dis 6.1.6 For 8 weeks or till dis 6.1.6 For 8 weeks or till dis 6.1.6 For 9 weeks 6.1.6 For 9 weeks 6.1.6 For 9 weeks 6.1.7 For 9 weeks 6.1.8 For 9 weeks 6 | df = 2 (P = 0.07 (P = 0.3 ccharge 2 2 e 0.00 (P = 0.3 6 0.00 (| 100 100 003) 60 45 69 135 47 200 73 372 91 110 104 49 1355 = 0.61 0003) | 18 18 18 6 5 1 7 3 3 10 0 8 15 10 7 6 6 9 3 7 10 12 3 7 10 12 1 | 599 488 67 1366 477 200 73 3788 95 111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 4.2% 6.3% 6.2% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 2.092] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.27] 0.31 [0.23, 1.61] 1.00 [0.36, 2.75] 0.33 [0.07, 1.57] 0.54 [0.38, 0.75] | |
| eleterogeneity: Chi² = 0.01, (*est for overall effect: Z = 0.5.1.6 For 8 weeks or till dis Jilli 2015. Unitational (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.7 Till discharge (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 tussain 2016 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 tussain 2016 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or unclear ernández-Carrocera 2014 (*est for overall effect: Z = 3.5.1.8 Not stated or uncle | df = 2 (P - P - O) (P = 0) (P | 94) 100 100 003) 60 45 69 135 47 73 372 91 110 104 49 1355 = 0.61 0003) 75 150 37 250 30 542 | 18 18 18 18 6 5 5 1 7 7 3 10 8 8 15 15 10 7 6 6 93 37 10 12 1 1 7 7 2 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 6 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 2.9% 2.55% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.15 [0.05, 1.14] 0.15 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] 0.54 [0.38, 0.75] | |
| leterogeneity. Chi² = 0.01, cest for overall effect: Z = 0. 3.1.6 For 8 weeks or till disolilli 2015 3.1.1.6 For 8 weeks or till disolilli 2015 3.1.1.6 For 8 weeks or till disolilli 2015 3.1.7 Till discharge 3.1.7 Till discharge 3.1.7 Till discharge 3.1.8 T | $ \begin{aligned} & \text{df} = 2 \ (P - \alpha) \\ & \text{or} \ (P = 0, 0) \\ & \text{or} \ (P = 0, 0) \\ & \text{e} \end{aligned} $ | 94) 100 100 003) 60 45 69 135 47 200 73 377 210 104 49 1355 = 0.61 0003) 75 150 30 542 € 0.22); | 18 18 18 6 5 1 7 3 3 10 0 8 15 15 10 7 6 6 12 37 10 12 1 7 10 12 17 2 31 9 31 9 | 59 48 67 136 47 200 73 378 95 111 104 49 1367 6 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 2.9% 2.55% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.15 [0.05, 1.14] 0.15 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] 0.54 [0.38, 0.75] | |
| leterogeneity: Chi² = 0.01, cest for overall effect: Z = 0. 1.1.6 For 8 weeks or till dis will 2015 uibtotal (95% Ct) otal events leterogeneity: Not applicable est for overall effect: Z = 3. 1.1.7 Till discharge (howdhury 2016 to 10 to 1 | $\begin{aligned} & \text{df} = 2 \ (P - \alpha) \\ & \text{or} \ (P = 0, 0) \\ & \text{or} \ (P = 0, 0) \\ & \text{e} \end{aligned}$ | 94) 100 100 003) 60 45 69 135 47 200 73 377 210 104 49 1355 = 0.61 0003) 75 150 30 542 € 0.22); | 18 18 18 6 5 1 7 3 3 10 0 8 15 15 10 7 6 6 12 37 10 12 1 7 10 12 17 2 31 9 31 9 | 59 48 67 136 47 200 73 378 9111 104 49 1367 | 7.6% 2.5% 2.0% 0.4% 2.9% 4.2% 3.4% 6.3% 6.2% 2.9% 2.55% 39.0% | 0.16 [0.02, 1.32] 0.21 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.14 [0.01, 2.50] 0.14 [0.01, 2.50] 0.15 [0.05, 1.14] 0.15 [0.27, 1.38] 0.35 [0.13, 0.92] 0.16 [0.23, 1.61] 1.00 [0.36, 2.75] 0.54 [0.38, 0.75] | |
| eleterogeneity: Chi² = 0.01, c'est for overall effect: Z = 0. 5.1.6 For 8 weeks or till dis 5.1.6 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.1 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 5.1.2 For 8 weeks or till dis 6.1.2 For 8 weeks or till dis 6.1.3 For 8 weeks or till dis 6.1.4 For 8 weeks or till dis 6.1.5 For 8 weeks or till dis 6.1.5 For 8 weeks or till dis 6.1.5 For 9 weeks 6.1.5 Fo | $ \begin{aligned} & \text{df} = 2 \ (P - \alpha) \\ & \text{or} \ (P = 0, 0) \\ & \text{or} \ (P = 0, 0) \\ & \text{e} \end{aligned} $ | 94) 100 100 003) 60 45 69 135 47 200 1100 1355 = 0.61 0003) 75 150 30 542 0.22); 000001) | $ ^2 = 0\%$ 18 18 6 5 1 7 7 3 10 7 6 93 10 12 37 10 12 17 10 12 17 10 12 17 10 12 23 7 23 23 23 233 | 599 488 667 1366 477 2000 73 3788 755 1111 1044 499 1367 66 3015 | 7.6% 2.5% 2.0% 2.9% 1.5% 4.2% 3.4% 6.2% 4.28 3.99.0% 5.0% 3.0.4% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.19 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.25] 0.35 [0.13, 0.25] 0.36 [0.13, 1.61] 1.00 [0.36, 7.57] 0.34 [0.38, 0.75] 0.50 [0.20, 1.26] 0.19 [0.09, 0.41] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.58 [0.20, 1.26] 0.17 [0.04, 0.74] 1.00 [0.07, 15.26] 0.30 [0.19, 0.48] | |
| leterogeneity. Chi² = 0.01, cest for overall effect: Z = 0. 3.1.6 For 8 weeks or till dis 3.1.2 Silli 2015 Jet 10 Silli 2015 Jet 201 | df = 2 (P - Q) $ df = 2 (P - Q) $ $ e = 0.00 (P = 0) $ $ e = 0.00 ($ | 94) 100 100 003) 60 45 69 135 47 200 73 377 291 110 104 49 1355 = 0.61 0003) 75 150 30 37 250 30 250 3114 P = 0.3 | $ ^2 = 0\%$ 18 18 6 6 5 17 7 3 10 0 7 6 93 10 12 37 10 12 12 23 73 10 12 23 73 10 12 23 73 10 12 12 23 73 10 12 12 12 12 12 12 13 13 14 15 15 15 16 17 18 18 18 18 18 18 18 18 18 | 599 488 667 1366 477 2000 73 3788 755 1111 1044 499 1367 66 3015 | 7.6% 2.5% 2.0% 2.9% 1.5% 4.2% 3.4% 6.2% 4.28 3.99.0% 5.0% 3.0.4% | 0.11 [0.03, 0.47] 0.16 [0.02, 1.32] 0.19 [0.03, 1.76] 1.94 [0.18, 20.92] 0.86 [0.30, 2.50] 0.80 [0.32, 1.99] 0.25 [0.05, 1.14] 0.61 [0.27, 1.38] 0.35 [0.13, 0.25] 0.35 [0.13, 0.25] 0.36 [0.13, 1.61] 1.00 [0.36, 7.57] 0.34 [0.38, 0.75] 0.50 [0.20, 1.26] 0.19 [0.09, 0.41] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.57 [0.23, 1.40] 0.58 [0.20, 1.26] 0.17 [0.04, 0.74] 1.00 [0.07, 15.26] 0.30 [0.19, 0.48] | • • • • • • • • • • • • • • • • • • • |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause neonatal mortality

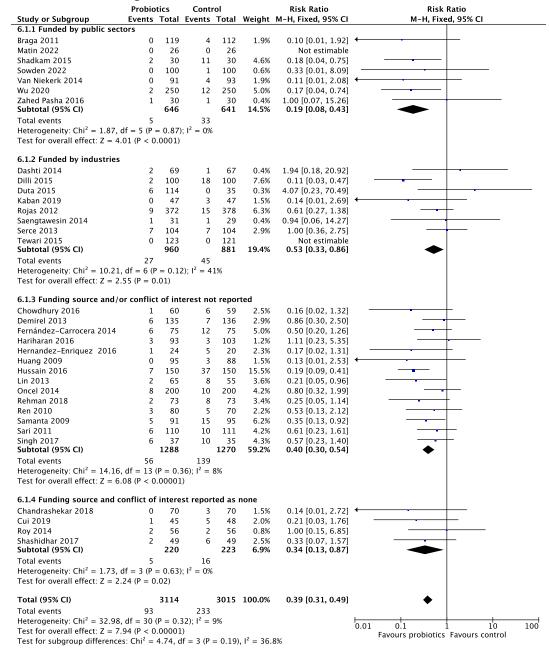
| | Probio | | Conti | | | Risk Ratio | Risk Ratio |
|---|------------------------|-------------------|------------------------------|-------------------|----------------|---|------------------------------------|
| Study or Subgroup 5.2.1 For 1 week | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not ap | plicable | | | | | | |
| 5.2.2 For 10-14 days | | | | | | | |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 2.0% | 0.25 [0.03, 2.18] | |
| Duta 2015 | 8 2 | 114 24 | 2 | 35 20 | 1.6% | 1.23 [0.27, 5.52] | |
| Hernandez-Enriquez 2016 Shadkam 2015 | 1 | 30 | 2 | 30 | 0.3% 1.0% | 4.20 [0.21, 82.72] 0.50 [0.05, 5.22] | |
| Subtotal (95% CI) | | 238 | | 155 | 4.9% | 0.84 [0.33, 2.12] | * |
| Total events | 12 | | 8 | | | | |
| Heterogeneity: Chi ² = 2.76, d Test for overall effect: Z = 0. | IT = 3 (P 37 (P = 0 | = 0.43).71) |); 1" = 0% | | | | |
| 5.2.3 For 3 weeks | | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not ap | plicable | | | | | | |
| 5.2.4 For 4 weeks or till disc | charge | | | | | | |
| Braga 2011 | 26 | 119 | 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | + |
| Li 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | · |
| Matin 2022 Sinha 2015 | 0 | 26 668 | 0 | 26 672 | 1.0% | Not estimable | |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.50 [0.05, 5.53] 0.33 [0.01, 8.09] | |
| Van Niekerk 2014 | 5 | 91 | 6 | 93 | 3.0% | 0.85 [0.27, 2.69] | |
| Subtotal (95% CI) | | 1020 | | 1017 | 19.9% | 0.83 [0.54, 1.27] | ◆ |
| Total events | 32 | | 37 | | | | |
| Heterogeneity: Chi ² = 1.04, d Test for overall effect: Z = 0.3 | | |); I ⁻ = 0% | | | | |
| 5.2.5 For 6 weeks or till disc | charge | | | | | | |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Roy 2014 | 7 | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | | Not estimable | |
| Tewari 2015 Subtotal (95% CI) | 12 | 123 303 | 14 | 121 309 | 7.2% 13.7% | 0.84 [0.41, 1.75] 0.86 [0.51, 1.46] | |
| Total events | 23 | 303 | 27 | 303 | 13.770 | 0.00 [0.51, 1.40] | T |
| Heterogeneity: Chi ² = 0.01, d | | = 1.00 | | | | | |
| Test for overall effect: $Z = 0$. | 56 (P = 0 |).58) | | | | | |
| 5.2.6 For 8 weeks or till dise | | | | | | | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Subtotal (95% CI) Total events | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Heterogeneity: Not applicable | | | 12 | | | | |
| Test for overall effect: $Z = 2.2$ | | 0.03) | | | | | |
| 5.2.7 Till discharge | | | | | | | |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | |
| Demirel 2013 Kaban 2019 | 5 1 | 135 47 | 5 4 | 136 47 | 2.5% | 1.01 [0.30, 3.40] | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.2% | 0.25 [0.03, 2.15] 0.75 [0.40, 1.42] | · |
| Rehman 2018 | 4 | 73 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | - |
| Samanta 2009 | 4 | 91 | 14 | 95 | 7.0% | 0.30 [0.10, 0.87] | |
| Sari 2011 Serce 2013 | 3 5 | 110 104 | 3 | 111 104 | 1.5% | 1.01 [0.21, 4.89] 1.25 [0.35, 4.52] | |
| Shashidhar 2017 | 1 | 49 | 3 | 49 | 1.5% | 0.33 [0.04, 3.09] | |
| Subtotal (95% CI) | | 1310 | _ | 1319 | 49.9% | 0.75 [0.56, 1.00] | ◆ |
| Total events | 73 | | 98 | | | | |
| Heterogeneity: Chi ² = 8.03, d Test for overall effect: Z = 1.9 | | | 3); I ² = 0 | % | | | |
| 5.2.8 Not stated or unclear | | | | | | | |
| Fernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.6% | 0.95 [0.20, 4.38] | |
| Wu 2020 | 0 | 250 | 0 | 250 | | Not estimable | |
| Zahed Pasha 2016 Subtotal (95% CI) | 2 | 30 392 | 0 | 30 390 | 0.3% 5.4% | 5.00 [0.25, 99.95] | |
| Total events | 6 | 392 | 10 | 590 | 5.4% | 0.61 [0.23, 1.58] | |
| Heterogeneity: $Chi^2 = 4.10$, d | If = 2 (P | | | % | | | |
| Test for overall effect: Z = 1.0 | 02 (P = 0 |).31) | | | | | |
| Total (95% CI) | | 3363 | | 3290 | 100.0% | 0.75 [0.61, 0.92] | ◆ |
| Total events Heterogeneity: Chi ² = 19.62, | 149 df = 26 | (P = 0 | 192 81): I ² = | N% | | | |
| Test for overall effect: Z = 2.3 | | | O1), I = | U/II | | | 0.01 0.1 1 10 100 |
| Test for subgroup differences | | | df = 5 (P | = 0.58) |), $I^2 = 0\%$ | | Favours probiotics Favours control |
| | | | | | | | |

Outcome: *Invasive infection*

| Study or Subgroup | Probio Events | | Conti Events | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|--|------------------|-------------------|---------------------|-------------------|---------------|--|----------------------------------|
| 5.3.1 For 1 week Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Fotal events | 0 | U | 0 | U | | Not estimable | |
| leterogeneity: Not applicable | | | Ü | | | | |
| est for overall effect: Not ap | | | | | | | |
| i.3.2 For 10-14 days | | | | | | | |
| Chandrashekar 2018 | 15 | 70 | 13 | 70 | 2.8% | 1.15 [0.59, 2.24] | |
| Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | 5.00 [0.66, 38.15] | + |
| hadkam 2015 | 0 | 30 | 0 | 30 | 2 401 | Not estimable | _ |
| Subtotal (95% CI) | | 124 | | 120 | 3.1% | 1.45 [0.78, 2.70] | — |
| otal events Heterogeneity: Chi² = 1.88, c | 21 | 0.17) | . 12 47 | 0/ | | | |
| Fest for overall effect: $Z = 1$. | | | ,1 = 47 | 70 | | | |
| 5.3.3 For 3 weeks | | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not ap | plicable | | | | | | |
| 5.3.4 For 4 weeks or till dis | | | | | | | |
| raga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | |
| Matin 2022 Inha 2015 | 0 84 | 26 668 | 3 107 | 26 672 | 0.8% | 0.14 [0.01, 2.63] | |
| Jan Niekerk 2014 | 84 15 | 91 | 107 | 93 | 23.1% | 0.79 [0.61, 1.03] 1.53 [0.73, 3.23] | <u> </u> |
| (u 2016 | 4 | 65 | 6 | 60 | 1.4% | 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) | , | 969 | 3 | 963 | 36.8% | 0.84 [0.69, 1.03] | ♦ |
| Total events | 143 | | 168 | | | | |
| Heterogeneity: $Chi^2 = 4.51$, of Fest for overall effect: $Z = 1$. | | | $ I^2 = 11$ | % | | | |
| 5.3.5 For 6 weeks or till dis | | | | | | | |
| Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | 0.62 [0.29, 1.34] | + |
| Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | 0.72 [0.30, 1.72] | |
| Subtotal (95% CI) | | 303 | | 300 | 15.1% | 0.72 [0.55, 0.95] | • |
| Total events | 50 | 0.04 | 70 | | | | |
| Heterogeneity: Chi² = 0.41, o Test for overall effect: Z = 2.: | | | ; 1 = 0% | | | | |
| 5.3.6 For 8 weeks or till dis | charge | | | | | | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Subtotal (95% CI) | | 100 | | 100 | 2.8% | 0.62 [0.27, 1.42] | → |
| Total events | 8 | | 13 | | | | |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.: | | .26) | | | | | |
| 5.3.7 Till discharge | | | | | | | |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | + |
| Outa 2015 | 10 | 114 | 6 | 35 | 2.0% | 0.51 [0.20, 1.31] | |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | |
| Oncel 2014 Samanta 2009 | 13 13 | 200 91 | 25 28 | 200 95 | 5.4% 5.9% | 0.52 [0.27, 0.99] 0.48 [0.27, 0.88] | |
| Sari 2011 | 29 | 110 | 28 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | <u></u> |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | -+ |
| Shashidhar 2017 | 6 | 49 | 7 | 49 | 1.5% | 0.86 [0.31, 2.37] | |
| Subtotal (95% CI) Fotal events | 113 | 895 | 145 | 825 | 31.9% | 0.74 [0.59, 0.92] | • |
| Heterogeneity: Chi ² = 8.49, d | If = 8 (P | | | | | | |
| Test for overall effect: Z = 2.0 | อช (P = 0 | .007) | | | | | |
| 5.3.8 Not stated or unclear | | | | | 0 ==: | 0.0510 = 2.55 | |
| Fernández–Carrocera 2014 Vu 2020 | 42 | 75 250 | 44 4 | 75 250 | 9.5% 0.9% | 0.95 [0.72, 1.26] | |
| Nu 2020 Subtotal (95% CI) | 3 | 250 325 | 4 | 250 325 | 0.9% 10.4% | 0.75 [0.17, 3.32] 0.94 [0.71, 1.24] | |
| Fotal events | 45 | 3.3 | 48 | 323 | 10.170 | 5.54 [0.7 1, 1.24] | T |
| Heterogeneity: Chi² = 0.10, c Test for overall effect: Z = 0.4 | If = 1 (P | | | | | | |
| Fotal (95% CI) | , - | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | • |
| Total events | 380 | | 458 | | | ,, | • |
| i otai events | | | | | | | |
| rotal events Heterogeneity: Chi² = 20.67, | | (P = 0.5) | $(54); I^2 = (54);$ | 0% | | | 0.01 0.1 1 10 |

