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 overuse 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 bahrain or bangladesh or barbados or "republic of belarus" or belarus or byelarus or belorussia or byelorussian 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 cameron or cameroun or "central african republic" or "ubangi shari" or chad or chile or china or colombia or comoros or "comoro islands" or "iles comores" or mayotte or "democratic republic of the congo" or "democratic republic congo" or congo or zaire or "costa rica" or "cote d'ivoire" or "cote d' ivoire" or "cote divoire" or "cote d ivoire" or "ivory coast" or croatia or cuba or cyprus or "czech republic" or czechoslovakia or djibouti or "french somaliland" or dominica or "dominican republic" or ecuador or egypt or "united arab republic" or "el salvador" or "equatorial guinea" or "spanish guinea" or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or "gabonese republic" or gambia or "georgia (republic)" or georgian or ghana or "gold coast" or gibraltar or greece or grenada or guam or guatemala or guinea or "guinea bissau" or guyana or "british guiana" or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or "isle of man" or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or "republic of korea" or "north korea" or "south korea" or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or "kyrgyz republic" or kirghiz or laos or "lao pdr" or "lao people's democratic republic" or latvia or lebanon or "lebanese republic" or lesotho or basutoland or liberia or libya or "libyan arab jamahiriya" or lithuania or macau or macao or "republic of north macedonia" or macedonia or madagascar or "malagasy republic" or malawi or nyasaland or malaysia or "malay federation" or "malaya federation" or maldives or "indian ocean islands" or "indian ocean" or mali or malta or micronesia or "federated states of micronesia" or kiribati or "marshall islands" or nauru or "northern mariana islands" or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or morocco or ifni or mozambique or "portuguese east africa" or myanmar or burma or namibia or nepal or "netherlands antilles" or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or "papua new guinea" or "new guinea" or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or "portuguese republic" or "puerto rico" or romania or russia or "russian federation" or rwanda or ruanda or samoa or "pacific islands" or polynesia or "samoan islands" or "navigator island" or "navigator islands" or "sao tome and principe" or "saudi arabia" or senegal or serbia or seychelles or "sierra leone" or slovakia or "slovak republic" or slovenia or melanesia or "solomon island" or "solomon islands" or "norfolk island" or "norfolk islands" or somalia or "south africa" or "south sudan" or "sri lanka" or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or "saint lucia" or "st. lucia" or "saint vincent and the grenadines" or "saint vincent" or "st. vincent" or grenadines or sudan or suriname or surinam or "dutch guiana" or "netherlands guiana" or syria or "syrian arab republic" or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or "timor leste" or "east timor" or togo or "togolese republic" or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or "new hebrides" or venezuela or vietnam or "viet nam" or "middle east" or "west bank" or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or "northern rhodesia"

	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 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.
11	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	***Primary outcomes:*** 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. ***Secondary outcomes:*** Duration of antibiotic therapy, proportion of neonates receiving any antibiotic, length of hospital stay	Randomized or quasi-randomized trials, observational studies, program evaluations, and implementation studies

				(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	***Primary outcomes:*** 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)

Review Group's IPD meta-analysis) and a review from Zhou 2022 [3]				-Possible serious bacterial infections (PSBIs) (Any PSBI: Presence of any one of the following symptoms or signs: stopped feeding, severe chest indrawing, movements only on stimulation, fever (>38^{o}C axillary), hypothermia (<35.5^{o}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 emollients for preterm neonates ***– as-is review from Cleminson 2021 [5]***	Preterm infants (< 37 weeks' gestation)	Ointment or cream versus routine skincare • Oil versus routine skincare • Ointment or cream versus oil •One oil (or combination) versus another oil (or combination)	Standard of care	***Primary outcomes:*** Invasive infection diagnosed more than 48 hours after birth as determined by culture from a normally sterile site: cerebrospinal fluid; blood; urine (obtained by sterile urethral catheterisation or suprapubic bladder tap); bone or joint, peritoneum, pleural space, or central venous line tip; or findings on autopsy examination consistent with invasive microbial infection. If sufficient data were available, we planned to examine specific effects on infection with these organisms: • Coagulase-negative staphylococci • Other bacteria (gram-negative bacilli, Saureus, enterococci) • Fungi ***Secondary outcomes:*** • Death (all cause) before hospital discharge (in facility-based trials), or at latest assessment in community trials • Growth: weight gain (g/kg/day); linear growth (mm/week); head circumference (mm/week); skinfold thickness (mm/week) during the trial period • Neurodevelopmental outcomes assessed at more than 12 months post-term (measured using validated	Controlled trials using random or quasi-random participant allocation. Cluster-randomized trials where the unit of randomization was a group of infants (for example, in a neonatal unit) were eligible for inclusion.

				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)	
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 where the intervention was started in the neonatal period.	Standard of care	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 supplementation ***– as-is review from Sharif 2020 [7]***	Included very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants (pre-specified analyses for	Included enteral administration of any probiotic or probiotic combination for at least one week compared to placebo or no treatment. Categorised probiotic preparations at the genus level	Standard of care	***Primary outcomes:*** •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	Included RCTs and quasi-RCTs

	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 ◦lethargy, 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

– as-is review from Imdad 2020 [8]	birth weight and preterm infants	-All-cause infant mortality at 6 months (death between 0 days to 6 months of life) -All-cause infant mortality at 12 months (death between 0 days to 12 months life). In the event that the outcomes were not reported in the follow-up periods mentioned (e.g., 28 days, 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. ***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	quasi-experimental studies that were designed as RCTs. Other study designs were considered, such as before-after studies, regression discontinuity designs, interrupted time series (ITS) but none of these studies were included.

				-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 system; or free air in the abdomen •All-cause mortality before discharge from hospital	Randomized or quasi-randomized (predictable allocation) controlled trials, including cluster-RCTs.

				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 ***– as-is review from Imdad 2020 [8]***	Included neonates regardless of health status, including low birth weight and preterm infants	Neonatal oral probiotics/synbiotics supplementation	No probiotic supplementation/ placebo	***Primary outcomes:*** -All-cause neonatal mortality (death between 0–28 days of life) -All-cause infant mortality at 6 months (death between 0 days to 6 months of life) -All-cause infant mortality at 12 months (death between 0 days to 12 months life). In the event that the outcomes were not reported in the follow-up periods mentioned (e.g., 28 days, 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	Studies selected for inclusion in this review were either experimental or quasi-experimental studies that were designed as RCTs. Other study designs were considered, such as before-after studies, regression discontinuity designs, ITS but none of these

				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 sensory outcomes.	studies were included.
Prophylactic systemic antifungal agents	Very preterm or VLBW infants, with or without evidence of fungal colonisation but without	Systemic antifungal prophylaxis, given by intravenous or enteral route	Placebo or no drug, oral or topical antifungal prophylaxis, or another systemic	***Primary outcomes:*** 1. Confirmed invasive fungal infection as determined by • culture of fungus from a normally sterile site e.g. cerebrospinal fluid, blood, urine, bone or joint, peritoneum, pleural space;	Randomized controlled trials or quasi-randomized controlled trials

- ***updated review from Cleminson 2015 [10]***	evidence of invasive fungal infection at study entry	antifungal agent or dose regimen	• findings on autopsy examination consistent with invasive fungal 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

				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.	<u>Comparison 1:</u> Community-based programmes of newborn care that include the initiation of antibiotics in the community for PSBI in LMICs <u>Comparison 2:</u> Community-based delivery of simplified injectable antibiotics or oral antibiotics, or both for PSBI in neonates	<u>Comparison 1:</u> 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) <u>Comparison 2:</u> Community-based delivery of seven to 10 days of injectable penicillin/ampicillin and an injectable aminoglycoside for PBSI in neonates	***Primary outcomes:*** 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:

1. Treatment failure - defined as any one of the following: 1) death within seven days after enrolment; 2) hospital admission within seven days after enrolment due to clinical deterioration; 3) 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

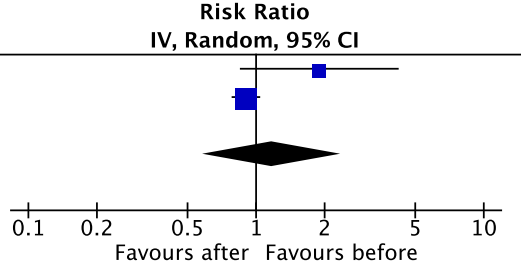
Single-Component Intervention: *Regulation*

Outcome: *Neonatal sepsis/suspected sepsis*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% 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: $Tau^2 = 0.19$; $Chi^2 = 3.26$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 0.45 (P = 0.65)



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

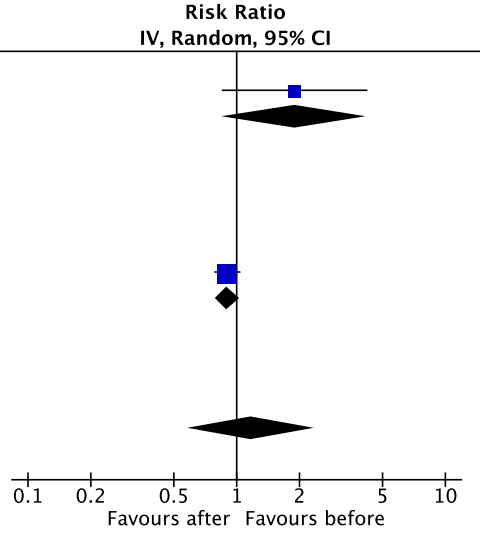
Outcome: *Neonatal sepsis/suspected sepsis by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Cross-sectional study						
Akintan 2024 (1)	12	19	5	15	35.5%	1.89 [0.86, 4.19]
Subtotal (95% CI)		**19**		**15**	**35.5%**	**1.89 [0.86, 4.19]**
Total events	12		5			
Heterogeneity: Not applicable						
Test for overall effect: 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 applicable						
Test for overall effect: 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); $I^2 = 69\%$

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: $Chi^2 = 3.26$, df = 1 (P = 0.07), $I^2 = 69.3\%$



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

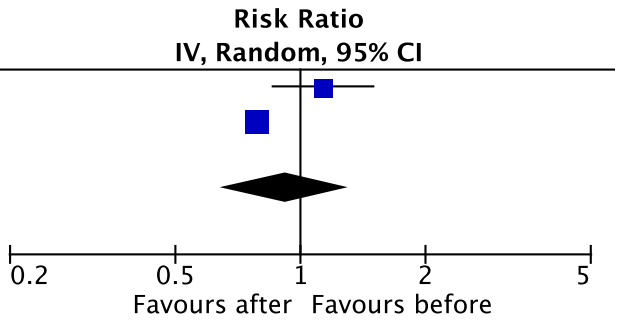
Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *Number of newborns receiving at least one antimicrobial*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.06$; $Chi^2 = 6.62$, df = 1 (P = 0.01); $I^2 = 85\%$

Test for overall effect: Z = 0.47 (P = 0.64)



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

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 Cross-sectional study						
Akintan 2024	17	19	15	19	42.5%	1.13 [0.86, 1.50]
Subtotal (95% CI)		**19**		**19**	**42.5%**	**1.13 [0.86, 1.50]**
Total events	17		15			
1.4.2 Cohort study						
Wang 2020	3328	4488	4478	4743	57.5%	0.79 [0.77, 0.80]
Subtotal (95% CI)		**4488**		**4743**	**57.5%**	**0.79 [0.77, 0.80]**
Total events	3328		4478			
Total (95% CI)		**4507**		**4762**	**100.0%**	**0.92 [0.64, 1.31]**
Total events	3345		4493			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.88 (P = 0.38)

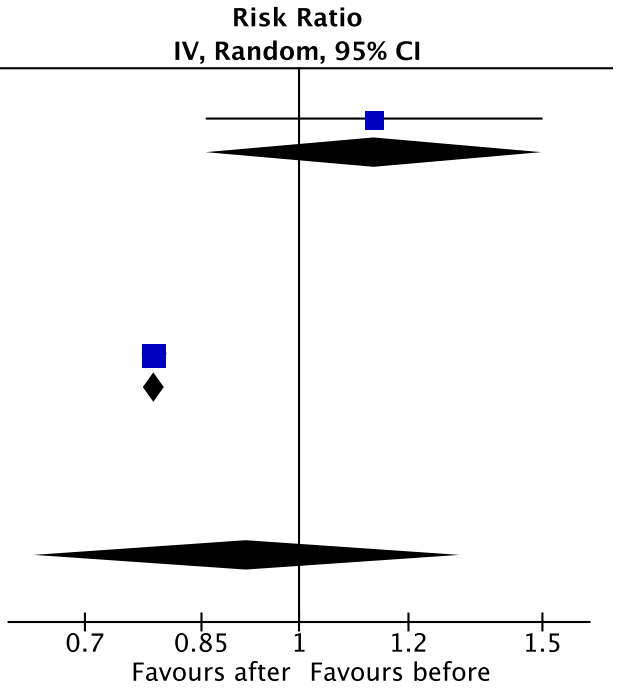
Heterogeneity: Not applicable

Test for overall effect: Z = 25.44 (P < 0.00001)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.62$, df = 1 (P = 0.01); $I^2 = 85\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: $Chi^2 = 6.62$, df = 1 (P = 0.01), $I^2 = 84.9\%$



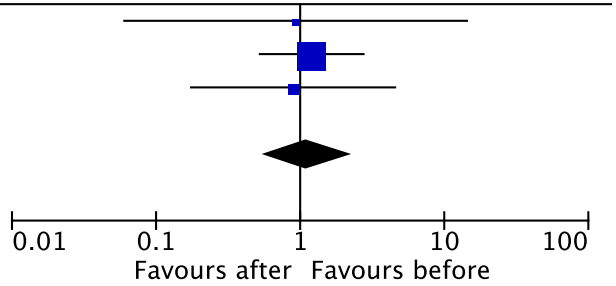
Single-Component Intervention: *Restriction*

Outcome: *Neonatal mortality*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Sathyan 2022	1	43	1	40	6.8%	0.93 [0.06, 14.38]
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]
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); $I^2 = 0\%$

Test for overall effect: Z = 0.30 (P = 0.76)



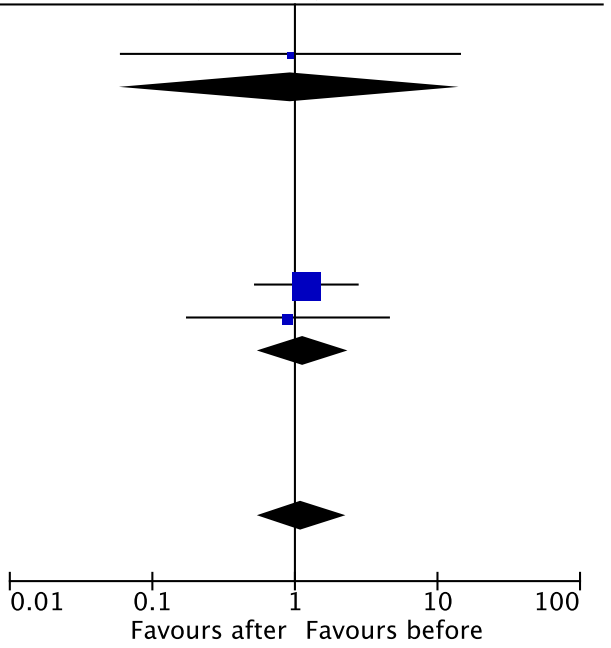
Outcome: *Neonatal mortality by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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 applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.6.2 Quasi-experimental 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 = 0.74)						
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); $I^2 = 0\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.89), $I^2 = 0\%$