Comparison: Probiotics versus control in preterm newborns by funding source

Outcome: Necrotizing enterocolitis



| | Probio | tics | Contr | ol | | Risk Ratio | Risk Ratio |
|--|--|---|--|---|--|---|--------------------|
| tudy or Subgroup | | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 5.2.1 Funded by public sec | tors | | | | | | |
| raga 2011 | 26 | 119 | 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | - |
| 1atin 2022 | 0 | 26 | 0 | 26 | | Not estimable | |
| hadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | |
| owden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.33 [0.01, 8.09] | · · · |
| an Niekerk 2014 | 5 | 91 | 6 | 93 | 3.0% | 0.85 [0.27, 2.69] | |
| Vu 2020 | 0 | 250 | 0 | 250 | | Not estimable | |
| ahed Pasha 2016 | 2 | 30 | 0 | 30 | 0.3% | 5.00 [0.25, 99.95] | - |
| ubtotal (95% CI) | | 646 | | 641 | 19.3% | 0.91 [0.60, 1.38] | • |
| otal events | 34 | | 36 | | | | |
| Heterogeneity: Chi ² = 1.89, eest for overall effect: Z = 0. | | | $I^2 = 0\%$ | | | | |
| i.2.2 Funded by industries | | | | | | | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | + |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Outa 2015 | 8 | 114 | 2 | 35 | 1.6% | 1.23 [0.27, 5.52] | - - |
| aban 2019 | 1 | 47 | 4 | 47 | 2.0% | 0.25 [0.03, 2.15] | • |
| lojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | + |
| aengtawesin 2014 | 0 | 31 | 0 | 29 | | Not estimable | |
| erce 2013 | 5 | 104 | 4 | 104 | 2.0% | 1.25 [0.35, 4.52] | - - |
| inha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | |
| ewari 2015 | 12 | 123 | 14 | 121 | 7.2% | 0.84 [0.41, 1.75] | |
| ubtotal (95% CI) | | 1628 | | 1553 | 36.3% | 0.78 [0.56, 1.10] | • |
| otal events | 60 | | 70 | | | | |
| 5.2.3 Funding source and/o | | | | - | | | |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.5% | 1.01 [0.30, 3.40] | |
| ernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 3.6% | 0.14 [0.02, 1.13] | - |
| lariharan 2016 | 4 | 93 24 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Hernandez-Enriquez 2016 | 2 | | | 20 | 0.3% | | |
| | • | | 0 | | | 4.20 [0.21, 82.72] | |
| i 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | <u> </u> |
| Oncel 2014 | 15 | 16 200 | 1 20 | 14 200 | 0.8% 10.2% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] | |
| Oncel 2014 Lehman 2018 | 15 4 | 16 200 73 | 1 20 6 | 14 200 73 | 0.8% 10.2% 3.1% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] | |
| Oncel 2014 Rehman 2018 amanta 2009 | 15 4 4 | 16 200 73 91 | 1 20 6 14 | 14 200 73 95 | 0.8% 10.2% 3.1% 7.0% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] | |
| Oncel 2014 Sehman 2018 amanta 2009 ari 2011 | 15 4 4 3 | 16 200 73 91 110 | 1 20 6 14 3 | 14 200 73 95 111 | 0.8% 10.2% 3.1% 7.0% 1.5% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] | |
| Oncel 2014 Sehman 2018 amanta 2009 ari 2011 ingh 2017 | 15 4 4 | 16 200 73 91 110 37 | 1 20 6 14 | 14 200 73 95 111 35 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] | |
| Oncel 2014 Sehman 2018 amanta 2009 ari 2011 | 15 4 4 3 | 16 200 73 91 110 | 1 20 6 14 3 | 14 200 73 95 111 | 0.8% 10.2% 3.1% 7.0% 1.5% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] | • |
| Oncel 2014 Lehman 2018 amanta 2009 ari 2011 ingh 2017 Lubtotal (95% CI) | 15 4 4 3 3 46 df = 10 (P | 16 200 73 91 110 37 914 | 1 20 6 14 3 3 | 14 200 73 95 111 35 921 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] | • |
| Oncel 2014 Lehman 2018 amanta 2009 ari 2011 Lingh 2017 Lubtotal (95% CI) Lotal events Leterogeneity: Chi ² = 7.28, i | 15 4 4 3 3 46 df = 10 (P .33 (P = 0 | 16 200 73 91 110 37 914 = 0.70 | 1 20 6 14 3 3 71); I ² = 09 | 14 200 73 95 111 35 921 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] | • |
| Oncel 2014 John 2018 John 2018 John 2019 John 2017 | 15 4 4 3 3 46 df = 10 (P .33 (P = 0 | 16 200 73 91 110 37 914 = 0.70 | 1 20 6 14 3 3 71); I ² = 09 | 14 200 73 95 111 35 921 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] | • |
| oncel 2014 John 2018 John 2018 John 2019 John 2017 John | 15 4 4 3 3 46 df = 10 (P .33 (P = 0 | 16 200 73 91 110 37 914 = 0.70 | 20 6 14 3 3 71 71 st report | 14 200 73 95 111 35 921 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] | • |
| oncel 2014 lehman 2018 amanta 2009 ari 2011 lingh 2017 lubtotal (95% CI) lotal events leterogeneity: Chi ² = 7.28, leter for overall effect: Z = 2. lotal chandrashekar 2018 | 15 4 4 3 3 3 46 df = 10 (P .33 (P = 0 | 16 200 73 91 110 37 914 = 0.70 .02) | 1 20 6 14 3 3 3 71 71 $1^2 = 0$ 5 st report 4 | 14 200 73 95 111 35 921 % | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] | • |
| chcel 2014 lehman 2018 amanta 2009 ari 2011 ingh 2017 ubtotal (95% CI) lotal events leterogeneity: Chi² = 7.28, if est for overall effect: Z = 2. 6.2.4 Funding source and chandrashekar 2018 loy 2014 | 15 4 4 3 3 46 df = 10 (P 33 (P = 0) | 16 200 73 91 110 37 914 = 0.70 .02) interes | 1 20 6 14 3 3 71 $ $ | 14 200 73 95 111 35 921 % | 0.8% 10.2% 3.1% 7.0% 1.5% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] 0.25 [0.03, 2.18] 0.88 [0.34, 2.25] | • |
| Oncel 2014 Lehman 2018 Lamanta 2009 Lari 2011 Lingh 2017 Lotal (95% CI) Lotal events Leterogeneity: Chi ² = 7.28, L | 15 4 4 3 3 46 df = 10 (P 33 (P = 0) | 16 200 73 91 110 37 914 2 = 0.70 .02) interes 70 56 49 | 1 20 6 14 3 3 71 $ $ | 14 200 73 95 111 35 921 % | 0.8% 10.2% 3.1% 7.0% 1.5% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] 0.25 [0.03, 2.18] 0.88 [0.34, 2.25] 0.33 [0.04, 3.09] | • |
| Oncel 2014 Lehman 2018 Lehman 2018 Lehman 2019 Lehman 2017 Lehman 2017 Lehman 2017 Lehman 2017 Lehman 2018 Leterogeneity: Chi² = 7.28, 1 Leterogeneity: Chi² | 15 4 4 3 3 3 46 df = 10 (P .33 (P = 0 onflict of 1 7 1 | 16 200 73 91 110 37 914 2 = 0.70 .02) interes 70 56 49 175 | 1 20 6 14 3 3 3 71 $I^2 = 0$ 5 st report 4 8 3 3 15 | 14 200 73 95 111 35 921 % | 0.8% 10.2% 3.1% 7.0% 1.5% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] 0.25 [0.03, 2.18] 0.88 [0.34, 2.25] 0.33 [0.04, 3.09] | • |
| check 2014 cehman 2018 amanta 2009 ari 2011 ingh 2017 ubtotal (95% CI) Total events leterogeneity: Chi² = 7.28, if the constant of the constant of the constant of the check of the constant o | 15 4 4 3 3 3 46 df = 10 (P .33 (P = 0 onflict of 1 7 1 | 16 200 73 91 110 37 914 2 = 0.70 .02) interes 70 56 49 175 | 1 20 6 14 3 3 3 71 $I^2 = 0$ 5 st report 4 8 3 3 15 | 14 200 73 95 111 35 921 % seed as 70 56 49 175 | 0.8% 10.2% 3.1% 7.0% 1.5% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] 0.25 [0.03, 2.18] 0.88 [0.34, 2.25] 0.33 [0.04, 3.09] | • |
| oncel 2014 tehman 2018 tehman 2018 tamanta 2009 ari 2011 ingh 2017 ubtotal (95% CI) otal events deterogeneity: Chi² = 7.28, test for overall effect: Z = 2. 6.2.4 Funding source and control of the con | 15 4 4 3 3 3 46 df = 10 (P .33 (P = 0 onflict of 1 7 1 | 16 200 73 91 110 37 914 = 0.70 .02) interes 70 56 49 175 = 0.47); | 1 20 6 14 3 3 3 71 $I^2 = 0$ 5 st report 4 8 3 3 15 | 14 200 73 95 111 35 921 % seed as 70 56 49 175 | 0.8% 10.2% 3.1% 7.0% 1.5% 1.6% 36.7% | 0.29 [0.01, 6.69] 0.75 [0.40, 1.42] 0.67 [0.20, 2.26] 0.30 [0.10, 0.87] 1.01 [0.21, 4.89] 0.95 [0.20, 4.38] 0.65 [0.46, 0.93] 0.25 [0.03, 2.18] 0.88 [0.34, 2.25] 0.33 [0.04, 3.09] 0.60 [0.27, 1.32] | • |

${\it Prevention \ and \ Treatment \ of \ Neonatal \ Infections \ in \ LMICs}$

Outcome: *Invasive infection*

| Study or Subgroup | Probio: | | Cont | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M–H, Fixed, 95% Cl |
|--|---------------|------------------|------------------|------------------|----------------------|--|--|
| 6.3.1 Funded by public sec | | 1 Otal | LVCIICS | i otal | Teignt | 11, 11xeu, 33/6 Cl | 11, 11, 11, 11, 11, 11, 11, 11, 11, 11, |
| Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | |
| Matin 2022 | 0 | 26 | 3 | 26 | 0.8% | 0.14 [0.01, 2.63] | - |
| Shadkam 2015 | 0 | 30 | 0 | 30 | 0.070 | Not estimable | |
| Van Niekerk 2014 | 15 | 91 | 10 | 93 | 2.1% | 1.53 [0.73, 3.23] | |
| Wu 2020 | 3 | 250 | 4 | 250 | 0.9% | 0.75 [0.17, 3.32] | |
| Subtotal (95% CI) | • | 516 | | 511 | 13.1% | 0.95 [0.70, 1.29] | * |
| Total events | 58 | | 59 | | | | |
| Heterogeneity: $Chi^2 = 3.41$, Test for overall effect: $Z = 0$. | | |); $I^2 = 12$ | % | | | |
| 6.3.2 Funded by industries | | | | | | | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 2.8% | 0.62 [0.27, 1.42] | |
| Duta 2015 | 10 | 114 | 6 | 35 | 2.0% | 0.51 [0.20, 1.31] | |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | |
| Sinha 2015 | 84 | 668 | 107 | 672 | 23.1% | 0.79 [0.61, 1.03] | |
| Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | 0.72 [0.30, 1.72] | • |
| Xu 2016 | 4 | 65 | 6 | 60 | 1.4% | 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) Total events | 136 | 1252 | 172 | 1159 | 38.0% | 0.74 [0.60, 0.92] | ◆ |
| Heterogeneity: $Chi^2 = 1.82$, Test for overall effect: $Z = 2$. | .78 ($P = 0$ | 005) | | | | | |
| 6.3.3 Funding source and/o | | | | • | | | |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Fernández-Carrocera 2014 | 42 | 75 | 44 | 75 | 9.5% | 0.95 [0.72, 1.26] | T |
| Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | 0.62 [0.29, 1.34] | <u> </u> |
| Hernandez-Enriquez 2016 Oncel 2014 | 6 13 | 24 200 | 1 25 | 20 200 | 0.2% 5.4% | 5.00 [0.66, 38.15] | |
| Samanta 2009 | 13 | 91 | 25 28 | 95 | 5.4% | 0.52 [0.27, 0.99] 0.48 [0.27, 0.88] | |
| Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | |
| Subtotal (95% CI) | 23 | 728 | 20 | 740 | 34.6% | 0.83 [0.68, 1.01] | • |
| Total events | 132 | | 161 | | | | Ť |
| Heterogeneity: $Chi^2 = 11.68$ | | = 0.0 | | 9% | | | |
| Test for overall effect: $Z = 1$ | .87 ($P = 0$ | 06) | | | | | |
| 6.3.4 Funding source and c | | | • | | | | |
| Chandrashekar 2018 | 15 | 70 | 13 | 70 | 2.8% | 1.15 [0.59, 2.24] | |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | - |
| Roy 2014 | 31 | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | • |
| Shashidhar 2017 Subtotal (95% CI) | 6 | 49 220 | 7 | 49 223 | 1.5% 14.3% | 0.86 [0.31, 2.37] 0.82 [0.63, 1.07] | • |
| Total events Heterogeneity: Chi² = 1.83, Test for overall effect: Z = 1. | | | 66); $I^2 = 0\%$ | i | | | |
| Total (95% CI) | | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | • |
| Total events | 380 | | 458 | | | | |
| Heterogeneity: Chi ² = 20.67 Test for overall effect: Z = 3. | .49 (P = 0.1) | 0005) | | | $I_{1}^{2} = 0\%$ | | 0.01 0.1 1 10 Favours probiotics Favours control |

Comparison: Probiotics versus control in preterm newborns by risk of bias

Outcome: Necrotizing enterocolitis

| Probio | tics | Contr | വ | | Risk Ratio | Risk Ratio |
|----------|---|--|-------------------------|------------------------|--|---|
| | | | | Weight | | M-H, Fixed, 95% CI |
| | | | | | | |
| 2 | 100 | 18 | 100 | 7.6% | 0.11 [0.03, 0.47] | |
| | | | | | | |
| - | | - | | 4 2% | | |
| | | | | | | |
| | | | | | | |
| | | | | 0.070 | | |
| | | | | 1 00/ | | |
| _ | 968 | | 974 | 20.7% | 0.44 [0.27, 0.72] | • |
| | | | | | | |
| | |); I ² = 469 | % | | | |
| | | | | | | |
| 0 | 119 | 4 | 112 | 1.9% | 0.10 [0.01, 1.92] | |
| 1 | 45 | 5 | 48 | 2.0% | 0.21 [0.03, 1.76] | · · |
| 2 | 69 | 1 | 67 | 0.4% | 1.94 [0.18, 20.92] | |
| 6 | 114 | 0 | 35 | | | - |
| 6 | 75 | 12 | 75 | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | - | | | | |
| - | | | | | | |
| 2 | | 12 | | | | |
| | 1213 | 100 | 1131 | 43.2/0 | 0.30 [0.23, 0.32] | ~ |
| | | | 30% | | | |
| | | _ | | . =0/ | 0.4.4.50.04.0.703 | |
| | | | | | | • |
| | | | | | | • |
| | | | | | | |
| | | | | | | |
| | | | | | | • |
| - | | | | | | |
| - | | | 47 | 1.5% | 0.14 [0.01, 2.69] | • |
| 2 | 150 | 9 | 150 | 3.8% | 0.22 [0.05, 1.01] | - |
| 2 | 73 | 8 | 73 | 3.4% | 0.25 [0.05, 1.14] | |
| 3 | 80 | 5 | 70 | 2.2% | 0.53 [0.13, 2.12] | |
| 1 | 31 | 1 | 29 | 0.4% | 0.94 [0.06, 14.27] | - |
| 5 | 91 | 15 | 95 | 6.2% | 0.35 [0.13, 0.92] | |
| 6 | 37 | 10 | 35 | 4.3% | 0.57 [0.23, 1.40] | |
| 1 | 30 | 1 | 30 | 0.4% | 1.00 [0.07, 15.26] | |
| | 1016 | | 1005 | 34.1% | 0.40 [0.27, 0.59] | ◆ |
| | | | % | | | |
| | 3199 | | 3110 | 100.0% | 0.39 [0.31, 0.49] | ◆ |
| 93 | | 234 | | | _ | · |
| | D – Ω | | Ω% | | | |
| ar = 300 | $_{i}r = v$. | 33), I = | J/0 | | | 0.01 0.1 1 10 |
| | 2 0 8 8 9 2 0 0 0 0 1 1 2 2 6 6 6 7 7 6 6 7 7 2 2 2 0 0 2 2 3 3 1 5 6 6 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | 2 100 0 26 8 200 9 372 2 56 0 123 0 91 968 21 If = 4 (P = 0.12) 26 (P = 0.001) 0 119 1 45 2 69 6 114 6 75 7 150 6 110 7 104 2 30 2 49 0 100 2 250 1215 41 df = 11 (P = 0. 59 (P < 0.00001) 0 70 1 60 6 135 3 93 1 24 0 47 2 150 2 73 3 80 1 24 0 47 2 150 2 73 3 80 1 31 5 91 6 37 1 30 1016 31 If = 13 (P = 0.7' 62 (P < 0.00001) | Events Total Events | Total Events Total | Events Total Events Total Weight | Events Total Events Total Weight M-H, Fixed, 95% CI 2 100 18 100 7.6% 0.11 [0.03, 0.47] 0 26 0 26 Not estimable 8 200 10 200 4.2% 0.80 [0.32, 1.99] 9 372 15 378 6.2% 0.61 [0.27, 1.38] 0 123 0 121 Not estimable 0 91 4 93 1.9% 0.11 [0.01, 2.08] 968 974 20.7% 0.44 [0.27, 0.72] 21 4 93 1.9% 0.11 [0.01, 2.08] 4ff = 4 (P = 0.12); I² = 46% 20 0.21 [0.03, 1.76] 0.26 (P = 0.001) 21 4 93 1.9% 0.10 [0.01, 1.92] 1 45 5 48 2.0% 0.21 [0.03, 1.76] 2 6 (P = 0.001) 1 10 0.33 [0.01, 2.0] 0.0 6 1 14 0 35 0.33 [0.01, 2.0] 0.0 0.01 [0.02, 1.26] |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause neonatal mortality

| 6. 1. 6.1 | Probio | | Conti | | | Risk Ratio | Risk Ratio |
|--|-------------|--------------------|------------------|-------------------|----------------------|--|--|
| Study or Subgroup | Events | Total | Events | Total | weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 9.2.1 Low | _ | | | | | | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 6.1% | 0.25 [0.07, 0.86] | |
| Matin 2022 | 0 | 26 | 0 | 26 | 40.00 | Not estimable | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 10.2% | 0.75 [0.40, 1.42] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 14.2% | 0.80 [0.47, 1.37] | |
| Roy 2014 | 7 | 56 | 8 | 56 | 4.1% | 0.88 [0.34, 2.25] | |
| Sinha 2015 | 1 | 668 | 2 | 672 | 1.0% | 0.50 [0.05, 5.53] | - |
| Tewari 2015 | 12 | 123 | 14 | 121 | 7.2% | 0.84 [0.41, 1.75] | |
| Van Niekerk 2014 Subtotal (95% CI) | 5 | 91 1636 | 6 | 93 1646 | 3.0% 46.0% | 0.85 [0.27, 2.69] 0.73 [0.53, 0.98] | |
| Total events | 65 | 1030 | 90 | 10.10 | 10.070 | 0.75 [0.55, 0.50] | ~ |
| Heterogeneity: Chi ² = 3.47, (| | 0.75 | | | | | |
| Test for overall effect: $Z = 2$. | | |), I = U% | | | | |
| | • | , | | | | | |
| 9.2.2 Unclear Braga 2011 | 26 | 110 | 27 | 112 | 1/1 20/ | 0.01 [0.56 1.45] | |
| • | | 119 | 27 | 112 | 14.2% | 0.91 [0.56, 1.45] | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 2.1% | 1.94 [0.61, 6.15] | |
| Duta 2015 | 8 | 114 75 | 2 7 | 35 75 | 1.6% | 1.23 [0.27, 5.52] | |
| Fernández-Carrocera 2014 | 1 | | | | 3.6% | 0.14 [0.02, 1.13] | <u> </u> |
| Sari 2011 | 3 | 110 | 3 | 111 | 1.5% | 1.01 [0.21, 4.89] | |
| Serce 2013 | 5 | 104 | 4 | 104 | 2.0% | 1.25 [0.35, 4.52] | |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 1.0% | 0.50 [0.05, 5.22] | |
| Shashidhar 2017 | 1 | 49 | 3 | 49 | 1.5% | 0.33 [0.04, 3.09] | <u></u> |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.8% | 0.33 [0.01, 8.09] | • |
| Wu 2020 Subtotal (95% CI) | 0 | 250 1020 | 0 | 250 933 | 28.4% | Not estimable 0.87 [0.61, 1.25] | • |
| Total events Heterogeneity: Chi² = 6.62, (Test for overall effect: Z = 0. | | | 53); $I^2 = 0\%$ | | | | |
| 9.2.3 High | | | | | | | |
| | | 70 | | 70 | 2.00/ | 0.25 [0.02.2.10] | |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 2.0% | 0.25 [0.03, 2.18] | <u> </u> |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 3.6% | 0.70 [0.24, 2.09] | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.5% | 1.01 [0.30, 3.40] | |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.4% | 0.89 [0.25, 3.20] | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.3% | 4.20 [0.21, 82.72] | |
| Kaban 2019 | 1 | 47 | 4 | 47 | 2.0% | 0.25 [0.03, 2.15] | <u> </u> |
| _i 2019 | 0 | 16 | 1 | 14 | 0.8% | 0.29 [0.01, 6.69] | • |
| Rehman 2018 | 4 | 73 | 6 | 73 | 3.1% | 0.67 [0.20, 2.26] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | | Not estimable | |
| Samanta 2009 | 4 | 91 | 14 | 95 | 7.0% | 0.30 [0.10, 0.87] | - |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.6% | 0.95 [0.20, 4.38] | |
| Zahed Pasha 2016 Subtotal (95% CI) | 2 | 30 707 | 0 | 30 711 | 0.3% 25.7% | 5.00 [0.25, 99.95] 0.65 [0.42, 0.99] | • |
| Total events | 31 | | 49 | | | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | - |
| Heterogeneity: Chi² = 8.04, o Fest for overall effect: Z = 2. | | | 3); $I^2 = 0$ | % | | | |
| Fotal (95% CI) | | 3363 | | 3290 | 100.0% | 0.75 [0.61, 0.92] | • |
| Total events | 149 | | 192 | 55 | | [3.02, 0.3 2] | • |
| Heterogeneity: Chi ² = 19.62, | | D _ 0 | | Λ% | | | 0.01 0.1 1 10 |
| Test for overall effect: Z = 2. Test for subgroup difference | .80 (P = 0) | .005) | | | $ \cdot ^2 = 0\%$ | | 0.01 0.1 1 10 Favours probiotics Favours control |

Outcome: *Invasive infection*

| Study or Subgroup | Probio Events | | Contr | | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|------------------|-------------------|-------------|-------------------|----------------------|--|---------------------------------------|
| 9.3.1 Low | LVCIIIS | iotai | Lvents | i otal | weight | 11, 11xeu, 33/6 Cl | Wi-11, 11Xeu, 93% Ci |
| | 0 | 100 | 10 | 100 | 2 00/ | 0.62 [0.27 1.42] | |
| Dilli 2015 Matin 2022 | 8 | 100 26 | 13 3 | 100 26 | 2.8% | 0.62 [0.27, 1.42] | |
| | | | | | 0.8% | 0.14 [0.01, 2.63] | ` |
| Oncel 2014 | 13 31 | 200 | 25 | 200 | 5.4% | 0.52 [0.27, 0.99] | <u></u> |
| Roy 2014 | | 56 | 42 | 56 | 9.1% | 0.74 [0.56, 0.98] | <u>- 1</u> |
| Sinha 2015 | 84 | 668 | 107 | 672 | 23.1% | 0.79 [0.61, 1.03] | |
| Tewari 2015 | 8 | 123 | 11 | 121 | 2.4% | 0.72 [0.30, 1.72] | <u></u> |
| Van Niekerk 2014 Subtotal (95% CI) | 15 | 91 1264 | 10 | 93 1268 | 2.1% 45.8% | 1.53 [0.73, 3.23] 0.76 [0.63, 0.91] | • |
| Total events | 159 | | 211 | | , | [,, | • |
| Heterogeneity: $Chi^2 = 6.39$, | df = 6 (P : | = 0.38) | $I^2 = 6\%$ | | | | |
| Test for overall effect: $Z = 3$. | | | , | | | | |
| 9.3.2 Unclear | | | | | | | |
| Braga 2011 | 40 | 119 | 42 | 112 | 9.4% | 0.90 [0.63, 1.27] | + |
| Cui 2019 | 2 | 45 | 4 | 48 | 0.8% | 0.53 [0.10, 2.77] | • |
| Duta 2015 | 10 | 114 | 6 | 35 | 2.0% | 0.51 [0.20, 1.31] | |
| Fernández-Carrocera 2014 | 42 | 75 | 44 | 75 | 9.5% | 0.95 [0.72, 1.26] | - |
| Sari 2011 | 29 | 110 | 26 | 111 | 5.6% | 1.13 [0.71, 1.78] | |
| Serce 2013 | 19 | 104 | 25 | 104 | 5.4% | 0.76 [0.45, 1.29] | |
| Shadkam 2015 | 0 | 30 | 0 | 30 | | Not estimable | |
| Shashidhar 2017 | 6 | 49 | 7 | 49 | 1.5% | 0.86 [0.31, 2.37] | |
| Wu 2020 Subtotal (95% CI) | 3 | 250 896 | 4 | 250 814 | 0.9% 35.2% | 0.75 [0.17, 3.32] 0.89 [0.74, 1.07] | |
| Total events | 151 | | 158 | | | | • |
| Heterogeneity: $Chi^2 = 3.35$, (| | = 0.85) | | | | | |
| Test for overall effect: $Z = 1$. | | | , 1 0/0 | | | | |
| 9.3.3 High | | | | | | | |
| Chandrashekar 2018 | 15 | 70 | 13 | 70 | 2.8% | 1.15 [0.59, 2.24] | - - - |
| Demirel 2013 | 20 | 135 | 21 | 136 | 4.5% | 0.96 [0.55, 1.69] | |
| Hariharan 2016 | 9 | 93 | 16 | 103 | 3.3% | 0.62 [0.29, 1.34] | - |
| Hernandez-Enriquez 2016 | 6 | 24 | 1 | 20 | 0.2% | 5.00 [0.66, 38.15] | + |
| Kaban 2019 | 1 | 47 | 3 | 47 | 0.7% | 0.33 [0.04, 3.09] | · · · · · · · · · · · · · · · · · · · |
| Saengtawesin 2014 | 2 | 31 | 1 | 20 | 0.3% | 1.29 [0.13, 13.31] | |
| Samanta 2009 | 13 | 91 | 28 | 95 | 5.9% | 0.48 [0.27, 0.88] | |
| Xu 2016 | 4 | 65 | 6 | 60 | 1.4% | 0.62 [0.18, 2.08] | |
| Subtotal (95% CI) | | 556 | | 551 | 19.1% | 0.79 [0.59, 1.06] | ◆ |
| Total events | 70 | | 89 | | | | |
| Heterogeneity: $Chi^2 = 8.77$, (Test for overall effect: $Z = 1$. | • | | $I^2 = 20$ | % | | | |
| Total (95% CI) | | 2716 | | 2633 | 100.0% | 0.81 [0.72, 0.91] | • |
| Total events | 380 | | 458 | | | | |
| Heterogeneity: $Chi^2 = 20.67$, | df = 22 | (P = 0.9) | | 0% | | | 0.01 0.1 1 10 |
| Test for overall effect: $Z = 3$. | | | | | | | |
| Test for subgroup difference | | | lf = 2 (P | = 0.44) | $1^2 = 0\%$ | | Favours probiotics Favours control |

Comparison: Probiotics versus control in extremely preterm or ELBW newborns by probiotic type

Outcome: Necrotizing enterocolitis

| | Probio | tics | Conti | rol | | Risk Ratio | Risk Ratio | | |
|--|--------------|-----------------|----------|-------------------|-----------------------|---|------------------------------------|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | | |
| 1.1.1 Lactobacillus s | pp. | | | | | | | | |
| Oncel 2014 Subtotal (95% CI) | 5 | 93 93 | 9 | 103 103 | 89.5% 89.5% | 0.62 [0.21, 1.77] 0.62 [0.21, 1.77] | | | |
| Total events | 5 | | 9 | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | Z = 0.90 | P = 0 |).37) | | | | | | |
| 1.1.2 Bacillus clausii | | | | | | | | | |
| Tewari 2015 Subtotal (95% CI) | 0 | 61 61 | 0 | 59 59 | | Not estimable Not estimable | | | |
| · | 0 | 61 | 0 | 39 | | Not estimable | | | |
| Total events | 0 Disable | | 0 | | | | | | |
| Heterogeneity: Not ap Test for overall effect: | • | licablo | | | | | | | |
| rest for overall effect. | . Νοι αρρ | псарте | | | | | | | |
| 1.1.3 Bifidobacteriun | n spp. pl | us Lact | obacillu | s spp. | | | | | |
| Roy 2014 | 1 | 11 | 1 | 11 | 10.5% | 1.00 [0.07, 14.05] | | | |
| Subtotal (95% CI) | | 11 | | 11 | 10.5% | 1.00 [0.07, 14.05] | | | |
| Total events | 1 | | 1 | | | | | | |
| Heterogeneity: Not ap | • | | | | | | | | |
| Test for overall effect: | Z = 0.00 | P = 1 | L.00) | | | | | | |
| Total (95% CI) | | 165 | | 173 | 100.0% | 0.66 [0.25, 1.74] | | | |
| Total events | 6 | | 10 | | | | | | |
| Heterogeneity: $Chi^2 = 0.11$, $df = 1$ (P = 0.74); $I^2 = 0\%$ | | | | | | | | | |
| Test for overall effect: | | | | | | _ | Favours probiotics Favours control | | |
| Test for subgroup differences: $Chi^2 = 0.11$, $df = 1$ (P = 0.74), $I^2 = 0\%$ | | | | | | | | | |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause mortality

| | Probio | tics | Conti | rol | | Risk Ratio | Risk Ratio |
|---|---------------|--------------------|---------------|-------------------|-----------------------|--------------------|-------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.2.1 Lactobacillus s | pp. | | | | | | |
| Oncel 2014 Subtotal (95% CI) | 11 | 93 93 | 17 | 103 103 | 63.8% 63.8% | | |
| Total events | 11 | | 17 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect | Z = 0.93 | 3 (P = 0) |).35) | | | | |
| 1.2.2 Bacillus clausii | | | | | | | |
| Tewari 2015 Subtotal (95% CI) | 8 | 61 61 | 9 | 59 59 | 36.2% 36.2% | - , - | |
| Total events | 8 | | 9 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect | Z = 0.34 | 4 (P = 0) |).74) | | | | |
| Total (95% CI) | | 154 | | 162 | 100.0% | 0.77 [0.44, 1.33] | • |
| Total events | 19 | | 26 | | | | |
| Heterogeneity: Chi ² = | 0.10, df | = 1 (P | = 0.75); | $I^2 = 0\%$ | ó | | 0.01 0.1 1 10 100 |
| Test for overall effect: | Z = 0.94 | 4 (P = 0) |).35) | | | | Favours probiotics Favours control |
| Test for subgroup dif | ferences: | Chi ² = | 0.10, df | = 1 (P | = 0.75), I | $1^2 = 0\%$ | . a. cars producted Tarours control |

Outcome: *Invasive infection*

| • | Probio | tics | Conti | rol | | Risk Ratio | Risk Ratio |
|---|---------------|-----------------|---------------|-----------------|-------------------------|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.3.1 Bacillus clausii | | | | | | | |
| Tewari 2015 Subtotal (95% CI) | 14 | 61 61 | 17 | 59 59 | 100.0% 100.0% | 0.80 [0.43, 1.47] 0.80 [0.43, 1.47] | |
| Total events | 14 | | 17 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 0.73 | B (P = 0) |).46) | | | | |
| Total (95% CI) | | 61 | | 59 | 100.0% | 0.80 [0.43, 1.47] | • |
| Total events | 14 | | 17 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | 0.01 0.1 1 10 100 |
| Test for overall effect: | Z = 0.73 | 3 (P = 0) |).46) | | | | 0.01 0.1 1 10 100 Favours probiotics Favours control |
| Test for subgroup diff | ferences: | Not ap | plicable | | | | ravours problemes ravours control |

Comparison: Probiotics versus control in extremely preterm or ELBW newborns by feeding type

Outcome: *Necrotizing enterocolitis*

| | Probio | tics | Conti | rol | | Risk Ratio | Risk Ratio | |
|-----------------------------------|-----------|--------|-----------|-------------|--------|--------------------|--|-----------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI | |
| 7.1.1 Human milk on | ly | | | | | | | |
| Roy 2014 | 1 | 11 | 1 | 11 | 10.5% | 1.00 [0.07, 14.05] | | |
| Tewari 2015 | 0 | 61 | 0 | 59 | | Not estimable | 2 | |
| Subtotal (95% CI) | | 72 | | 70 | 10.5% | 1.00 [0.07, 14.05] | | |
| Total events | 1 | | 1 | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | |
| Test for overall effect: | Z = 0.00 | P = 2 | 1.00) | | | | | |
| 7.1.2 Mixed- human | milk or f | formul | a or botl | h | | | | |
| Oncel 2014 | 5 | 93 | 9 | 103 | 89.5% | 0.62 [0.21, 1.77] | ı | |
| Subtotal (95% CI) | | 93 | | 103 | 89.5% | 0.62 [0.21, 1.77] | | |
| Total events | 5 | | 9 | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | |
| Test for overall effect: | Z = 0.90 | P = 0 |).37) | | | | | |
| Total (95% CI) | | 165 | | 173 | 100.0% | 0.66 [0.25, 1.74] | | |
| Total events | 6 | | 10 | | | | | |
| Heterogeneity: Chi ² = | 0.11, df | = 1 (P | = 0.74); | $I^2 = 0\%$ | I | | | \exists |
| Test for overall effect: | | | | | | | 0.01 0.1 1 10 10 Favours probiotics Favours control | IU |
| Test for subgroup diff | _ | | | | | | ravouis Diodioues Favouis Control | |