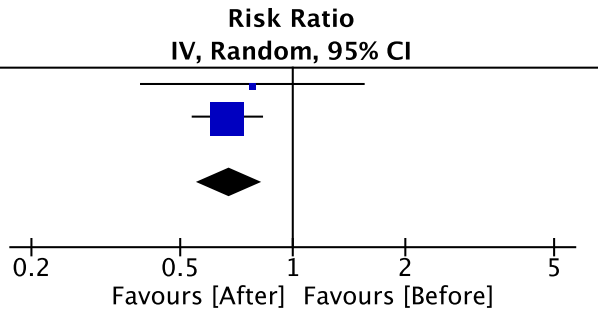


Outcome: *Culture-positive sepsis*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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%

Test for overall effect: Z = 3.74 (P = 0.0002)

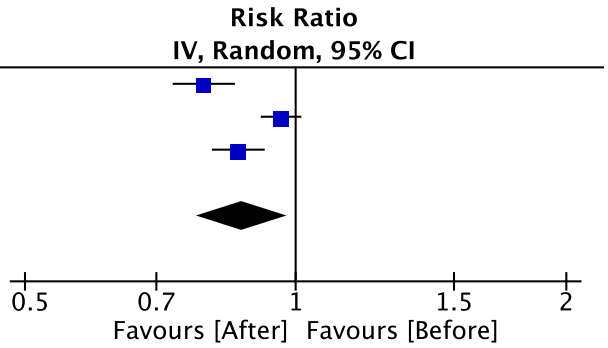


Outcome: *Number of newborns on antibiotics*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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, df = 2 (P < 0.0001); I^2 = 90%

Test for overall effect: Z = 2.35 (P = 0.02)

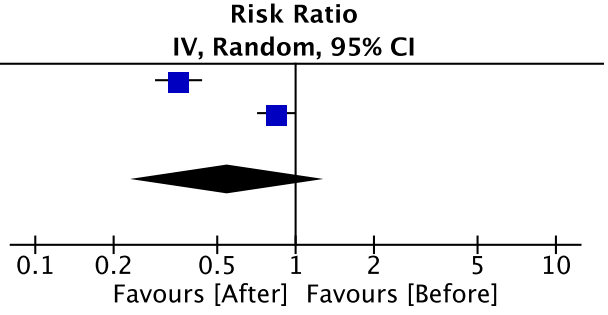


Outcome: *Number of newborns on amikacin*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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]
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, df = 1 (P < 0.00001); I^2 = 98%

Test for overall effect: Z = 1.39 (P = 0.17)

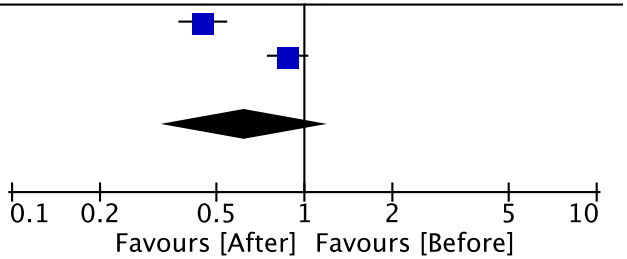


Outcome: *Number of newborns on amikacin (of newborns on any antibiotic)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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: $Tau^2 = 0.22$; $Chi^2 = 29.78$, df = 1 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 1.39 (P = 0.16)

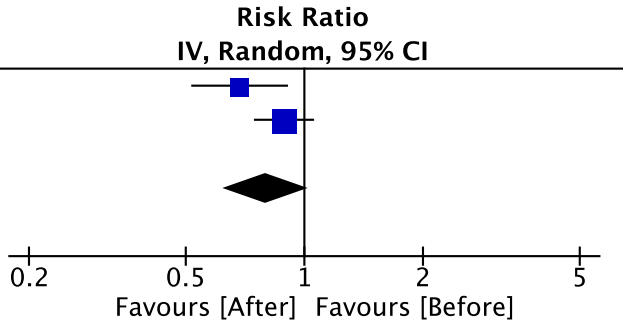


Outcome: *Number of newborns on piperacillin-tazobactam*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.02$; $Chi^2 = 2.46$, df = 1 ($P = 0.12$); $I^2 = 59\%$

Test for overall effect: Z = 1.76 (P = 0.08)

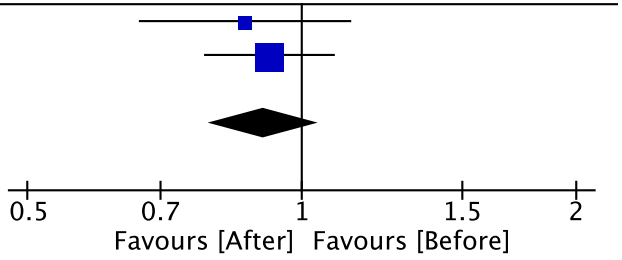


Outcome: *Number of newborns on piperacillin-tazobactam (of newborns on any antibiotic)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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			

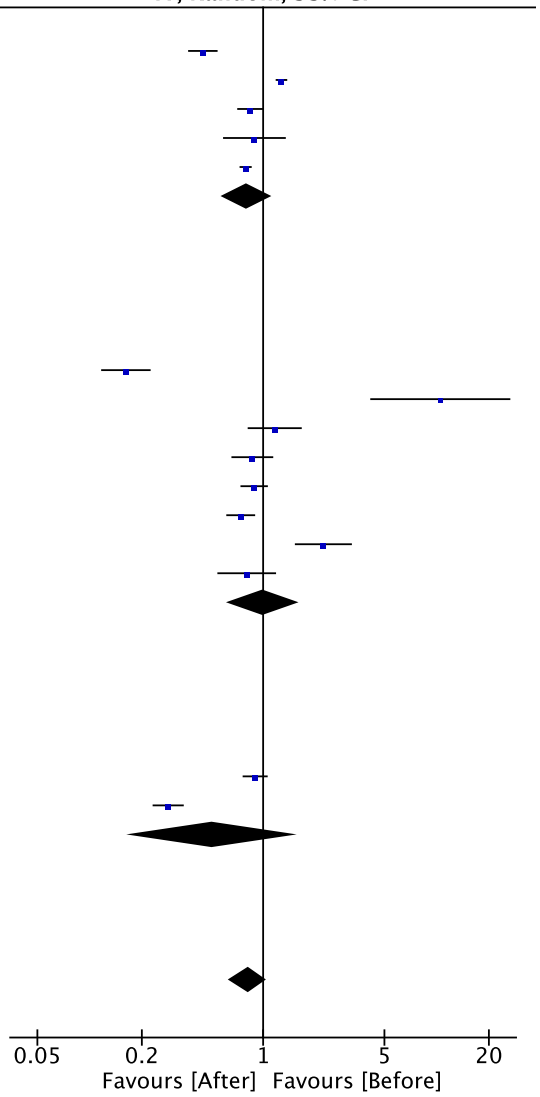
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 1 ($P = 0.70$); $I^2 = 0\%$

Test for overall effect: Z = 1.39 (P = 0.16)



Outcome: *AWaRe antibiotic usage*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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 ($P < 0.00001$); $I^2 = 98\%$						
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 ($P < 0.00001$); $I^2 = 96\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.3.3 Mix of Access and Watch group						
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	100	470	126	168	7.1%	0.28 [0.23, 0.34]
Subtotal (95% CI)		**898**		**597**	**14.3%**	**0.51 [0.16, 1.57]**
Total events	275		321			
Heterogeneity: $Tau^2 = 0.66$; $Chi^2 = 83.07$, df = 1 ($P < 0.00001$); $I^2 = 99\%$						
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			
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 486.74$, df = 14 ($P < 0.00001$); $I^2 = 97\%$						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: $Chi^2 = 1.32$, df = 2 (P = 0.52), $I^2 = 0\%$						



Footnotes

(1) Amikacin, Ampicillin, and Piperacillin-Tazobactam

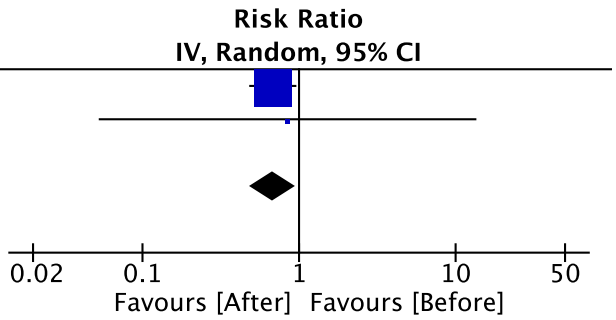
Multi-Component Intervention: *Regulation & Restriction*

Outcome: *Neonatal mortality due to nosocomial bloodstream infection*

	After Intervention		Before Intervention			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% 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: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$

Test for overall effect: Z = 2.28 (P = 0.02)



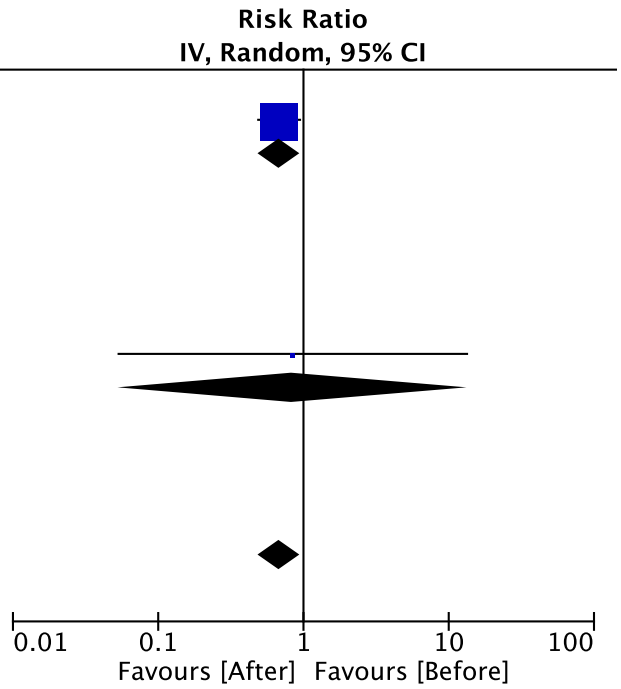
Outcome: *Neonatal mortality due to nosocomial bloodstream infection by level of care*

	After Intervention		Before Intervention			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**
1.16.1 Tertiary or higher						
El-Baky 2020	59	617	65	462	98.6%	0.68 [0.49, 0.95]
Subtotal (95% CI)		**617**		**462**	**98.6%**	**0.68 [0.49, 0.95]**
Total events	59		65			
Heterogeneity: Not applicable						
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 applicable						
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: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$

Test for overall effect: Z = 2.28 (P = 0.02)

Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$



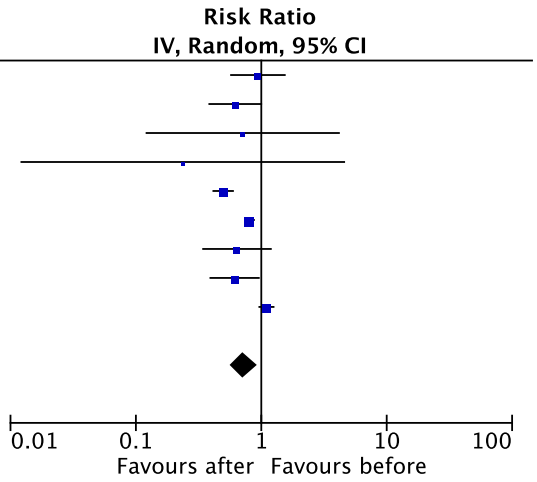
Multi-Component Intervention: *Regulation, Education & Restriction*

Outcome: *Neonatal mortality*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: Tau² = 0.08; Chi² = 54.12, df = 8 (P < 0.00001); I² = 85%

Test for overall effect: Z = 2.57 (P = 0.01)



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

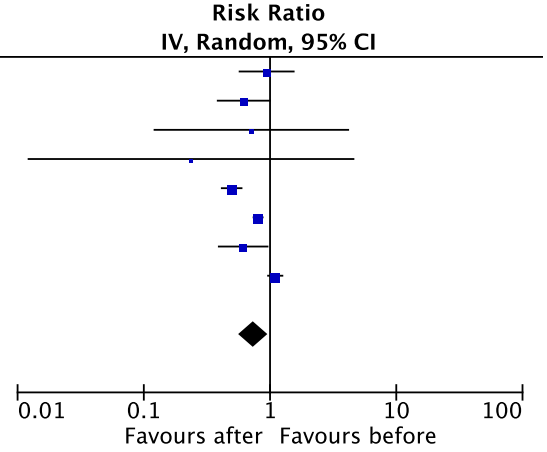
(3) Jain 2021 reported neonatal mortality per 1000 live births

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

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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]
Feng 2022	0	2901	3	4804	0.7%	0.24 [0.01, 4.58]
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: Tau² = 0.08; Chi² = 53.57, df = 7 (P < 0.00001); I² = 87%

Test for overall effect: Z = 2.34 (P = 0.02)



Footnotes

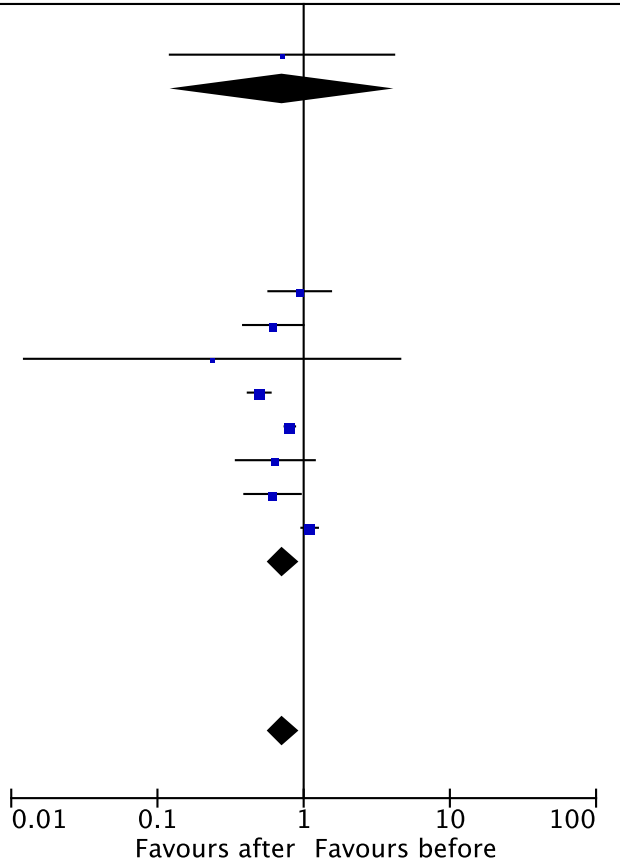
(1) Gill 2009 reported neonatal mortality in NICU 1 as deaths per 1000 admissions