Outcome: All-cause neonatal mortality

| | Probiot | tics | Conti | ol | | Risk Ratio | | Risk Ratio | | |
|-----------------------------------|---------------|--------------------|---------------|-------------|----------|--------------------|------|-----------------------|------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% | CI | |
| 7.2.1 Human milk o | nly | | | | | | | | | |
| Tewari 2015 | 8 | 61 | 9 | 59 | 36.2% | 0.86 [0.36, 2.08] | | | | |
| Subtotal (95% CI) | | 61 | | 59 | 36.2% | 0.86 [0.36, 2.08] | | | | |
| Total events | 8 | | 9 | | | | | | | |
| Heterogeneity: Not ap | pplicable | | | | | | | | | |
| Test for overall effect | t: $Z = 0.34$ | (P = 0) |).74) | | | | | | | |
| 7.2.2 Mixed- human | ı milk or f | ormul | a or botl | 1 | | | | | | |
| Oncel 2014 | 11 | 93 | 17 | 103 | 63.8% | 0.72 [0.35, 1.45] | | | | |
| Subtotal (95% CI) | | 93 | | 103 | 63.8% | 0.72 [0.35, 1.45] | | | | |
| Total events | 11 | | 17 | | | | | | | |
| Heterogeneity: Not ap | pplicable | | | | | | | | | |
| Test for overall effect | t: $Z = 0.93$ | (P = 0) |).35) | | | | | | | |
| Total (95% CI) | | 154 | | 162 | 100.0% | 0.77 [0.44, 1.33] | | • | | |
| Total events | 19 | | 26 | | | | | | | |
| Heterogeneity: Chi ² = | = 0.10, df | = 1 (P) | = 0.75); | $I^2 = 0\%$ | ó | | 0.01 | 0.1 | 10 | 100 |
| Test for overall effect | t: Z = 0.94 | (P = 0 | 0.35) | | | | | ours probiotics Favou | | 100 |
| Test for subgroup dif | fferences: | Chi ² = | 0.10, df | = 1 (P | = 0.75), | $1^2 = 0\%$ | iavo | ais problotics ravou | 13 CONTROL | |

Outcome: *Invasive infection*

| | Probio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|--|--------------|-----------------|---------------|-----------------|-------------------------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 7.3.1 Human milk o | nly | | | | | | |
| Tewari 2015 Subtotal (95% CI) | 14 | 61 61 | 17 | 59 59 | 100.0% 100.0% | , | |
| Total events | 14 | | 17 | | | | |
| Heterogeneity: Not a | pplicable | | | | | | |
| Test for overall effect | t: $Z = 0.7$ | 3 (P = 0) |).46) | | | | |
| Total (95% CI) | | 61 | | 59 | 100.0% | 0.80 [0.43, 1.47] | |
| Total events | 14 | | 17 | | | | |
| Heterogeneity: Not a | pplicable | | | | | | |
| Test for overall effect: $Z = 0.73$ (P = 0.46) | | | | | | | 0.01 0.1 1 10 100 Favours probiotics Favours control |
| Test for subgroup dif | fferences: | Not ap | plicable | | | | 1 avours probletics Tavours control |

Comparison: Probiotics versus control in extremely preterm or ELBW newborns by duration of intervention

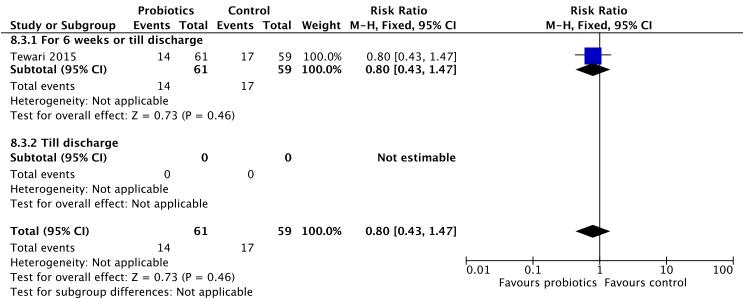
Outcome: Necrotizing enterocolitis

| outcome: Weer ouzmig | | | <u> </u> | | | D: 1 D .: | | | D' D .: | | |
|-----------------------------------|---------------|--------------------|----------|-------------|----------|--------------------|------|-------------|--------------|-------------|-----|
| | Probio | | Conti | | | Risk Ratio | | | Risk Ratio | | |
| | | | Events | Total | Weight | M-H, Fixed, 95% CI | | M- | H, Fixed, 95 | % CI | |
| 8.1.1 For 6 weeks or | r till discl | narge | | | | | | | | | |
| Roy 2014 | 1 | 11 | 1 | 11 | 10.5% | 1.00 [0.07, 14.05] | | - | + | - | |
| Tewari 2015 | 0 | 61 | 0 | 59 | | Not estimable | | | | | |
| Subtotal (95% CI) | | 72 | | 70 | 10.5% | 1.00 [0.07, 14.05] | | | | | |
| Total events | 1 | | 1 | | | | | | | | |
| Heterogeneity: Not a | pplicable | | | | | | | | | | |
| Test for overall effect | t: $Z = 0.00$ | O(P = 1) | 1.00) | | | | | | | | |
| 8.1.2 Till discharge | | | | | | | | | | | |
| Oncel 2014 | 5 | 93 | 9 | 103 | 89.5% | 0.62 [0.21, 1.77] | | _ | _ | | |
| Subtotal (95% CI) | | 93 | | 103 | 89.5% | 0.62 [0.21, 1.77] | | • | | | |
| Total events | 5 | | 9 | | | | | | | | |
| Heterogeneity: Not a | pplicable | | | | | | | | | | |
| Test for overall effect | t: $Z = 0.90$ | O(P = 0) | 0.37) | | | | | | | | |
| Total (95% CI) | | 165 | | 173 | 100.0% | 0.66 [0.25, 1.74] | | - | | | |
| Total events | 6 | | 10 | | | | | | | | |
| Heterogeneity: Chi ² = | = 0.11, df | = 1 (P | = 0.74); | $I^2 = 0\%$ | ó | | 0.01 | | | 10 | 100 |
| Test for overall effect | 5 (P = 0 | 0.40) | | 0.01 | 0.1 | l Niotics Favo | 10 | 100 | | | |
| Test for subgroup dif | fferences: | Chi ² = | 0.11. df | = 1 (P | = 0.74). | $I^2 = 0\%$ | Г | avours proi | oiotics Favo | urs control | |

Outcome: All-cause neonatal mortality

| | Probioti | ics | Contr | ol | | Risk Ratio | | | Risk Ratio | | |
|--|-------------|-----------------|---------------|-------------------|-----------------------|--------------------|------------|-------------------|-------------------|------------------|-----|
| Study or Subgroup | Events - | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-F | I, Fixed, 95% | CI | |
| 8.2.1 For 6 weeks or | till discha | arge | | | | | | | | | |
| Tewari 2015 Subtotal (95% CI) | 8 | 61 61 | 9 | 59 59 | 36.2% 36.2% | . , . | | | | | |
| Total events | 8 | | 9 | | | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | | | |
| Test for overall effect: | Z = 0.34 | (P = 0) |).74) | | | | | | | | |
| 8.2.2 Till discharge | | | | | | | | | | | |
| Oncel 2014 Subtotal (95% CI) | 11 | 93 93 | 17 | 103 103 | 63.8% 63.8% | . , . | | | | | |
| Total events | 11 | | 17 | | | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | | | | | |
| Test for overall effect: | Z = 0.93 | (P = 0) |).35) | | | | | | | | |
| Total (95% CI) | | 154 | | 162 | 100.0% | 0.77 [0.44, 1.33] | | | | | |
| Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff | Z = 0.94 | (P = 0) |).35) | | | $1^2 = 0\%$ | 0.01 Fa | 0.1 vours prob | 1 iotics Favou | 10 rs control | 100 |

Outcome: Invasive infection



Comparison: Combined probiotics or synbiotics versus control (i.e., probiotics with or without prebiotics versus control) in preterm/LBW and extremely preterm/ELBW newborns

Outcome: All-cause neonatal mortality

| | Probiotics or syn | biotics | Conti | ol | | Risk Ratio | Risk Ratio |
|---|---|---------|--------|-------|--------------|--------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% C | M-H, Fixed, 95% CI |
| 4.2.1 Probiotics | | | | | | | |
| Braga 2011 | 26 | 119 | 27 | 112 | 11.6% | 0.91 [0.56, 1.45] | |
| Chandrashekar 2018 | 1 | 70 | 4 | 70 | 1.7% | 0.25 [0.03, 2.18] | |
| Chowdhury 2016 | 5 | 60 | 7 | 59 | 2.9% | 0.70 [0.24, 2.09] | |
| Dashti 2014 | 8 | 69 | 4 | 67 | 1.7% | 1.94 [0.61, 6.15] | |
| Demirel 2013 | 5 | 135 | 5 | 136 | 2.1% | 1.01 [0.30, 3.40] | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 5.0% | 0.25 [0.07, 0.86] | |
| Duta 2015 | 8 | 114 | 2 | 35 | 1.3% | 1.23 [0.27, 5.52] | |
| Fernández-Carrocera 2014 | 1 | 75 | 7 | 75 | 2.9% | 0.14 [0.02, 1.13] | · · |
| Hariharan 2016 | 4 | 93 | 5 | 103 | 2.0% | 0.89 [0.25, 3.20] | |
| Hernandez-Enriquez 2016 | 2 | 24 | 0 | 20 | 0.2% | 4.20 [0.21, 82.72] | - |
| Kaban 2019 | 1 | 47 | 4 | 47 | 1.7% | 0.25 [0.03, 2.15] | |
| Matin 2022 | 0 | 26 | 0 | 26 | , 0 | Not estimable | |
| Oncel 2014 | 15 | 200 | 20 | 200 | 8.4% | 0.75 [0.40, 1.42] | |
| Rehman 2018 | 4 | 73 | 6 | 73 | 2.5% | 0.67 [0.20, 2.26] | |
| Rojas 2012 | 22 | 372 | 28 | 378 | 11.6% | 0.80 [0.47, 1.37] | |
| Roy 2014 | 7 | 56 | 8 | 56 | 3.3% | 0.88 [0.34, 2.25] | |
| Saengtawesin 2014 | 0 | 31 | 0 | 29 | 3.3 /0 | Not estimable | |
| Saerigiawesiii 2014 Samanta 2009 | | 91 | 14 | 95 | E 70/ | | |
| | 4 | | 3 | | 5.7% 1.2% | 0.30 [0.10, 0.87] | |
| Sari 2011 | 3 | 110 | | 111 | | 1.01 [0.21, 4.89] | |
| Serce 2013 | 5 | 104 | 4 | 104 | 1.7% | 1.25 [0.35, 4.52] | |
| Shadkam 2015 | 1 | 30 | 2 | 30 | 0.8% | 0.50 [0.05, 5.22] | |
| Shashidhar 2017 | 1 | 49 | 3 | 49 | 1.3% | 0.33 [0.04, 3.09] | <u> </u> |
| Singh 2017 | 3 | 37 | 3 | 35 | 1.3% | 0.95 [0.20, 4.38] | |
| Sinha 2015 | 1 | 668 | 2 | 672 | 0.8% | 0.50 [0.05, 5.53] | • |
| Sowden 2022 | 0 | 100 | 1 | 100 | 0.6% | 0.33 [0.01, 8.09] | |
| Tewari 2015 | 12 | 123 | 14 | 121 | 5.9% | 0.84 [0.41, 1.75] | |
| √an Niekerk 2014 | 5 | 91 | 6 | 93 | 2.5% | 0.85 [0.27, 2.69] | • |
| Wu 2020 | 0 | 250 | 0 | 250 | | Not estimable | |
| Zahed Pasha 2016 | 2 | 30 | 0 | 30 | 0.2% | 5.00 [0.25, 99.95] | |
| Subtotal (95% CI) | | 3347 | | 3276 | 81.0% | 0.75 [0.61, 0.92] | • |
| Total events | 149 | | 191 | | | | |
| Heterogeneity: Chi² = 19.25, Fest for overall effect: Z = 2.7 | | = 0% | | | | | |
| I.2.2 Synbiotics | | | | | | | |
| Dilli D 2015 | 3 | 100 | 12 | 100 | 5.0% | 0.25 [0.07, 0.86] | |
| El 2017 | 5 | 52 | 4 | 46 | 1.8% | 1.11 [0.32, 3.87] | |
| Guney-Varal 2017 | 7 | 76 | 12 | 43 | 6.4% | 0.33 [0.14, 0.78] | |
| .i 2019 | 0 | 16 | 1 | 14 | 0.7% | 0.29 [0.01, 6.69] | • |
| Vandhini 2016 | 10 | 108 | 9 | 110 | 3.7% | 1.13 [0.48, 2.68] | |
| Sreenivasa 2015 | 0 | 100 | 3 | 100 | 1.5% | 0.14 [0.01, 2.73] | · · |
| Subtotal (95% CI) | - | 452 | | 413 | 19.0% | 0.52 [0.33, 0.83] | • |
| Total events | 25 | | 41 | | | | · |
| Heterogeneity: Chi² = 7.83, d Fest for overall effect: Z = 2.7 | f = 5 (P = 0.17); I ² = | 36% | | | | | |
| Total (95% CI) | | 3799 | | 3689 | 100.0% | 0.71 [0.59, 0.85] | ◆ |
| Total events | 174 | | 232 | | | - / | ' [|
| Heterogeneity: Chi ² = 28.78, Test for overall effect: Z = 3.6 Test for subgroup differences | df = 31 (P = 0.58); I ² 64 (P = 0.0003) | | | 3% | | | 0.01 0.1 1 10 Favours pro or synbiotics Favours control |

4.1.5. Synbiotics Supplementation

Comparison: Synbiotics versus control in preterm or LBW infants by the duration of intervention

Outcome: Necrotizing enterocolitis

| _ | Synbio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|--|------------|--------------------|----------|-----------------|---------------------|---|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.1.1 Till discharge | | | | | | | |
| Guney-Varal 2017 Subtotal (95% CI) | 0 | 70 70 | 4 | 40 40 | 8.7% 8.7% | 0.06 [0.00, 1.16] 0.06 [0.00, 1.16] | |
| Total events | 0 | | 4 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 1.86 | 5 (P = 0) |).06) | | | | |
| 1.1.2 For 8 weeks or | till discl | narge | | | | | |
| Dilli 2015 | 4 | 100 | 18 | 100 | 27.6% | 0.22 [0.08, 0.63] | |
| Subtotal (95% CI) | | 100 | | 100 | 27.6% | 0.22 [0.08, 0.63] | |
| Total events | 4 | | 18 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 2.83 | L(P=0) |).005) | | | | |
| 1.1.3 For 7-10 days | | | | | | | |
| Amini 2017 | 10 | 60 | 28 | 60 | 42.9% | 0.36 [0.19, 0.67] | - |
| El 2017 | 0 | 47 | 2 | 42 | 4.0% | 0.18 [0.01, 3.63] | |
| Nandhini 2016 | 0 | 108 | 3 | | 5.3% | 0.15 [0.01, 2.78] | • |
| Subtotal (95% CI) | | 215 | | 212 | 52.2% | 0.32 [0.18, 0.59] | • |
| Total events | 10 | | 33 | | | | |
| Heterogeneity: $Chi^2 =$ | | | | $I^2 = 0\%$ | ó | | |
| Test for overall effect: | Z = 3.68 | 8 (P = 0) |).0002) | | | | |
| 1.1.4 Till full enteral | feeds | | | | | | |
| Sreenivasa 2015 | 0 | 100 | 7 | | 11.5% | | |
| Subtotal (95% CI) | | 100 | | 100 | 11.5% | 0.07 [0.00, 1.15] | |
| Total events | 0 | | 7 | | | | |
| Heterogeneity: Not ap | | | | | | | |
| Test for overall effect: | Z = 1.86 | 5 (P = 0) | 0.06) | | | | |
| Total (95% CI) | | 485 | | 452 | 100.0% | 0.24 [0.15, 0.40] | • |
| Total events | 14 | | 62 | | | | |
| Heterogeneity: Chi ² = | | | | | Ó | | 0.01 0.1 1 10 100 |
| Test for overall effect: | | | | | | | Favours synbiotics Favours control |
| Test for subgroup diff | ferences: | Chi ² = | 2.33, df | r = 3 (P) | = 0.51), | $I^2 = 0\%$ | . a. out of the out of |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: All-cause mortality till discharge

| | Synbio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|---------------------------------------|------------|--------------------|----------|-------------|-----------------------|--------------------|--------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.2.1 Till discharge | | | | | | | |
| Guney-Varal 2017 | 7 | 76 | 12 | 43 | 34.8% | | |
| Subtotal (95% CI) | | 76 | | 43 | 34.8% | 0.33 [0.14, 0.78] | |
| Total events | . 7 | | 12 | | | | |
| Heterogeneity: Not ap | • | 4 (5) | . 01) | | | | |
| Test for overall effect | Z = 2.54 | + (P = C) |).01) | | | | |
| 1.2.2 For 8 weeks or | till disch | narge | | | | | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 27.3% | 0.25 [0.07, 0.86] | |
| Subtotal (95% CI) | _ | 100 | | 100 | 27.3% | | |
| Total events | 3 | | 12 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect | Z = 2.20 | P = 0 |).03) | | | | |
| 1.2.3 For 7-10 days | | | | | | | |
| = = = = = = = = = = = = = = = = = = = | _ | F-2 | 4 | 4.0 | 0.00/ | 1 11 [0 22 2 07] | |
| El 2017 Nandhini 2016 | 5 10 | 52 | 4 | 46 110 | 9.6% 20.3% | - / - | |
| Subtotal (95% CI) | 10 | 108 160 | 9 | 156 | 20.3% 29.9% | - , - | |
| Total events | 15 | 100 | 13 | 130 | 23.370 | 1.12 [0.55, 2.20] | |
| Heterogeneity: Chi ² = | | = 1 (P | | $I^2 = 0\%$ |) | | |
| Test for overall effect | | | | - | | | |
| | | | | | | | |
| 1.2.4 Till full enteral | feeds | | | | | | |
| Sreenivasa 2015 | 0 | 100 | 3 | 100 | 8.0% | | |
| Subtotal (95% CI) | _ | 100 | _ | 100 | 8.0% | 0.14 [0.01, 2.73] | |
| Total events | 0 | | 3 | | | | |
| Heterogeneity: Not ap | • |) (D (| . 20) | | | | |
| Test for overall effect | Z = 1.29 | $\theta (P = 0)$ |).20) | | | | |
| Total (95% CI) | | 436 | | 399 | 100.0% | 0.53 [0.33, 0.85] | • |
| Total events | 25 | | 40 | | | | |
| Heterogeneity: Chi ² = | | | | $I^2 = 48$ | % | | 0.01 0.1 1 10 100 |
| Test for overall effect | | , | , | | | | Favours synbiotics Favours control |
| Test for subgroup diff | ferences: | Chi ² = | 7.63, df | = 3 (P) | = 0.05), | $I^2 = 60.7\%$ | . a. care symptotics rations control |

${\it Prevention \ and \ Treatment \ of \ Neonatal \ Infections \ in \ LMICs}$

Outcome: *Invasive infection*

| , | Synbio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|--|-----------------|--------------------|----------|-------------------|-----------------------|--------------------|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.3.1 Till discharge | | | | | | | |
| Guney-Varal 2017 Subtotal (95% CI) | 12 | 70 70 | 14 | 40 40 | 41.2% 41.2% | - , - | |
| Total events Heterogeneity: Not ap | 12 policable | | 14 | | | | |
| Test for overall effect: | • | P = 0 |).04) | | | | |
| 1.3.2 For 8 weeks or | till disch | narge | | | | | |
| Dilli 2015 Subtotal (95% CI) | 8 | 100 100 | 13 | 100 100 | 30.1% 30.1% | | |
| Total events | 8 | | 13 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 1.14 | 1 (P = 0) |).26) | | | | |
| 1.3.3 For 7-10 days | | | | | | | |
| El 2017 | 17 | 47 | 8 | 42 | 19.5% | 1.90 [0.92, 3.94] | • |
| Nandhini 2016 | 4 | 108 | 4 | 110 | 9.2% | 1.02 [0.26, 3.97] | |
| Subtotal (95% CI) | | 155 | | 152 | 28.7% | 1.62 [0.85, 3.07] | • |
| Total events | 21 | | 12 | | | | |
| Heterogeneity: $Chi^2 =$ | | | | $I^2 = 0\%$ |) | | |
| Test for overall effect: | Z = 1.48 | B (P = 0) |).14) | | | | |
| 1.3.4 Till full enteral | feeds | | | | | | |
| Subtotal (95% CI) | | 0 | | 0 | | Not estimable | |
| Total events | 0 | | 0 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Not app | licable | | | | | |
| Total (95% CI) | | 325 | | 292 | 100.0% | 0.85 [0.58, 1.26] | • |
| Total events | 41 | | 39 | | | | |
| Heterogeneity: Chi ² = | 7.93, df | = 3 (P | = 0.05); | $I^2 = 62$ | % | | 0.01 0.1 1 10 100 |
| Test for overall effect: | | | | | | | Favours synbiotics Favours control |
| Test for subgroup diff | ferences: | Chi ² = | 7.09, df | = 2 (P) | = 0.03), | $I^2 = 71.8\%$ | Tavours symbiotics Tavours control |

Comparison: Synbiotics versus control in preterm or LBW infants by funding source

Outcome: Necrotizing enterocolitis

| | Synbio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|-----------------------------------|------------|--------------------|-----------|-------------|----------|--------------------|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.1.1 Not stated or r | eported a | as non | e | | | | |
| Dilli 2015 | 4 | 100 | 18 | 100 | 27.6% | 0.22 [0.08, 0.63] | |
| El 2017 | 0 | 47 | 2 | 42 | 4.0% | 0.18 [0.01, 3.63] | • |
| Guney-Varal 2017 | 0 | 70 | 4 | 40 | 8.7% | 0.06 [0.00, 1.16] | • |
| Nandhini 2016 | 0 | 108 | 3 | 110 | 5.3% | | |
| Sreenivasa 2015 | 0 | 100 | 7 | 100 | 11.5% | . , . | |
| Subtotal (95% CI) | | 425 | | 392 | 57.1% | 0.16 [0.07, 0.36] | |
| Total events | 4 | | 34 | | | | |
| Heterogeneity: Chi ² = | | | | $I^2 = 0\%$ | , i | | |
| Test for overall effect | Z = 4.33 | 3 (P < 0 |).0001) | | | | |
| 3.1.2 Funded by pub | lic sector | rs or u | niversiti | es | | | |
| Amini 2017 | 10 | 60 | 28 | 60 | 42.9% | | - |
| Subtotal (95% CI) | | 60 | | 60 | 42.9% | 0.36 [0.19, 0.67] | |
| Total events | 10 | | 28 | | | | |
| Heterogeneity: Not ap | | | | | | | |
| Test for overall effect | Z = 3.22 | P = 0 |).001) | | | | |
| Total (95% CI) | | 485 | | 452 | 100.0% | 0.24 [0.15, 0.40] | • |
| Total events | 14 | | 62 | | | | |
| Heterogeneity: Chi ² = | 3.24, df | = 5 (P | = 0.66); | $I^2 = 0\%$ |) | | 0.01 0.1 1 10 100 |
| Test for overall effect | Z = 5.50 | P < 0 | 0.00001) | | | | Favours synbiotics Favours control |
| Test for subgroup dif | ferences: | Chi ² = | 2.38, df | = 1 (P | = 0.12), | $I^2 = 58.0\%$ | Tavours symplotics Tavours control |

Outcome: All-cause neonatal mortality

| | Synbio | tics | Conti | ol | | Risk Ratio | Risk Ratio |
|-----------------------------------|-----------|---------|---------------|------------|--------|--------------------|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.2.1 Not stated or r | eported a | ıs non | е | | | | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 27.3% | 0.25 [0.07, 0.86] | |
| El 2017 | 5 | 52 | 4 | 46 | 9.6% | 1.11 [0.32, 3.87] | |
| Guney-Varal 2017 | 7 | 76 | 12 | 43 | 34.8% | 0.33 [0.14, 0.78] | |
| Nandhini 2016 | 10 | 108 | 9 | 110 | 20.3% | 1.13 [0.48, 2.68] | |
| Sreenivasa 2015 | 0 | 100 | 3 | 100 | 8.0% | 0.14 [0.01, 2.73] | - |
| Subtotal (95% CI) | | 436 | | 399 | 100.0% | 0.53 [0.33, 0.85] | • |
| Total events | 25 | | 40 | | | | |
| Heterogeneity: Chi ² = | 7.67, df | = 4 (P) | = 0.10); | $I^2 = 48$ | % | | |
| Test for overall effect | Z = 2.66 | S(P=0) | (800.0 | | | | |
| Total (95% CI) | | 436 | | 200 | 100.0% | 0.53 [0.33, 0.85] | |
| | 2.5 | 436 | 40 | 399 | 100.0% | 0.55 [0.55, 0.65] | |
| Total events | 25 | | 40 | | | | |
| Heterogeneity: Chi ² = | | | | $I^2 = 48$ | % | | 0.01 0.1 1 10 100 |
| Test for overall effect | Z = 2.66 | S(P=0) |).008) | | | | Favours synbiotics Favours control |
| Test for subgroup dif | ferences: | Not ap | plicable | | | | , |

Outcome: *Invasive infection*

| | Synbio | tics | Cont | rol | | Risk Ratio | Risk Ratio |
|-----------------------------------|---------------|-----------|---------------|------------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 3.3.1 Not stated or r | eported a | as non | e | | | | |
| Dilli 2015 | 8 | 100 | 13 | 100 | 30.1% | 0.62 [0.27, 1.42] | |
| El 2017 | 17 | 47 | 8 | 42 | 19.5% | 1.90 [0.92, 3.94] | • |
| Guney-Varal 2017 | 12 | 70 | 14 | 40 | 41.2% | 0.49 [0.25, 0.95] | |
| Nandhini 2016 | 4 | 108 | 4 | 110 | 9.2% | 1.02 [0.26, 3.97] | |
| Subtotal (95% CI) | | 325 | | 292 | 100.0% | 0.85 [0.58, 1.26] | • |
| Total events | 41 | | 39 | | | | |
| Heterogeneity: Chi ² = | 7.93, df | = 3 (P) | = 0.05); | $I^2 = 62$ | % | | |
| Test for overall effect | Z = 0.8 | 1 (P = 0) |).42) | | | | |
| Total (95% CI) | | 325 | | 292 | 100.0% | 0.85 [0.58, 1.26] | • |
| Total events | 41 | | 39 | | | | |
| Heterogeneity: Chi ² = | 7.93, df | = 3 (P) | = 0.05); | $I^2 = 62$ | % | | |
| Test for overall effect | Z = 0.8 | 1 (P = 0) |).42) | | | | 0.01 0.1 1 10 100 Favours synbiotics Favours control |
| Test for subgroup dif | ferences: | Not ap | plicable | | | | ravours symbiotics ravours control |

Comparison: Synbiotics versus control in preterm or LBW infants by synbiotics' volume

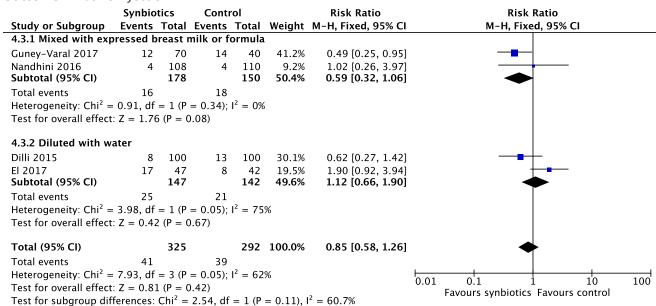
Outcome: Necrotizing enterocolitis

| | Synbio | tics | Conti | ol | | Risk Ratio | Risk Ratio |
|-----------------------------------|---------------|---------|---------------|-------------|---------|--------------------|------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 4.1.1 Mixed with exp | ressed b | reast i | nilk or f | ormula | l | | |
| Amini 2017 | 10 | 60 | 28 | 60 | 42.9% | 0.36 [0.19, 0.67] | - |
| Guney-Varal 2017 | 0 | 70 | 4 | 40 | 8.7% | 0.06 [0.00, 1.16] | • |
| Nandhini 2016 | 0 | 108 | 3 | 110 | 5.3% | 0.15 [0.01, 2.78] | - |
| Sreenivasa 2015 | 0 | 100 | 7 | 100 | 11.5% | 0.07 [0.00, 1.15] | • |
| Subtotal (95% CI) | | 338 | | 310 | 68.4% | 0.25 [0.14, 0.46] | • |
| Total events | 10 | | 42 | | | | |
| Heterogeneity: Chi ² = | = 2.98, df | = 3 (P) | = 0.40); | $I^2 = 0\%$ | | | |
| Test for overall effect | z = 4.59 | (P < 0 |).00001) | | | | |
| 4.1.2 Diluted with w | ater | | | | | | |
| Dilli 2015 | 4 | 100 | 18 | 100 | 27.6% | 0.22 [0.08, 0.63] | |
| El 2017 | 0 | 47 | 2 | | 4.0% | | |
| Subtotal (95% CI) | Ů | 147 | _ | 142 | 31.6% | | |
| Total events | 4 | | 20 | | | - , - | |
| Heterogeneity: Chi ² = | = 0.02. df | = 1 (P | = 0.89): | $I^2 = 0\%$ | ,) | | |
| Test for overall effect | | | | . •, | | | |
| Total (95% CI) | | 485 | | 452 | 100.0% | 0.24 [0.15, 0.40] | • |
| Total events | 14 | | 62 | | | | |
| Heterogeneity: Chi ² = | | = 5 (P | = 0.66): | $I^2 = 0\%$ | ,) | | |
| Test for overall effect | | | | | | | 0.01 0.1 1 10 100 |
| Test for subgroup dif | | | | | = 0.78) | $I^2 = 0\%$ | Favours synbiotics Favours control |

Outcome: All-cause neonatal mortality

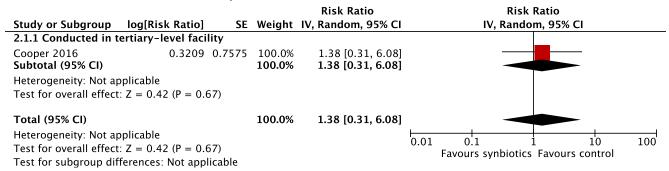
| | Synbiot | ics | Conti | rol | | Risk Ratio | Risk Ratio |
|---|----------|-------------------|---------------|-------------------|----------------------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 4.2.1 Mixed with exp | ressed b | reast r | nilk or f | ormula | | | |
| Guney-Varal 2017 | 7 | 76 | 12 | 43 | 34.8% | 0.33 [0.14, 0.78] | |
| Nandhini 2016 | 10 | 108 | 9 | 110 | 20.3% | 1.13 [0.48, 2.68] | |
| Sreenivasa 2015 Subtotal (95% CI) | 0 | 100 284 | 3 | 100 253 | 8.0% 63.1% | | • |
| Total events | 17 | | 24 | | | | |
| Heterogeneity: Chi ² = | 4.86, df | = 2 (P | = 0.09); | $I^2 = 59$ | % | | |
| Test for overall effect: | Z = 1.99 | (P = 0) |).05) | | | | |
| 4.2.2 Diluted with wa | ater | | | | | | |
| Dilli 2015 | 3 | 100 | 12 | 100 | 27.3% | 0.25 [0.07, 0.86] | |
| El 2017 | 5 | 52 | 4 | 46 | 9.6% | 1.11 [0.32, 3.87] | |
| Subtotal (95% CI) | | 152 | | 146 | 36.9% | 0.47 [0.21, 1.09] | |
| Total events | 8 | | 16 | | | | |
| Heterogeneity: Chi ² = | 2.79, df | = 1 (P | = 0.10); | $I^2 = 64$ | % | | |
| Test for overall effect: | Z = 1.76 | (P = 0) | 0.08) | | | | |
| Total (95% CI) | | 436 | | 399 | 100.0% | 0.53 [0.33, 0.85] | • |
| Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff | Z = 2.66 | (P = 0) | .008) | | | $I^2 = 0\%$ | 0.01 0.1 1 10 100 Favours synbiotics Favours control |

Outcome: *Invasive infection*



Comparison: Synbiotics versus control in term newborns by facility level

Outcome: All-cause neonatal mortality



Comparison: Synbiotics versus control in term newborns by the duration of intervention

Outcome: All-cause neonatal mortality

| | | | | Risk Ratio | Risk Ratio |
|---|--------------------|--------|-------------------------|---|---|
| Study or Subgroup | log[Risk Ratio] | SE | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 5.1.1 For 6 months | | | | | |
| Cooper 2016 Subtotal (95% CI) | 0.3209 | 0.7575 | 100.0% 100.0% | 1.38 [0.31, 6.08] 1.38 [0.31, 6.08] | |
| Heterogeneity: Not ap Test for overall effect: | | 67) | | | |
| Total (95% CI) Heterogeneity: Not ap Test for overall effect: Test for subgroup diff | Z = 0.42 (P = 0.6) | • | 100.0% | 1.38 [0.31, 6.08] | 0.01 0.1 1 10 100 Favours synbiotics Favours control |

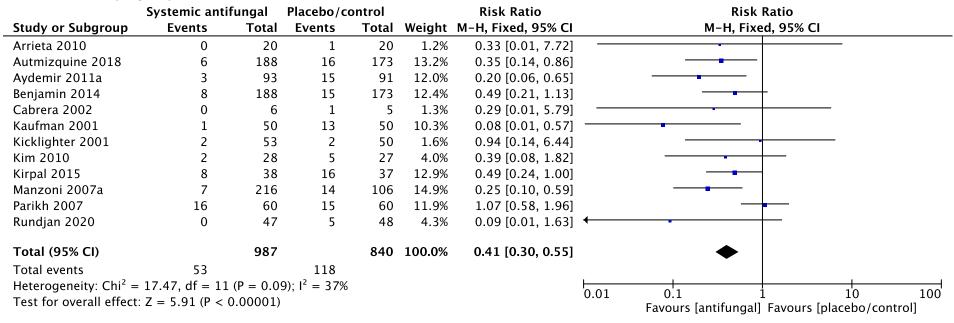
Comparison: Synbiotics versus control in term newborns by funding source

Outcome: All-cause neonatal mortality

| Study or Subgroup | log[Risk Ratio] | SE Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI | |
|--|-----------------|----------------------------|----------------------------------|--|-----|
| 6.1.1 Funded by indu | ustry | | | | |
| Cooper 2016 Subtotal (95% CI) | 0.3209 0.75 | 75 100.0% 100.0% | | | |
| Heterogeneity: Not ap Test for overall effect | • | | | | |
| Total (95% CI) Heterogeneity: Not ap Test for overall effect Test for subgroup dif | • | 100.0% | 1.38 [0.31, 6.08] | 0.01 0.1 1 10 Favours synbiotics Favours control | 100 |

4.1.6. Prophylactic Systemic Antifungal Agents

Outcome: *Invasive fungal infections (Total)*



Outcome: *Invasive fungal infections (LMICs only)*

| | Systemic anti | fungal | Placebo/c | ontrol | | Risk Ratio | | Risk Ratio | | |
|-----------------------------------|--------------------|----------|--------------|--------|--------|--------------------|-------------|--------------------------------------|----------------|---------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% | CI | |
| Aydemir 2011a | 3 | 93 | 15 | 91 | 29.3% | 0.20 [0.06, 0.65] | | | | |
| Kirpal 2015 | 8 | 38 | 16 | 37 | 31.3% | 0.49 [0.24, 1.00] | | - | | |
| Parikh 2007 | 16 | 60 | 15 | 60 | 28.9% | 1.07 [0.58, 1.96] | | | | |
| Rundjan 2020 | 0 | 47 | 5 | 48 | 10.5% | 0.09 [0.01, 1.63] | | • | | |
| Total (95% CI) | | 238 | | 236 | 100.0% | 0.53 [0.35, 0.80] | | • | | |
| Total events | 27 | | 51 | | | | | | | |
| Heterogeneity: Chi ² = | = 9.22, df = 3 (P) | = 0.03); | $I^2 = 67\%$ | | | | 0.01 | | 10 | 100 |
| Test for overall effect | t: $Z = 3.03 (P =$ | 0.002) | | | | | 0.01 | 0.1 I Favours [antifungal] Favour | s [placebo/con | 100 itrol] |