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

Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *Neonatal mortality by study design*

Study or Subgroup	After Intervention Events	After Intervention Total	Before Intervention Events	Before Intervention Total	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 Cohort study						
Chu 2023	2	90	3	96	1.7%	0.71 [0.12, 4.16]
Subtotal (95% CI)		**90**		**96**	**1.7%**	**0.71 [0.12, 4.16]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
1.7.2 Quasi-experimental 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	388	5786	473	7754	18.5%	1.10 [0.97, 1.25]
Subtotal (95% CI)		**12759**		**15983**	**98.3%**	**0.73 [0.57, 0.93]**
Total events	1134		1467			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 54.10$, df = 7 ($P < 0.00001$); $I^2 = 87\%$						
Test for overall effect: Z = 2.52 (P = 0.01)						
Total (95% CI)		**12849**		**16079**	**100.0%**	**0.73 [0.57, 0.93]**
Total events	1136		1470			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 54.12$, df = 8 ($P < 0.00001$); $I^2 = 85\%$						
Test for overall effect: Z = 2.57 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.98), $I^2 = 0\%$						



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

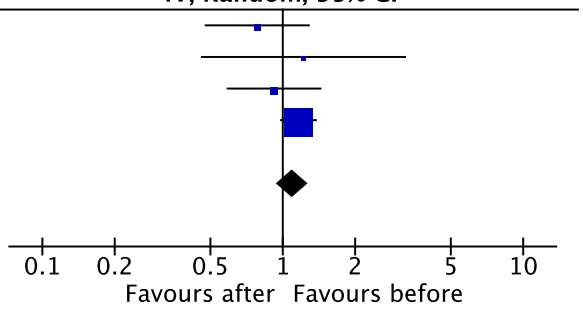
(3) Jain 2021 reported neonatal mortality per 1000 live births

Outcome: *Necrotizing enterocolitis (any Bell stage)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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]
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: Z = 1.22 (P = 0.22)



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*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 Cohort study						
Chu 2023	8	90	7	96	2.3%	1.22 [0.46, 3.22]
Subtotal (95% CI)		**90**		**96**	**2.3%**	**1.22 [0.46, 3.22]**
Total events	8		7			
1.9.2 Quasi-experimental 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			
Total (95% CI)		**9641**		**12944**	**100.0%**	**1.10 [0.95, 1.27]**
Total events	336		369			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

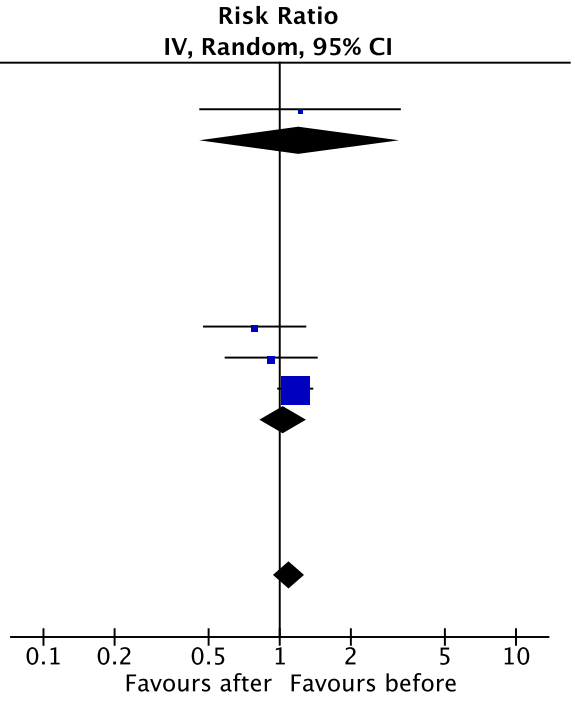
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.86$, df = 2 (P = 0.24); $I^2 = 30\%$

Test for overall effect: Z = 0.30 (P = 0.77)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.91$, df = 3 (P = 0.41); $I^2 = 0\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$

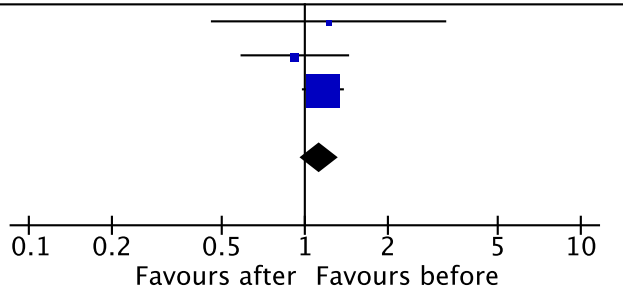


Outcome: *Necrotizing enterocolitis (Bell stage ≥ II)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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]
Total (95% CI)		**8777**		**12654**	**100.0%**	**1.13 [0.97, 1.32]**
Total events	287		348			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0\%$

Test for overall effect: Z = 1.58 (P = 0.11)



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

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.11.1 Cohort study						
Chu 2023	8	90	7	96	2.5%	1.22 [0.46, 3.22]
Subtotal (95% CI)		**90**		**96**	**2.5%**	**1.22 [0.46, 3.22]**
Total events	8		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

1.11.2 Quasi-experimental study						
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]
Subtotal (95% CI)		**8687**		**12558**	**97.5%**	**1.13 [0.97, 1.32]**
Total events	279		341			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.94$, df = 1 (P = 0.33); $I^2 = 0\%$

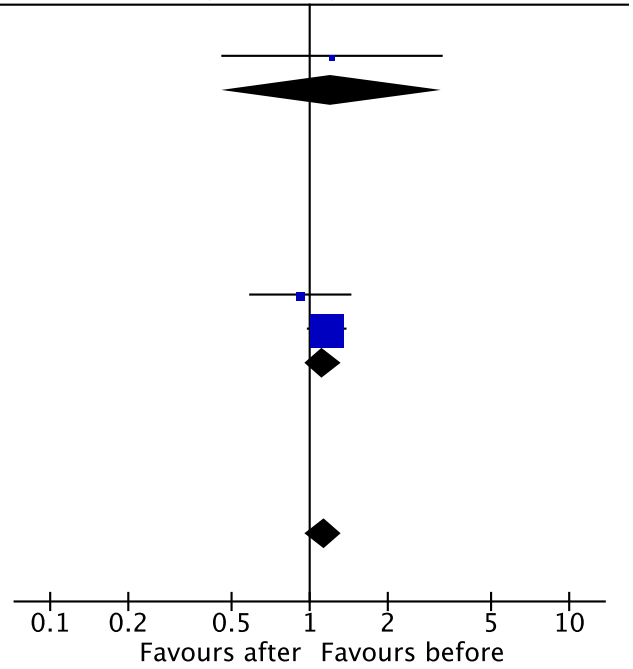
Test for overall effect: Z = 1.53 (P = 0.12)