Prevention and Treatment of Neonatal Infections in LMICs
Outcome: Neonatal mortality prior to hospital discharge (Total)

| | Systemic anti | fungal | Placebo/c | ontrol | | Risk Ratio | Risk Ratio |
|-----------------------------------|------------------|----------|----------------|--------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Arrieta 2010 | 1 | 20 | 1 | 20 | 0.7% | 1.00 [0.07, 14.90] | |
| Aydemir 2011a | 8 | 93 | 11 | 91 | 8.3% | 0.71 [0.30, 1.69] | |
| Benjamin 2014 | 34 | 188 | 33 | 173 | 25.7% | 0.95 [0.62, 1.46] | |
| Jannatdoust 2015 | 9 | 43 | 15 | 50 | 10.4% | 0.70 [0.34, 1.43] | |
| Kaufman 2001 | 4 | 50 | 10 | 50 | 7.5% | 0.40 [0.13, 1.19] | |
| Kicklighter 2001 | 5 | 53 | 10 | 53 | 7.5% | 0.50 [0.18, 1.36] | |
| Kim 2010 | 2 | 28 | 2 | 27 | 1.5% | 0.96 [0.15, 6.37] | |
| Kirpal 2015 | 7 | 38 | 12 | 37 | 9.1% | 0.57 [0.25, 1.28] | - |
| Manzoni 2007a | 18 | 216 | 10 | 106 | 10.0% | 0.88 [0.42, 1.85] | |
| Parikh 2007 | 17 | 60 | 17 | 60 | 12.7% | 1.00 [0.57, 1.77] | |
| Rundjan 2020 | 7 | 47 | 9 | 48 | 6.7% | 0.79 [0.32, 1.96] | |
| Total (95% CI) | | 836 | | 715 | 100.0% | 0.78 [0.62, 0.99] | • |
| Total events | 112 | | 130 | | | | |
| Heterogeneity: Chi ² = | 4.61, df = 10 (| P = 0.92 |); $I^2 = 0\%$ | | | | 0.1 0.2 0.5 1 2 5 10 |
| Test for overall effect | Z = 2.06 (P = 0) | 0.04) | | | | | 0.1 0.2 0.5 1 2 5 10 Favours [antifungal] Favours [placebo/control] |

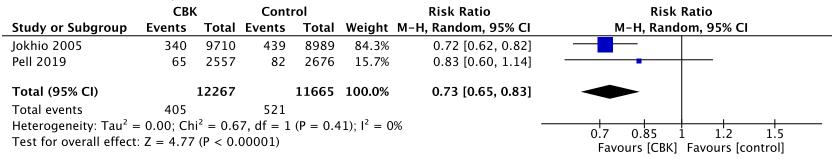
Outcome: Neonatal mortality prior to hospital discharge (LMICs only)

| | , , | , | | | | | | | | | | |
|-----------------------------------|---------------------|----------|-------------|--------|--------|--------------------|--------------|------------|---|-------------------|-------------|-------------|
| | Systemic anti | fungal | Placebo/c | ontrol | | Risk Ratio | | | Risk Rati | O | | |
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | | M-H, Fixed, 9 | 5% CI | | |
| Aydemir 2011a | 8 | 93 | 11 | 91 | 17.6% | 0.71 [0.30, 1.69] | | | • | | | |
| Jannatdoust 2015 | 9 | 43 | 15 | 50 | 22.0% | 0.70 [0.34, 1.43] | | | - | - | | |
| Kirpal 2015 | 7 | 38 | 12 | 37 | 19.3% | 0.57 [0.25, 1.28] | | | - | | | |
| Parikh 2007 | 17 | 60 | 17 | 60 | 27.0% | 1.00 [0.57, 1.77] | | | | | | |
| Rundjan 2020 | 7 | 47 | 9 | 48 | 14.1% | 0.79 [0.32, 1.96] | | | • | | | |
| Total (95% CI) | | 281 | | 286 | 100.0% | 0.77 [0.55, 1.07] | | | | | | |
| Total events | 48 | | 64 | | | | | | | | | |
| Heterogeneity: Chi ² = | = 1.45, df = 4 (P | = 0.83); | $I^2 = 0\%$ | | | | | 0 2 | | | | |
| Test for overall effect | z = 1.55 (P = 1.55) | 0.12) | | | | | 0.1 | 0.2 | 0.5 1 antifungall Fav | Z Zoure Inlace | bo/contr | .01] |
| | | | | | | | | ravours la | antinunudii FdV | ours place | :DO/CONT | UII |

4.2 Mixed Level Forest Plots

4.2.1. Clean Birth Kits

Outcome: Neonatal mortality



Outcome: Any omphalitis



4.2.2. Chlorhexidine Cleansing

Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

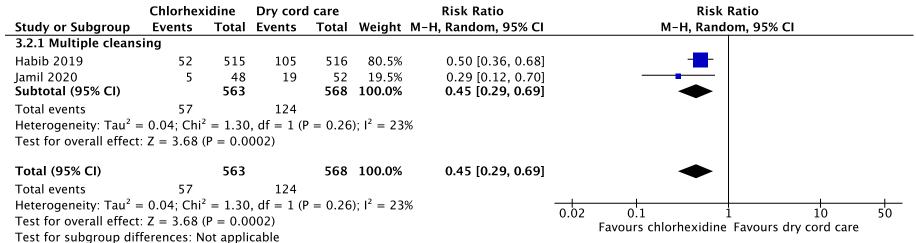
Outcome: Neonatal mortality

| | Chlorhe | kidine | Dry core | d care | | Risk Ratio | | | Risk Ratio | | |
|-------------------------|---------------|-----------|---------------|--------|--------|---------------------|------|-----------------|---------------|---------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | | M-H, | Random, 95% | 6 CI | |
| Habib 2019 | 17 | 515 | 19 | 516 | 100.0% | 0.90 [0.47, 1.70] | | _ | | | |
| Total (95% CI) | | 515 | | 516 | 100.0% | 0.90 [0.47, 1.70] | | - | | | |
| Total events | 17 | | 19 | | | | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | 0.05 | 0.2 | 1 | <u> </u> | 20 |
| Test for overall effect | z = 0.33 | (P = 0.7) | 4) | | | | 0.03 | Favours chlorhe | xidine Favour | s dry cord ca | |

Outcome: Omphalitis

| | Chlorhex | idine | Dry core | d care | | Risk Ratio | Risk Ratio |
|--|----------|-------|----------|----------|---------------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Habib 2019 | 52 | 515 | 105 | 516 | 80.5% | 0.50 [0.36, 0.68] | - |
| Jamil 2020 | 5 | 48 | 19 | 52 | 19.5% | 0.29 [0.12, 0.70] | |
| Total (95% CI) | | 563 | | 568 | 100.0% | 0.45 [0.29, 0.69] | • |
| Total events | 57 | | 124 | | | | |
| Heterogeneity: Tau ² = Test for overall effect | | | | P = 0.26 |); $I^2 = 23$ | % | 0.01 0.1 1 10 100 Favours chlorhexidine Favours dry cord care |

Outcome: Omphalitis by cleansing frequency



Outcome: Bloodstream infection/sepsis

| | Chlorhex | cidine . | Dry cord | l care | | Risk Ratio | Risk Ratio |
|-------------------------|---------------|-----------|---------------|--------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Habib 2019 | 90 | 515 | 135 | 516 | 100.0% | 0.67 [0.53, 0.85] | - |
| Total (95% CI) | | 515 | | 516 | 100.0% | 0.67 [0.53, 0.85] | • |
| Total events | 90 | | 135 | | | | |
| Heterogeneity: Not ap | plicable | | | | | • | 0.1 0.2 0.5 1 2 5 10 |
| Test for overall effect | Z = 3.34 | (P = 0.0) | 009) | | | | Favours chlorhexidine Favours dry cord care |

4.2.3. Topical Emollients

Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: Rate of weight gain (g/kg/day)

| | Topical oil | | | Routine skin care | | | | Mean Difference | Mean Difference |
|------------------------------|-------------|---------------|----------|--|---------------|-------|--------|-------------------|-------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Arora 2005 | 10.9 | 4.4 | 20 | 8.5 | 4.7 | 42 | 20.8% | 2.40 [0.00, 4.80] | |
| Kumar 2013 | 11.6 | 5.6 | 25 | 8.4 | 5.5 | 23 | 12.1% | 3.20 [0.06, 6.34] | |
| Sankaranarayanan 2005 | 11 | 2.6 | 32 | 8.5 | 2.8 | 31 | 67.1% | 2.50 [1.16, 3.84] | - |
| Total (95% CI) | | | 77 | | | 96 | 100.0% | 2.56 [1.47, 3.66] | • |
| Heterogeneity: $Chi^2 = 0.1$ | .8, df = | 2 (P = | = 0.91); | - | -10 -5 0 5 10 | | | | |
| Test for overall effect: Z = | = 4.60 (F | P < 0. | .00001) | -10 -5 0 5 10 Favours routine skin care Favours topical oil | | | | | |

Outcome: Change in crown-heel length (mm/week)

| 9 | | _ | | • | | | | | | | |
|------------------------------|-----------|--------|----------|---------|---------|-------|--------|--------------------|--|--|--|
| | Top | ical (| oil | Routine | e skin | care | | Mean Difference | Mean Difference | | |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI | | |
| Arora 2005 | 7.5 | 2.1 | 20 | 6.4 | 7.6 | 42 | 41.5% | 1.10 [-1.38, 3.58] | - • | | |
| Kumar 2013 | 6.5 | 2.3 | 25 | 5.8 | 5.6 | 23 | 42.0% | 0.70 [-1.76, 3.16] | - | | |
| Sankaranarayanan 2005 | 6.3 | 6.8 | 32 | 5.6 | 8.9 | 31 | 16.5% | 0.70 [-3.22, 4.62] | | | |
| Total (95% CI) | | | 77 | | | 96 | 100.0% | 0.87 [-0.73, 2.46] | • | | |
| Heterogeneity: $Chi^2 = 0.0$ | 6, df = | 2 (P = | = 0.97); | _ | 10 5 10 | | | | | | |
| Test for overall effect: Z = | = 1.06 (F | P = 0 | .29) | | | | | | -10 -5 0 5 10 Favours routine skin care Favours topical oil | | |

Outcome: Change in circumference (mm/week)

| | Top | ical (| oil | Routine | e skin | care | | Mean Difference | Mean Difference | |
|--|------|--------|-------|-------------|--------|-------|--------|------------------------|--|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI | |
| Arora 2005 | 7.2 | 6.3 | 20 | 6.12 | 9.1 | 42 | 17.3% | 1.08 [-2.82, 4.98] | | |
| Kumar 2013 | 6 | 7 | 25 | 6 | 6.7 | 23 | 17.5% | 0.00 [-3.88, 3.88] | | |
| Sankaranarayanan 2005 | 4.9 | 2.8 | 32 | 4.7 | 5 | 31 | 65.2% | 0.20 [-1.81, 2.21] | | |
| Total (95% CI) | | | 77 | | | 96 | 100.0% | 0.32 [-1.30, 1.94] | | |
| Heterogeneity: $Chi^2 = 0.1$ Test for overall effect: Z = | | | | $I^2 = 0\%$ | | | | | -10 -5 0 5 10 Favours routine skin care Favours topical oil | _ |

Outcome: Change in triceps skinfold thickness (mm/week)

| | Тор | oical | oil | Routin | e skin | care | | Mean Difference | Mean Difference |
|--|------|-------|---------|--------|--------|-------|--------|--------------------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Arora 2005 | 0.1 | 0.1 | 20 | 0.05 | 0.15 | 19 | 100.0% | 0.05 [-0.03, 0.13] | |
| Total (95% CI) | | | 20 | | | 19 | 100.0% | 0.05 [-0.03, 0.13] | |
| Heterogeneity: Not ap Test for overall effect | | | = 0.22) |) | | | | | -0.5 -0.25 0 0.25 0.5 Favours routine skin care Favours topical oil |

Comparison: One topical oil (or combination) versus another oil (or combination)

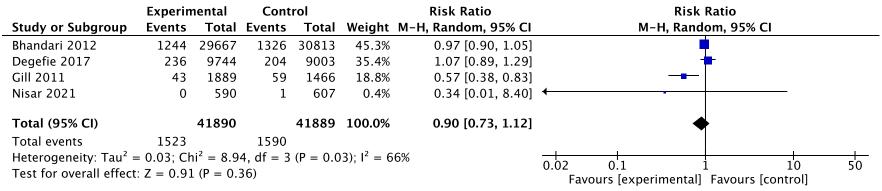
Outcome: *Growth*

| | Coco | onut (| oil | Min | eral (| oil | | Mean Difference | Mean Difference |
|--|----------|--------|-----------------|----------------------|--------|-----------------|----------------------|--|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| 4.1.1 Rate of weight gain | (g/kg/ | 'day) | | | | | | | |
| Sankaranarayanan 2005 Subtotal (95% CI) | 11 | 2.6 | 32 32 | 9 | 2.1 | 32 32 | 4.5% 4.5% | | |
| Heterogeneity: Not applica Test for overall effect: Z = | | = 0.0 | 0007) | | | | | | |
| 4.1.2 Change in crown-h | eel leng | gth (n | nm/we | ek) | | | | | |
| Sankaranarayanan 2005 Subtotal (95% CI) | 6.3 | 1.2 | 32 32 | 5.9 | 1.6 | 32 32 | | 0.40 [-0.29, 1.09] 0.40 [-0.29, 1.09] | |
| Heterogeneity: Not applica Test for overall effect: Z = | | = 0.2 | 26) | | | | | | |
| 4.1.3 Change in head circ | cumfere | nce (| (mm/w | eek) | | | | | |
| Sankaranarayanan 2005 Subtotal (95% CI) | 4.9 | 0.5 | 32 32 | 4.8 | 0.6 | 32 32 | | 0.10 [-0.17, 0.37] 0.10 [-0.17, 0.37] | * |
| Heterogeneity: Not applica Test for overall effect: Z = | | = 0.4 | 47) | | | | | | |
| Total (95% CI) Heterogeneity: Chi ² = 10.0 | | | | 6); I ² = | 80% | 96 | 100.0% | 0.22 [-0.02, 0.47] | -4 -2 0 2 4 |
| Test for overall effect: Z = Test for subgroup differen | | | | df = 2 (F | P = 0 | .006), I | ² = 80.2% | ,) | Favours mineral oil Favours coconut oil |

4.2.4. Mixed Setting Antibiotic Delivery for PSBIs

Comparison: Home-based & primary facility-based antibiotic delivery versus standard care (i.e., hospital referral)

Outcome: All-cause neonatal mortality



Outcome: Early neonatal mortality

| | Experim | nental | Conti | rol | | Risk Ratio | | | Risk | Ratio | | |
|-------------------------|---------------|-----------|---------------|-------|--------|---------------------|-----|------------------|-----------------------|-------------|-------------|----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | | | M-H, Rande | om, 95% CI | | |
| Gill 2011 | 35 | 1923 | 46 | 1508 | 100.0% | 0.60 [0.39, 0.92] | | | | | | |
| Total (95% CI) | | 1923 | | 1508 | 100.0% | 0.60 [0.39, 0.92] | | | | | | |
| Total events | 35 | | 46 | | | | | | | | | |
| Heterogeneity: Not ap | oplicable | | | | | | + | - | | | | 10 |
| Test for overall effect | Z = 2.33 | (P = 0.0) | 02) | | | | U.1 | 0.∠ avours [e | ر د.ه [xperimental | | o trol] | 10 |

Outcome: Late neonatal mortality

| | Experim | ental | Conti | rol | | Risk Ratio | Risk Ratio | |
|-------------------------|-------------|---------|---------------|-------|--------|---------------------|---|-------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95 | % CI |
| Gill 2011 | 8 | 1854 | 13 | 1420 | 100.0% | 0.47 [0.20, 1.13] | | |
| Total (95% CI) | | 1854 | | 1420 | 100.0% | 0.47 [0.20, 1.13] | | |
| Total events | 8 | | 13 | | | | | |
| Heterogeneity: Not ap | oplicable | | | | | | 002 01 1 | 10 50 |
| Test for overall effect | :: Z = 1.68 | (P = 0. | 09) | | | | 0.02 0.1 1 Favours [experimental] Favou | |

${\it Prevention \ and \ Treatment \ of \ Neonatal \ Infections \ in \ LMICs}$

Outcome: Sepsis-specific neonatal mortality

| | Experimental Control | | | ol | | Risk Ratio | Risk Ratio | | | |
|--|----------------------|---------|---------------|-------|--------|---------------------|---|--|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | | | |
| Gill 2011 | 16 | 1899 | 17 | 1466 | 100.0% | 0.73 [0.37, 1.43] | - | | | |
| Total (95% CI) | | 1899 | | 1466 | 100.0% | 0.73 [0.37, 1.43] | | | | |
| Total events | 16 | | 17 | | | | | | | |
| Heterogeneity: Not ap Test for overall effect | • | (P = 0. | 36) | | | | 0.02 0.1 1 10 50 Favours [experimental] Favours [control] | | | |

Comparison: Simplified antibiotic regimens versus standard antibiotic regimens

Outcome: All-cause neonatal mortality

| | Simplified re | Simplified regimen Standard regimen | | | | Risk Ratio | Risk Ratio |
|-----------------------------------|--------------------------------|-------------------------------------|----------------|-------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M–H, Random, 95% CI |
| AFRINEST(1) 2015 | 32 | 1325 | 9 | 446 | 41.5% | 1.20 [0.58, 2.49] | - |
| Baqui 2015 | 8 | 329 | 9 | 157 | 30.4% | 0.42 [0.17, 1.08] | |
| Mir 2017 | 11 | 814 | 6 | 405 | 28.1% | 0.91 [0.34, 2.45] | |
| Total (95% CI) | | 2468 | | 1008 | 100.0% | 0.81 [0.44, 1.50] | |
| Total events | 51 | | 24 | | | | |
| Heterogeneity: Tau ² = | = 0.10; Chi ² $= 2$ | 2.99, df = | = 2 (P = 0.22) | $I^2 = 339$ | % | | 0.02 0.1 1 10 50 |
| Test for overall effect | Z = 0.67 (P = 0.67) | 0.50) | | | | | Favours [simplified] Favours [standard] |

Outcome: *Treatment failure*

| | Simplified reg | gimen | Standard re | gimen | | Risk Ratio | Risk Ratio |
|-----------------------------------|--------------------------------|-----------|----------------|-------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| AFRINEST(1) 2015 | 52 | 1325 | 23 | 446 | 27.5% | 0.76 [0.47, 1.23] | |
| Baqui 2015 | 22 | 329 | 12 | 157 | 13.8% | 0.87 [0.44, 1.72] | |
| Mir 2017 | 89 | 814 | 49 | 405 | 58.8% | 0.90 [0.65, 1.25] | - |
| Total (95% CI) | | 2468 | | 1008 | 100.0% | 0.86 [0.67, 1.10] | • |
| Total events | 163 | | 84 | | | | |
| Heterogeneity: Tau ² = | = 0.00; Chi ² $= 0$ | .34, df = | = 2 (P = 0.84) | $I^2 = 0\%$ | | | 0.05 0.2 1 5 20 |
| Test for overall effect | Z = 1.19 (P = 1.19) | 0.23) | | | | | Favours [simplified] Favours [standard] |

Outcome: Adverse effects

| | Simplified re | implified regimen Standard regimen | | | | Risk Ratio | Risk Ratio |
|--|---------------|------------------------------------|----------------|-------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| AFRINEST(1) 2015 | 0 | 1325 | 0 | 446 | | Not estimable | |
| Baqui 2015 | 35 | 329 | 10 | 157 | 68.1% | 1.67 [0.85, 3.29] | + |
| Mir 2017 | 11 | 814 | 6 | 405 | 31.9% | 0.91 [0.34, 2.45] | |
| Total (95% CI) | | 2468 | | 1008 | 100.0% | 1.38 [0.79, 2.41] | |
| Total events | 46 | | 16 | | | | |
| Heterogeneity: Tau² = Test for overall effect | | | = 1 (P = 0.32) | $I^2 = 0\%$ | | | 0.05 0.2 1 5 20 Favours [simplified] Favours [standard] |

4.3 Community Level Forest Plots

4.3.1. Chlorhexidine Cleansing

Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

Outcome: Neonatal mortality

| | Chlorhexidine cl | Dry cor | d care | | Risk Ratio | Risk Ratio | |
|-----------------------------------|---------------------------------|-------------|-----------|----------------|------------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M–H, Random, 95% CI |
| Arifeen 2012 | 275 | 10329 | 283 | 10008 | 23.1% | 0.94 [0.80, 1.11] | |
| Mullany 2006 | 72 | 4924 | 98 | 5082 | 15.7% | 0.76 [0.56, 1.03] | |
| Sazawal 2016 | 189 | 18015 | 221 | 18896 | 21.4% | 0.90 [0.74, 1.09] | |
| Semrau 2016 | 282 | 18510 | 263 | 19346 | 22.9% | 1.12 [0.95, 1.32] | +- |
| Soofi 2012 | 79 | 3476 | 126 | 3481 | 16.9% | 0.63 [0.48, 0.83] | |
| Total (95% CI) | | 55254 | | 56813 | 100.0% | 0.88 [0.73, 1.05] | • |
| Total events | 897 | | 991 | | | | |
| Heterogeneity: Tau ² = | = 0.03; Chi ² = 14.3 | 8, df = 4 (| P = 0.006 | $(5); I^2 = 7$ | 2% | 0.2 | 0.5 1 2 5 |
| Test for overall effect | Z = 1.47 (P = 0.14) | 4) | | | | 0.2 | Favours [chlorhexidine] Favours [dry cord care] |

Subgroup Analysis: Chlorhexidine alone versus chlorhexidine in clean birth kits

Outcome: Neonatal mortality

| | Chlorhexidine cl | eansing | Dry cor | d care | | Risk Ratio | Risk Ratio |
|-----------------------------------|-------------------------|-------------|---------------|----------------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| 4.2.1 Chlorhexidine in | n birthing kit | | | | | | |
| Arifeen 2012 | 275 | 10329 | 283 | 10008 | 23.1% | 0.94 [0.80, 1.11] | |
| Mullany 2006 | 72 | 4924 | 98 | 5082 | 15.7% | 0.76 [0.56, 1.03] | |
| Semrau 2016 | 282 | 18510 | 263 | 19346 | 22.9% | 1.12 [0.95, 1.32] | +•- |
| Soofi 2012 | 79 | 3476 | 126 | 3481 | 16.9% | 0.63 [0.48, 0.83] | - |
| Subtotal (95% CI) | | 37239 | | 37917 | 78.6% | 0.86 [0.68, 1.09] | |
| Total events | 708 | | 770 | | | | |
| Heterogeneity: Tau ² = | 0.04 ; $Chi^2 = 14.2$ | 9, df = 3 (| P = 0.003 | 3); $I^2 = 7$ | 9% | | |
| Test for overall effect: | Z = 1.24 (P = 0.2) | 2) | | | | | |
| 4.2.2 Chlorhexidine a | lone | | | | | | |
| Sazawal 2016 | 189 | 18015 | 221 | 18896 | 21.4% | 0.90 [0.74, 1.09] | |
| Subtotal (95% CI) | | 18015 | | 18896 | 21.4% | 0.90 [0.74, 1.09] | |
| Total events | 189 | | 221 | | | | |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 1.10 (P = 0.2) | 7) | | | | | |
| Total (95% CI) | | 55254 | | 56813 | 100.0% | 0.88 [0.73, 1.05] | |
| Total events | 897 | | 991 | | | | |
| Heterogeneity: Tau ² = | 0.03 ; $Chi^2 = 14.3$ | 8, df = 4 | P = 0.006 | 5); $I^2 = 7$ | 2% | | .2 0.5 1 2 5 |
| Test for overall effect: | | | | | | 0. | .2 0.5 1 2 5 Favours [chlorhexidine] Favours [dry cord care] |
| Test for subgroup diff | erences: $Chi^2 = 0$. | 07, df = 1 | (P = 0.80) | $(1), I^2 = 0$ | 6 | | ravours (ciliornexiume) ravours (ury cord care) |

Outcome: Omphalitis

| | Chlorhexidine cl | leansing | Dry cor | d care | | Risk Ratio | Risk Ratio |
|-----------------------------------|---------------------------------|------------|-----------|----------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Arifeen 2012 | 16 | 10254 | 42 | 9924 | 18.8% | 0.37 [0.21, 0.66] | |
| Mekonnen 2020 | 1 | 107 | 5 | 89 | 3.5% | 0.17 [0.02, 1.40] | • |
| Mullany 2006 | 13 | 4930 | 52 | 5076 | 18.1% | 0.26 [0.14, 0.47] | |
| Sazawal 2016 | 2 | 18015 | 33 | 18896 | 6.7% | 0.06 [0.02, 0.26] | |
| Semrau 2016 | 82 | 18510 | 118 | 19346 | 25.6% | 0.73 [0.55, 0.96] | |
| Soofi 2012 | 166 | 4867 | 309 | 4874 | 27.3% | 0.54 [0.45, 0.65] | - |
| Total (95% CI) | | 56683 | | 58205 | 100.0% | 0.39 [0.26, 0.60] | • |
| Total events | 280 | | 559 | | | | |
| Heterogeneity: Tau ² = | = 0.16; Chi ² = 21.8 | 84, df = 5 | P = 0.000 | $(6); I^2 = 1$ | 77% | - | 2 0.1 1 10 50 |
| Test for overall effect | t: $Z = 4.32 (P < 0.0)$ | 001) | | | | 0.07 | 2 0.1 1 10 50 Favours [chlorhexidine] Favours [dry cord care] |

Prevention and Treatment of Neonatal Infections in LMICs Outcome: Omphalitis by cleansing frequency

| | Chlorhexidine cle | eansing | Dry core | d care | | Risk Ratio | Risk Ratio |
|-----------------------------------|----------------------------------|---------------|---------------|-----------------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M–H, Random, 95% CI |
| 4.4.1 Single cleansir | ng | | | | | | |
| Arifeen 2012 | 31 | 9354 | 42 | 9924 | 18.1% | 0.78 [0.49, 1.24] | |
| Subtotal (95% CI) | | 9354 | | 9924 | 18.1% | 0.78 [0.49, 1.24] | |
| Total events | 31 | | 42 | | | | |
| Heterogeneity: Not a | pplicable | | | | | | |
| Test for overall effect | t: $Z = 1.03 (P = 0.30)$ |)) | | | | | |
| 4.4.2 Multiple cleans | sing | | | | | | |
| Arifeen 2012 | 16 | 10254 | 42 | 9924 | 15.7% | 0.37 [0.21, 0.66] | |
| Mullany 2006 | 13 | 4930 | 52 | 5076 | 15.1% | 0.26 [0.14, 0.47] | |
| Sazawal 2016 | 2 | 18015 | 33 | 18896 | 5.4% | 0.06 [0.02, 0.26] | |
| Semrau 2016 | 82 | 18510 | 118 | 19346 | 22.0% | 0.73 [0.55, 0.96] | - |
| Soofi 2012 | 166 | 4867 | 309 | 4874 | 23.7% | 0.54 [0.45, 0.65] | * |
| Subtotal (95% CI) | | 56576 | | 58116 | 81.9% | 0.41 [0.26, 0.62] | • |
| Total events | 279 | | 554 | | | | |
| Heterogeneity: Tau ² : | · | | P = 0.000 | $(14); I^2 = 3$ | 81% | | |
| Test for overall effect | t: $Z = 4.10 (P < 0.00)$ | 001) | | | | | |
| Total (95% CI) | | 65930 | | 68040 | 100.0% | 0.46 [0.32, 0.67] | • |
| Total events | 310 | | 596 | | | | |
| Heterogeneity: Tau ² : | = 0.14; Chi ² = 23.06 | 6, df = 5 (1) | P = 0.000 | $(3); I^2 = 1$ | 78% | <u> </u> | 01 0.1 1 10 100 |
| Test for overall effect | t: $Z = 4.06 (P < 0.00)$ | 001) | | | | 0. | 01 0.1 1 10 100 Favours [chlorhexidine] Favours [dry cord care] |
| Test for subgroup di | fferences: $Chi^2 = 4.1$ | 14, df = 1 | (P = 0.04) | $(1)^2 = 75$ | 5.9% | | ravours [cinornexionie] ravours [ury cord care] |
| Э. | | • | , | | | | |

Outcome: Omphalitis by severity

| | Chlorhexidine c | _ | Dry co | | Wainba | Risk Ratio | Risk Ratio |
|---|------------------------------|----------------------|-------------|------------------------|---------------------|---|---|
| tudy or Subgroup | Events | | Events | ı otal | weignt | M-H, Random, 95% CI | M-H, Random, 95% CI |
| 1.5.1 Redness extendir | - | | | 0.55 | | 0.00/10.00 | |
| Arifeen 2012 | 1406 | 10254 | 1545 | 9924 | 10.0% | 0.88 [0.82, 0.94] | * |
| Mekonnen 2020 | 1 | 107 | 5 | 89 | 0.3% | 0.17 [0.02, 1.40] | · · · · · · · · · · · · · · · · · · · |
| Sazawal 2016 | 1413 | 18015 | 2183 | 18896 | 10.1% | 0.68 [0.64, 0.72] | |
| Subtotal (95% CI) | 2020 | 28376 | 2722 | 28909 | 20.4% | 0.76 [0.58, 0.98] | |
| otal events | 2820 | -0 15 2 /5 | 3733 | 201) 12 | 0.40/ | | |
| Heterogeneity: Tau² = 0 Test for overall effect: Z | , | | , < 0.000 |)(1); I ² = | 94% | | |
| I.5.2 Moderate or seve | re redness | | | | | | |
| Arifeen 2012 | 327 | 10254 | 403 | 9924 | 9.1% | 0.79 [0.68, 0.91] | - |
| Mekonnen 2020 | 4 | 107 | 32 | 89 | 1.4% | 0.10 [0.04, 0.28] | |
| Mullany 2006 | 438 | 4703 | 638 | 4859 | 9.5% | 0.71 [0.63, 0.80] | * |
| Sazawal 2016 | 1051 | 18015 | 1427 | 18896 | 9.9% | 0.77 [0.72, 0.83] | - |
| Soofi 2012 | 161 | 4867 | 290 | 4874 | 8.4% | 0.56 [0.46, 0.67] | - |
| Subtotal (95% CI) | | 37946 | | 38642 | 38.3% | 0.67 [0.56, 0.80] | ◆ |
| Total events | 1981 | | 2790 | . 5 | | | |
| Heterogeneity: $Tau^2 = 0$ | | | o.000 | $(11); I^2 = 8$ | 5% | | |
| Test for overall effect: Z | t = 4.52 (P < 0.0) | 00001) | | | | | |
| l.5.3 Moderate or seve | ere redness, wit | h pus, or s | evere re | dness alo | ne | | |
| Arifeen 2012 | 151 | 10254 | 258 | 9924 | 8.2% | 0.57 [0.46, 0.69] | - |
| Mekonnen 2020 | 4 | 107 | 9 | 89 | 1.1% | 0.37 [0.12, 1.16] | • |
| Mullany 2006 | 147 | 4883 | 315 | 5021 | 8.3% | 0.48 [0.40, 0.58] | - |
| Sazawal 2016 | 166 | 18015 | 286 | 18896 | 8.3% | 0.61 [0.50, 0.74] | - |
| Soofi 2012 | 63 | 4867 | 116 | 4874 | 6.4% | 0.54 [0.40, 0.74] | |
| Subtotal (95% CI) | | 38126 | | 38804 | 32.3% | 0.55 [0.49, 0.61] | • |
| Total events | 531 | | 984 | 2 | | | |
| Heterogeneity: Tau² = 0 Test for overall effect: Z | | | = 0.47); | $I^2 = 0\%$ | | | |
| 1.5.4 Severe redness w | ith pus | | | | | | |
| Arifeen 2012 | 16 | 10254 | 42 | 9924 | 3.2% | 0.37 [0.21, 0.66] | |
| Mullany 2006 | 13 | 4930 | 52 | 5076 | 3.0% | 0.26 [0.14, 0.47] | |
| Sazawal 2016 | 2 | 18015 | 33 | 18896 | 0.7% | 0.06 [0.02, 0.26] | • |
| Soofi 2012 Subtotal (95% CI) | 9 | 4867 38066 | 18 | 4874 38770 | 2.0% 8.9% | 0.50 [0.23, 1.11] 0.29 [0.16, 0.52] | • |
| Total events | 40 | | 145 | | | | |
| Heterogeneity: Tau² = 0 Fest for overall effect: Z | | | = 0.07); | $I^2 = 58\%$ | | | |
| Total (95% CI) | | 142514 | | 145125 | 100.0% | 0.59 [0.52, 0.67] | ◆ |
| Total events | 5372 | | 7652 | | | | |
| Heterogeneity: $Tau^2 = 0$ | 0.04; Chi ² = 125 | .42, df = 16 | 5 (P < 0.0) | 00001); I ² | = 87% | | 0.02 0.1 1 10 5 |
| Test for overall effect: Z | | | | *** | | | |
| Test for subgroup differ | ences Chi ² – 1 | 3.37 df = 3 | (P = 0.0) | $(0.04) I^2 = $ | 77 6% | | Favours [chlorhexidine] Favours [dry cord care] |

Comparison: Chlorhexidine whole-body cleansing versus water/saline

Outcome: Neonatal mortality

| | Chlorhex | cidine | Water/S | aline | | Risk Ratio | Risk Ratio |
|-------------------------|----------|-----------|---------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Teilsch 2007 | 264 | 8650 | 263 | 8880 | 100.0% | 1.03 [0.87, 1.22] | - |
| Total (95% CI) | | 8650 | | 8880 | 100.0% | 1.03 [0.87, 1.22] | |
| Total events | 264 | | 263 | | | | |
| Heterogeneity: Not ap | • | | | | | | 0.5 0.7 1 1.5 2 |
| Test for overall effect | Z = 0.35 | (P = 0.7) | 3) | | | | Favours [chlorhexidine] Favours [water/saline] |

4.3.2. Topical Emollients

Comparison: Topical emollient versus routine skin care in term neonates

Outcome: Atopic dermatitis

| · | Topical emo | llient | Contr | ol | | Risk Ratio | | Risk Ratio | |
|--|-------------|--------|--------|-------|--------|--------------------|------|---|------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI | |
| Techasatian 2021 | 16 | 74 | 39 | 72 | 90.1% | 0.40 [0.25, 0.65] | | - | |
| Thitthiwong 2020 | 0 | 25 | 4 | 27 | 9.9% | 0.12 [0.01, 2.12] | • | - | |
| Total (95% CI) | | 99 | | 99 | 100.0% | 0.37 [0.23, 0.60] | | • | |
| Total events | 16 | | 43 | | | | | | |
| Heterogeneity: Chi ² = Test for overall effect | | | | % | | | 0.01 | 0.1 1 10 Favours emollient Favours cont | 100 rol |

Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: *Invasive infection (any organism)*

| | Topica | l oil | Routine ski | n care | | Risk Ratio | | | Risk Ratio | | |
|--|---------------|----------|-------------|--------|--------|--------------------|------|--------------------|------------------------|--------------------|---------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | | M- | H, Fixed, 95% C | | |
| Konar 2019 | 12 | 1146 | 16 | 1148 | 100.0% | 0.75 [0.36, 1.58] | | | | | |
| Total (95% CI) | | 1146 | | 1148 | 100.0% | 0.75 [0.36, 1.58] | | | | | |
| Total events | 12 | | 16 | | | | | | | | |
| Heterogeneity: Not ap Test for overall effect | • | 5 (P = 0 |).45) | | | | 0.01 | 0.1 Favours ton | 1 Dical oil Favours | 10 routine skir | 100 n care |

Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: Severe neurodevelopmental disability

| | Topica | | Routine skin | | | Risk Ratio | Risk Ratio |
|--|----------------|-----------------|--------------|-----------------|-----------------------|--------------------|---|
| Study or Subgroup | Events | | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 5.7.1 BSID (3rd Ed): | • | | _ | | | | |
| Konar 2019 Subtotal (95% CI) | 1 | 27 27 | 5 | 27 27 | 23.4% 23.4% | | |
| Total events Heterogeneity: Not ap | 1 oplicable | | 5 | | | | |
| Test for overall effect | Z = 1.52 | P = 0 | 0.13) | | | | |
| 5.7.2 BSID (3rd Ed): | Language | e <70 | | | | | |
| Konar 2019 Subtotal (95% CI) | 2 | 27 27 | 8 | 24 24 | 39.6% 39.6% | | |
| Total events Heterogeneity: Not ap Test for overall effect | • | 3 (P = C | 8 ().04) | | | | |
| 5.7.3 BSID (3rd Ed): | Motor <7 | 0 | | | | | |
| Konar 2019 Subtotal (95% CI) | 1 | 27 27 | 5 | 24 24 | 24.7% 24.7% | | |
| Total events Heterogeneity: Not ap | 1 oplicable | | 5 | | | | |
| Test for overall effect | z = 1.63 | S (P = C) | 0.10) | | | | |
| 5.7.4 BSID (3rd Ed): | Social-en | notiona | al <70 | | | | |
| Konar 2019 Subtotal (95% CI) | 0 | 27 27 | 2 | 24 24 | 12.3% 12.3% | | |
| Total events Heterogeneity: Not ag | 0 anlicable | | 2 | | | | |
| Test for overall effect | • | B (P = C |).26) | | | | |
| Total (95% CI) | | 108 | | 99 | 100.0% | 0.20 [0.08, 0.53] | |
| Total events | 4 | 2 /- | 20 | | | | |
| Heterogeneity: Chi ² = | | | |)% | | | 0.01 0.1 1 10 100 |
| Test for overall effect | | • | | D 10 | 2 2 | ., | Favours topical oil Favours routine skin care |
| Test for subgroup dif | terences: | Chi' = | 0.04, dt = 3 | P = 1.00 | $(1), 1^2 = 0$ | % | |

Comparison: Sunflower seed oil versus mustard oil in mixed term and preterm newborns

Outcome: All-cause neonatal mortality (intention-to-treat)

| | Sunflower s | eed oil | Mustar | rd oil | | Risk Ratio | Risk Ratio |
|--|-------------|---------|---------------|--------|--------|--------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Katz 2024 (1) | 478 | 15676 | 520 | 16327 | 41.5% | 0.96 [0.85, 1.08] | |
| Kumar 2021 (2) | 718 | 13478 | 708 | 13109 | 58.5% | 0.99 [0.89, 1.09] | - |
| Total (95% CI) | | 29154 | | 29436 | 100.0% | 0.97 [0.90, 1.05] | |
| Total events | 1196 | | 1228 | | | | |
| Heterogeneity: Chi ² = Test for overall effect | | | $I^2 = 0\%$ | | | | 0.7 0.85 1 1.2 1.5 Favours SSO oil Favours mustard oil |

Footnotes

- (1) Intention-to-treat analysis
- (2) Intention-to-treat analysis

Outcome: All-cause neonatal mortality for low birthweight newborns (less than or equal to 2,500 grams) (intention-to-treat)

| | Sunflower se | ed oil | Mustar | d oil | | Risk Ratio | Risk Ratio |
|-----------------------------------|------------------|----------|---------------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Katz 2024 (1) | 126 | 3538 | 113 | 3713 | 25.9% | 1.17 [0.91, 1.50] | +- |
| Kumar 2021 (2) | 327 | 5622 | 304 | 5236 | 74.1% | 1.00 [0.86, 1.17] | * |
| Total (95% CI) | | 9160 | | 8949 | 100.0% | 1.05 [0.92, 1.19] | • |
| Total events | 453 | | 417 | | | | |
| Heterogeneity: Chi ² = | 1.09, df = 1 (P) | P = 0.30 | $; I^2 = 8\%$ | | | | 0.2 0.5 1 2 5 |
| Test for overall effect | Z = 0.67 (P = | 0.50) | | | | | Favours SSO oil Favours mustard oil |

Footnotes

- (1) newborns <2500 grams; intention-to-treat analysis
- (2) newborns ≤2500 grams; intention-to-treat analysis

Outcome: All-cause neonatal mortality for very low birthweight newborns (less than or equal to 1,500 grams) (intention-to-treat)

| | Sunflower se | ed oil | Mustar | d oil | | Risk Ratio | Risk Ratio |
|-----------------------------------|-----------------|----------|----------------|-------|--------|--------------------|-------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Katz 2024 (1) | 26 | 62 | 23 | 51 | 20.1% | 0.93 [0.61, 1.42] | |
| Kumar 2021 (2) | 78 | 311 | 95 | 278 | 79.9% | 0.73 [0.57, 0.94] | - |
| Total (95% CI) | | 373 | | 329 | 100.0% | 0.77 [0.62, 0.96] | • |
| Total events | 104 | | 118 | | | | |
| Heterogeneity: Chi ² = | 0.90, df = 1 (F | P = 0.34 |); $I^2 = 0\%$ | | | | 0.1 0.2 0.5 1 2 5 10 |
| Test for overall effect | Z = 2.32 (P = | 0.02) | | | | | Favours SSO oil Favours mustard oil |

Footnotes

- (1) newborns <1500 grams; intention-to-treat analysis (2) newborns ≤1500 grams; intention-to-treat analysis

Outcome: All-cause neonatal mortality (per protocol)

| | Sunflower s | eed oil | Mustar | d oil | | Risk Ratio | Risk Ratio |
|--|-------------|---------|--------|-------|--------|--------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Kumar 2021 (1) | 256 | 4096 | 498 | 4720 | 100.0% | 0.59 [0.51, 0.68] | • |
| Total (95% CI) | | 4096 | | 4720 | 100.0% | 0.59 [0.51, 0.68] | • |
| Total events | 256 | | 498 | | | | |
| Heterogeneity: Not ap Test for overall effect | • | 0.00001 |) | | | | 0.2 0.5 1 2 5 Favours SSO oil Favours mustard oil |

Footnotes

(1) Per protocol analysis

Outcome: Possible serious bacterial infections

| | Sunflower seed oil | | Mustard oil | | Risk Ratio | | Risk Ratio |
|-------------------------|---------------------|---------|---------------|-------|------------|--------------------|-------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Katz 2024 (1) | 1823 | 13483 | 1940 | 14145 | 100.0% | 0.99 [0.93, 1.05] | - |
| Total (95% CI) | | 13483 | | 14145 | 100.0% | 0.99 [0.93, 1.05] | • |
| Total events | 1823 | | 1940 | | | | |
| Heterogeneity: Not ap | oplicable | | | | | | 0.5 0.7 1 1.5 |
| Test for overall effect | Z = 0.47 (P = 0.47) | = 0.64) | | | | | Favours SSO oil Favours mustard oil |

Footnotes

(1) Intention-to-treat analysis

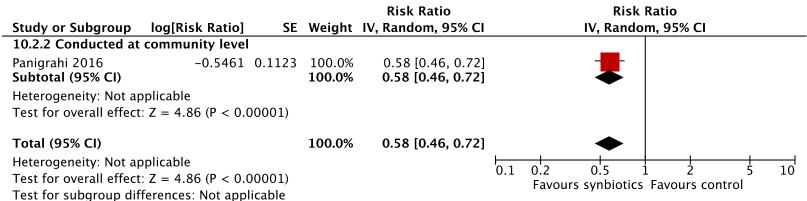
4.3.3. Synbiotics Supplementation

Comparison: Synbiotics versus control in term newborns

Outcome: All-cause neonatal mortality

| | | | Risk Ratio | Risk Ratio |
|---|-----------------|------------------|--------------------|---|
| Study or Subgroup | log[Risk Ratio] | SE Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 10.1.2 Conducted at | community-level | | | |
| Panigrahi 2016 Subtotal (95% CI) | 0.4055 0.64 | 100.0% 100.0% | ,, | |
| Heterogeneity: Not ap Test for overall effect | • | | | |
| Total (95% CI) | | 100.0% | 1.50 [0.42, 5.31] | |
| Heterogeneity: Not ap Test for overall effect Test for subgroup dif | • | le | | 0.01 0.1 1 10 100 Favours synbiotics Favours control |

Outcome: *Invasive infection*



4.3.4. Community-Based Antibiotic Delivery for PSBIs

Comparison: Community-based antibiotic delivery versus standard care (i.e., hospital referral)

Outcome: All-cause neonatal mortality

| | Experin | nental | Cont | rol | Risk Ratio | | Risk | k Ratio | |
|-----------------------------------|------------|--------------|-----------|-----------|-----------------|---------------------|-----------------------|----------------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | | |
| Baqui 2008 | 82 | 2812 | 125 | 2872 | 10.2% | 0.67 [0.51, 0.88] | <u> </u> | | |
| Soofi 2017 | 736 | 17705 | 1050 | 19163 | 89.8% | 0.76 [0.69, 0.83] | - | | |
| Total (95% CI) | | 20517 | | 22035 | 100.0% | 0.75 [0.69, 0.82] | • | | |
| Total events | 818 | | 1175 | | | | | | |
| Heterogeneity: Tau ² = | = 0.00; Ch | $ni^2 = 0.7$ | 1, df = 1 | (P = 0.4) | $I(0); I^2 = 0$ | % | 0.5 0.7 | 1 1 5 | |
| Test for overall effect | Z = 6.49 | P < 0.0 | 00001) | | | | Favours [experimental | l] Favours [control] | 2 |

Outcome: Early neonatal mortality

| Experimental | | nental | Control | | | Risk Ratio | Risk Ratio | | |
|-------------------------|-----------|-----------|------------------------|-------------------|--------|---------------------|---------------------|---------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | | |
| Soofi 2017 | 610 | 17705 | 871 | 19163 | 100.0% | 0.76 [0.68, 0.84] | _ | | |
| Total (95% CI) | | 17705 | | 19163 | 100.0% | 0.76 [0.68, 0.84] | | | |
| Total events | 610 | | 871 | | | | | | |
| Heterogeneity: Not ap | oplicable | | | | | - | 0.7 0.85 | 1 12 15 | |
| Test for overall effect | Z = 5.35 | 5 (P < 0. | Favours [experimental] | Favours [control] | | | | | |

Outcome: *Late neonatal mortality*

| | Experimental | | erimental Control | | | Risk Ratio | Risk Ratio | |
|-------------------------|---------------|-------------|-------------------|-------|--------|---------------------|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | |
| Soofi 2017 | 126 | 17705 | 179 | 19163 | 100.0% | 0.76 [0.61, 0.96] | | |
| Total (95% CI) | | 17705 | | 19163 | 100.0% | 0.76 [0.61, 0.96] | | |
| Total events | 126 | | 179 | | | | | |
| Heterogeneity: Not ap | - | | | | | | 05 07 1 15 2 | |
| Test for overall effect | Z = 2.35 | 5 (P = 0.0) | 02) | | | | Favours [experimental] Favours [control] | |

Outcome: Sepsis-specific neonatal mortality

| | Experin | nental | Cont | rol | | Risk Ratio | Risk Ratio | |
|-------------------------|---------------|-------------|---------------|-------|--------|---------------------|------------------------------------|---------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | |
| Soofi 2017 | 87 | 17705 | 120 | 19163 | 100.0% | 0.78 [0.60, 1.03] | - | |
| Total (95% CI) | | 17705 | | 19163 | 100.0% | 0.78 [0.60, 1.03] | | |
| Total events | 87 | | 120 | | | | | |
| Heterogeneity: Not ap | plicable | | | | | | 0.2 0.5 1 2 | <u></u> |
| Test for overall effect | Z = 1.73 | 8 (P = 0.0) | 08) | | | | Favours [experimental] Favours [co | ntrol] |

Appendix 5: Prophylactic Systemic Antifungal Agents Background, Methods, Results, and Discussion

Background

Yeast are naturally occurring on the skin and in the genitourinary tract and are transmitted vertically from mother to baby or horizontally within the hospital environment as a consequence of inadequate hand hygiene and IPC practices [14-17]; however, when colonizing yeast enter the newborn's bloodstream, severe systemic multi-organ infections can occur [18] with clinical presentations that are indistinguishable from invasive bacterial infections [10, 19]. To prevent systemic fungal infection, antifungal prophylaxis is frequently used, particularly for very preterm (<32 weeks' gestation) and very low birth weight (VLBW, <1500 grams) infants who are at greatest risk of fungemia due to their need for often lengthy hospitalization, surgeries, catheterization or mechanical ventilation, and prior or ongoing antibiotic therapy [10, 15, 20]. The most pervasive newborn nosocomial fungal infections are caused by *Candida* species [21], and prophylactic antifungal agents such as fluconazole, are normally the first choice for high-risk neonates, with amphotericin B commonly prescribed to treat invasive candidiasis [16]. Although invasive candidiasis is primarily diagnosed with blood culture, this test lacks sensitivity and high rates of false negative tests can hinder appropriate and timely antifungal treatment [14, 17, 22, 23]. There are also challenges in isolating higher than normal blood volumes and at greater frequency than normal to detect both the presence of infection and its clearance over time [16, 23, 24]. Because systemic antifungal infection is difficult to diagnose and therefore treat in a timely manner, there has been increased reliance on antifungal prophylaxis but gaps remain in the literature regarding its effect on mortality, morbidity, and its impact on the development of antifungal resistance [10] which is rising globally among *Candida auris*, *C. parapsilosis*, and *C. krusei* [14, 17, 21].

Methods

The review on prophylactic systemic antifungals searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL for randomized or quasi-randomized controlled trials pertaining to the effect of prophylactic systemic antifungal therapy versus control or placebo or another

antifungal agent or regimen on primary outcomes of confirmed invasive fungal infection and mortality prior to hospital discharge in very preterm or VLBW infants [10].

We re-ran the search in the same databases for relevant trials published after the review's final search date of May 2015, and identified three new trials whose evidence was synthesized with ten trials from the existing review. For this topic, by technical advisory group (TAG) recommendation, we leveraged data from HIC contexts, recognizing the cost of the intervention and that in many LMICs newborns may not survive long enough to develop secondary fungal infections. To compare HIC and LMIC combined estimates with LMIC-only estimates, we disaggregated LMIC studies to evaluate the effectiveness of prophylactic systemic antifungals in low-resource settings. All trials were conducted in tertiary care facilities with eight trials conducted in HICs and five trials, two new and three existing trials, conducted in LMICs.

Results

In treatment of suspected fungal infections in very preterm and very low birth weight (VLBW) newborns from high- and low-income facility-based settings, prophylactic systemic antifungal agents reduced the risk of invasive fungal infections by 59% (95% CI 45-70%) and mortality risk prior to hospital discharge by 22% (95% CI 1-38%), when compared to control or placebo. In very preterm and VLBW newborns from LMICs alone, prophylactic systemic antifungals reduced the risk of invasive fungal infections by 47% (95% CI 20-65%), but had no significant effect on mortality prior to hospital discharge (see *Appendix 7.1.6.*), when compared to control or placebo.

Table 4 Effect estimates for prophylactic systemic antifungal agents treat suspected neonatal infections in facility settings.

| Prophylactic systemic antifungal agents | | | | | | | | | |
|---|-----------------|-----------------|-------------------|------------------------|-----------------|---------------------------------|--|--|--|
| Comparison | Population | Outcome | Subgroup | No. of studies (No. of | Effect estimate | Heterogeneity (I ²) | | | |
| | | | | participants) | (95% CI) | | | | |
| Prophylactic | Very preterm or | Invasive fungal | Total* | 12 (1,827) | RR 0.41 | 37% | | | |
| systemic antifungals | VLBW neonates | infection | | | (0.30, 0.55) | | | | |
| vs. control or | | | | | | | | | |
| placebo | | | | | | | | | |
| Prophylactic | Very preterm or | Invasive fungal | Studies conducted | 4 (474) | RR 0.53 | 67% | | | |
| systemic antifungals | VLBW neonates | infection | in LMICs only | | (0.35, 0.80) | | | | |
| vs. control or | | | | | | | | | |
| placebo | | | | | | | | | |

| Prophylactic | Very preterm or | Neonatal | Total* | 11 (1,551) | RR 0.78 | 0% |
|----------------------|-----------------|--------------------|--------|------------|--------------|----|
| systemic antifungals | VLBW neonates | mortality prior to | | | (0.62, 0.99) | |
| vs. control or | | hospital discharge | | | | |
| placebo | | | | | | |

VLW, very low birth weight; bolded effect estimates are statistically significant (p<0.05)

Discussion

Prophylactic systemic antifungal agents were strongly effective in reducing the risk of invasive fungal infections but less effective in reducing the risk of neonatal mortality prior to hospital discharge when used in a high-resource settings for treatment of suspected fungal infections in very preterm and VLBW newborns. Comparatively, we found that systemic antifungal prophylaxis reduced the risk of invasive fungal infections but had no effect on mortality prior to hospital discharge in very preterm and VLBW newborns from LMICs. Similarly, the 2015 Cochrane review [10], which included trials at all income levels, found a statistically significant reduction in the risk of invasive fungal infection only, with no difference in mortality prior to discharge between treatment and control groups. Considerations that must be addressed in LMIC implementation include improving antifungal drug availability and ensuring laboratory diagnostic capacity for fungal infections [25]. In the absence of such resources, stricter attention to modifiable risk factors for nosocomial fungal infections such as the use of broad-spectrum antibiotics and central venous catheters are recommended to decrease fungal infection incidence [14]. More LMIC-based research is needed to evaluate the safety and effectiveness of this intervention, as well as considerations including cost-effectiveness, and barriers and facilitators to implementation, to further elucidate the viability of this intervention in LMICs.

^{*}Leveraged HIC data to produce an HIC and LMIC combined estimate.

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