Total (95% CI)		**8777**		**12654**	**100.0%**	**1.13 [0.97, 1.32]**
Total events	287		348			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0\%$

Test for overall effect: Z = 1.58 (P = 0.11)

Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$

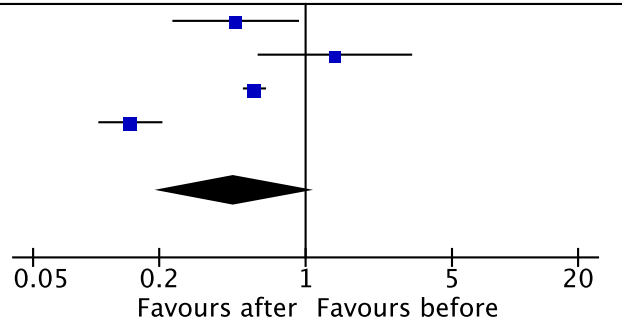


Outcome: *Neonatal sepsis (any)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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: $Tau^2 = 0.69$; $Chi^2 = 60.94$, df = 3 ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: Z = 1.77 (P = 0.08)



Footnotes

(1) A positive blood or CSF fluid culture, or clinical deterioration and ≥2 abnormal blood indicators or changes in CSF consistent with meningitis

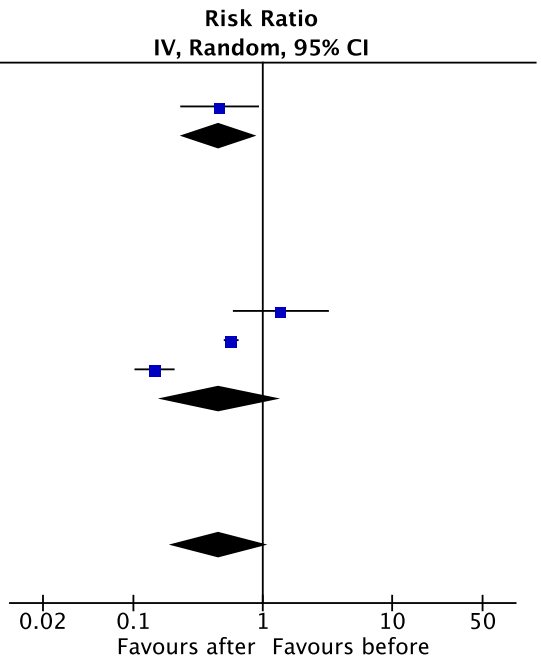
(2) LOS defined as >72 hours of age and positive pathogenic results in blood, urine, or CSF fluid specimens

(3) Late-onset defined as ≥72 hours after birth

(4) EOS defined as ≤72 hours after birth

Outcome: *Neonatal sepsis (any) by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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 applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
1.13.2 Quasi-experimental 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: $Tau^2 = 0.85$; $Chi^2 = 60.89$, df = 2 ($P < 0.00001$); $I^2 = 97\%$						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**9309**		**12807**	**100.0%**	**0.46 [0.19, 1.09]**
Total events	435		996			
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 60.94$, df = 3 ($P < 0.00001$); $I^2 = 95\%$						
Test for overall effect: Z = 1.77 (P = 0.08)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0\%$						

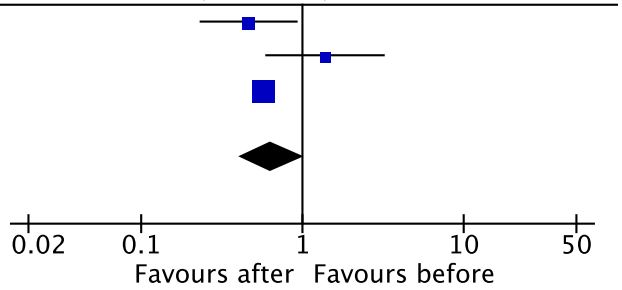


Outcome: *Late-onset sepsis (>72 hours after birth)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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); $I^2 = 56\%$

Test for overall effect: Z = 1.86 (P = 0.06)



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

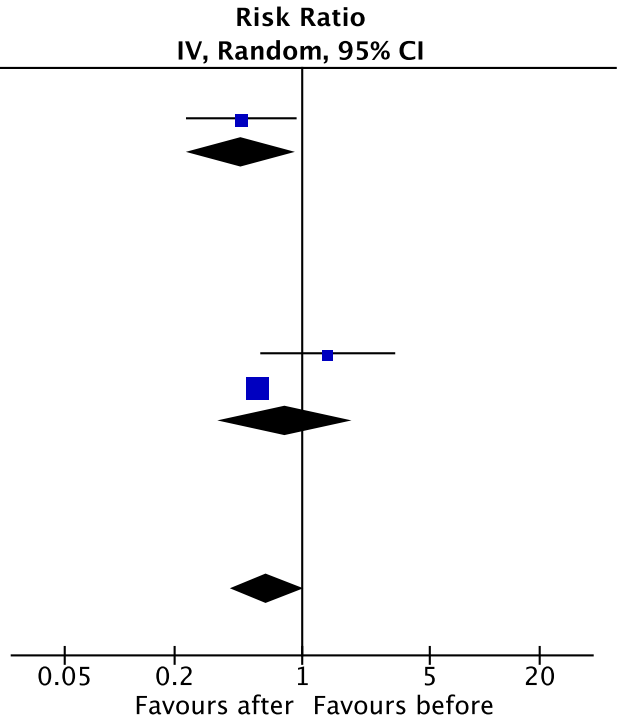
Outcome: *Late-onset sepsis (>72 hours after birth) by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.15.1 Cohort study						
Chu 2023	10	90	23	96	25.3%	0.46 [0.23, 0.92]
Subtotal (95% CI)		**90**		**96**	**25.3%**	**0.46 [0.23, 0.92]**
Total events	10		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
1.15.2 Quasi-experimental 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); $I^2 = 76\%$						
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); $I^2 = 56\%$

Test for overall effect: Z = 1.86 (P = 0.06)

Test for subgroup differences: $Chi^2 = 0.97$, df = 1 (P = 0.32), $I^2 = 0\%$

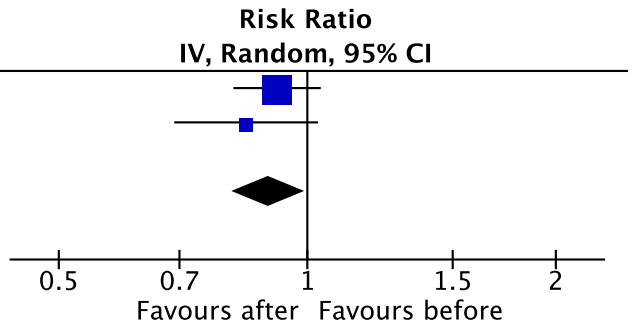


Outcome: *Culture-negative sepsis*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 1 (P = 0.46); $I^2 = 0\%$

Test for overall effect: Z = 2.07 (P = 0.04)



Footnotes

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

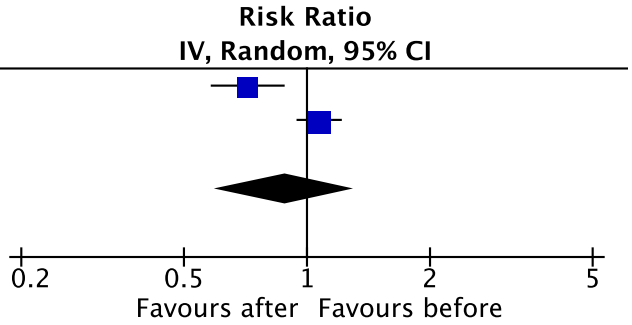
(2) Lu 2019 reported all infants treated for culture-negative sepsis

Outcome: *Pneumonia*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.07$; $Chi^2 = 11.19$, df = 1 (P = 0.0008); $I^2 = 91\%$

Test for overall effect: Z = 0.62 (P = 0.54)



Footnotes

(1) Feng 2022 reported infants treated in ≤5 days for pneumonia

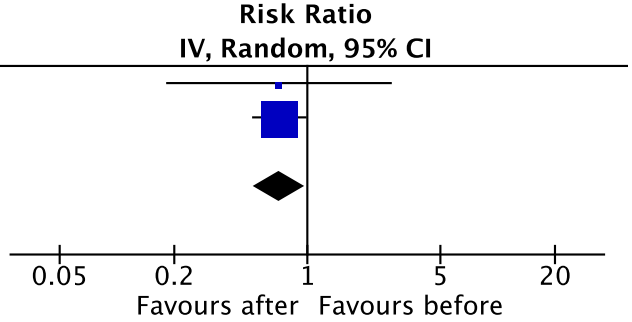
(2) Lu 2019 reported all infants treated for pneumonia

Outcome: *Multidrug-resistant organism infection or colonization*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 2.15 (P = 0.03)



Footnotes

(1) Feng 2022 reported multidrug-resistant organism infections

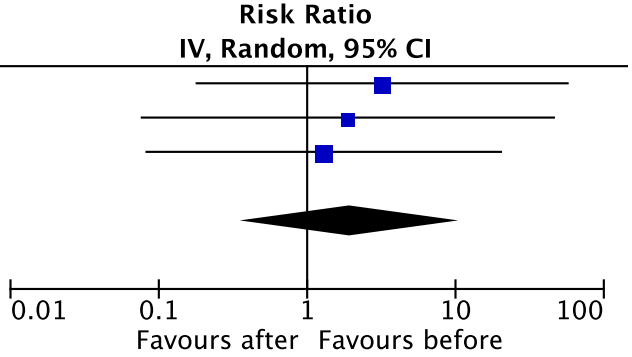
(2) Lu 2019 reported multidrug-resistant organism colonizations

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

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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: $Tau^2 = 0.00$; $Chi^2 = 0.20$, df = 2 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 0.78 (P = 0.43)

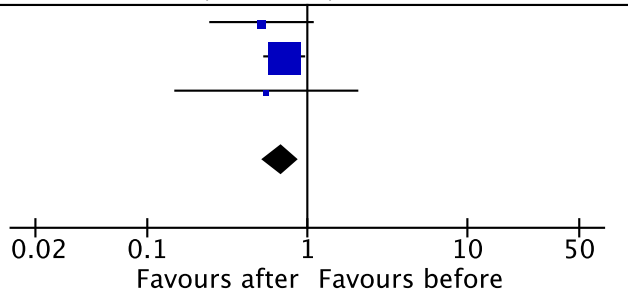


Outcome: *Bloodstream isolates of Klebsiella spp.*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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); $I^2 = 0\%$

Test for overall effect: Z = 2.88 (P = 0.004)



Footnotes

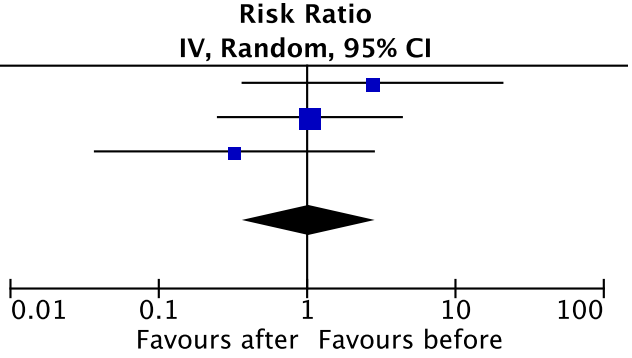
(1) Kommalur 2021 reported *Klebsiella pneumoniae* organisms

Outcome: *Bloodstream isolates of Acinetobacter spp.*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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); $I^2 = 1\%$

Test for overall effect: Z = 0.06 (P = 0.95)



Footnotes

(1) Gill 2009 reported *Acinetobacter baumanii* organisms

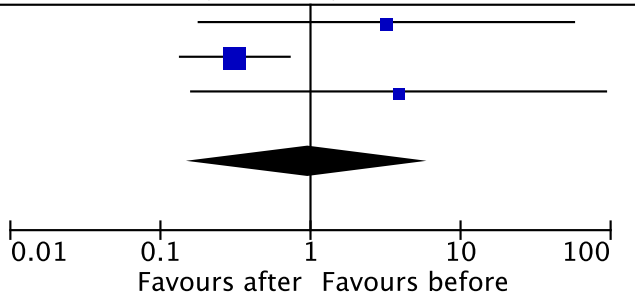
(2) Kommalur 2021 reported *Acinetobacter baumanii* organisms

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

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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); $I^2 = 53\%$

Test for overall effect: Z = 0.05 (P = 0.96)

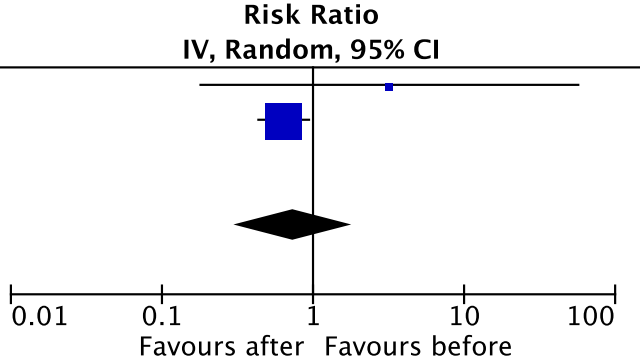


Outcome: *Bloodstream isolates of Enterobacter spp.*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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); $I^2 = 15\%$

Test for overall effect: Z = 0.64 (P = 0.52)

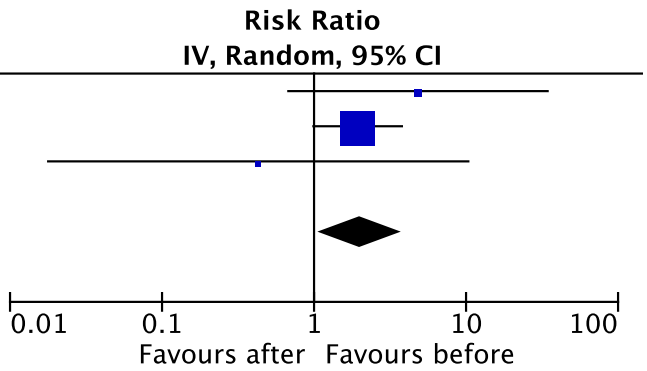


Outcome: *Bloodstream isolates of coagulase-negative staphylococci (CoNS)*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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: $Tau^2 = 0.00$; $Chi^2 = 1.68$, df = 2 (P = 0.43); $I^2 = 0\%$

Test for overall effect: Z = 2.19 (P = 0.03)



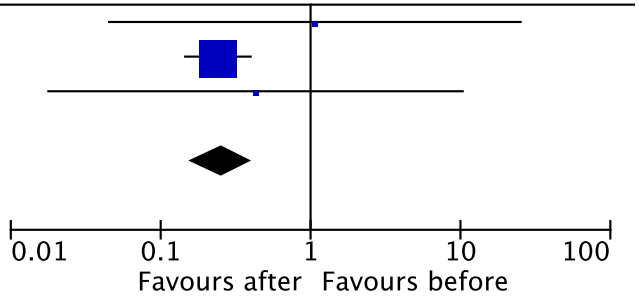
Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *Bloodstream isolates of Pseudomonas spp.*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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); $I^2 = 0\%$

Test for overall effect: Z = 5.49 (P < 0.00001)



Footnotes

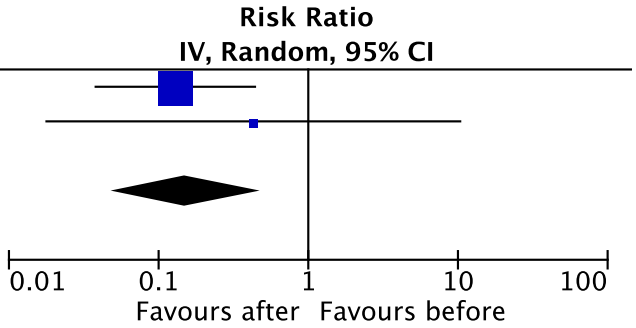
(1) Kommalur 2021 reported *Pseudomonas aeruginosa* organisms

Outcome: *Bloodstream isolates of Candida spp.*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% 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: $Tau^2 = 0.00$; $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0\%$

Test for overall effect: Z = 3.24 (P = 0.001)

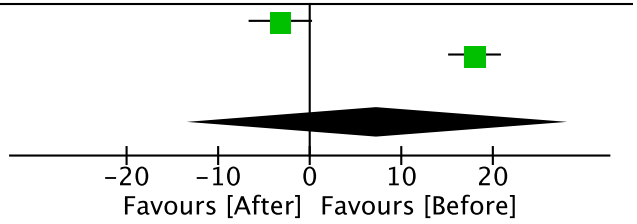


Outcome: *Mean length of hospital stay*

Study or Subgroup	After Intervention Mean	SD	Total	Before Intervention Mean	SD	Total	Weight	Mean Difference 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: $Tau^2 = 222.47$; $Chi^2 = 91.49$, df = 1 (P < 0.00001); $I^2 = 99\%$

Test for overall effect: Z = 0.70 (P = 0.48)

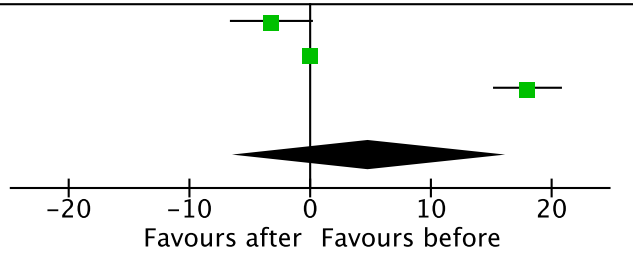


Outcome: *Mean length of hospital stay (including Feng 2022 [13])*

Study or Subgroup	After Intervention Mean	SD	Total	Before Intervention Mean	SD	Total	Weight	Mean Difference 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 = 97.36; Chi^2 = 165.66, df = 2 (P < 0.00001); I^2 = 99%

Test for overall effect: Z = 0.86 (P = 0.39)



Footnotes

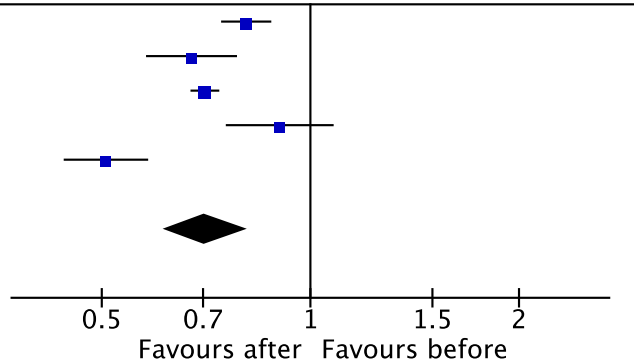
(1) Feng 2022 expressed length of hospital stay as median and IQR, assuming the distribution of data is symmetrical, we estimated mean and SD

Outcome: *Number of newborns receiving antibiotics*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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, df = 4 (P < 0.00001); I^2 = 90%

Test for overall effect: Z = 4.84 (P < 0.00001)



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

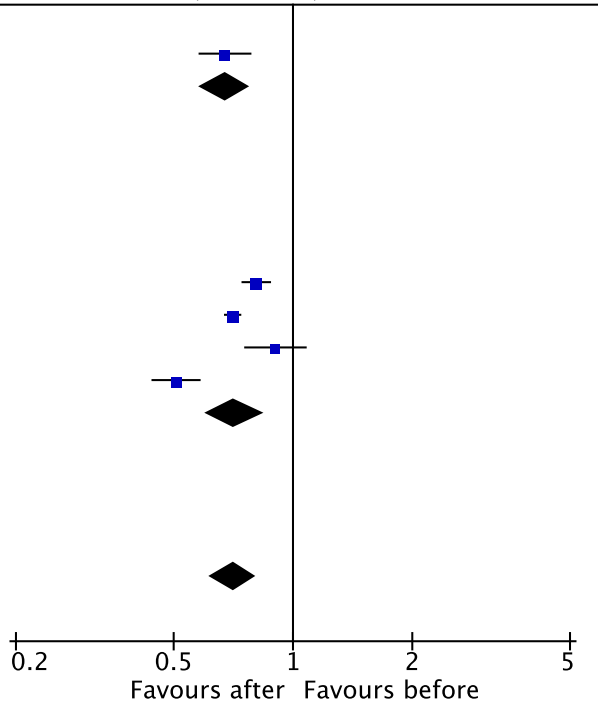
(3) Feng 2022 reported proportion of antibiotic exposure

(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

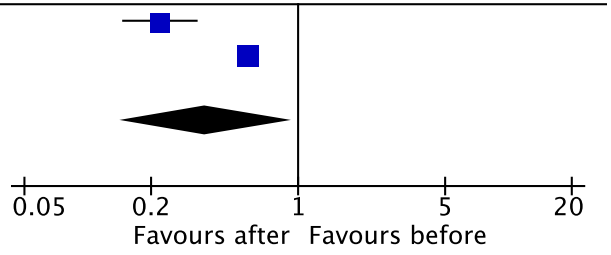
Outcome: *Number of newborns receiving antibiotics by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.29.1 Cohort study						
Chu 2023	60	90	95	96	18.7%	0.67 [0.58, 0.78]
Subtotal (95% CI)		**90**		**96**	**18.7%**	**0.67 [0.58, 0.78]**
Total events	60		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.25 (P < 0.00001)						
1.29.2 Quasi-experimental 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%	0.51 [0.44, 0.58]
Subtotal (95% CI)		**4355**		**5322**	**81.3%**	**0.71 [0.60, 0.84]**
Total events	2137		3560			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 40.55$, df = 3 (P < 0.00001); $I^2 = 93\%$						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Total (95% CI)		**4445**		**5418**	**100.0%**	**0.71 [0.61, 0.81]**
Total events	2197		3655			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 41.16$, df = 4 (P < 0.00001); $I^2 = 90\%$						
Test for overall effect: Z = 4.84 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.24$, df = 1 (P = 0.62), $I^2 = 0\%$						



Outcome: *Duration of antibiotic therapy >5 days*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 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: $Tau^2 = 0.44$; $Chi^2 = 21.21$, df = 1 (P < 0.00001); $I^2 = 95\%$						
Test for overall effect: Z = 2.11 (P = 0.03)						



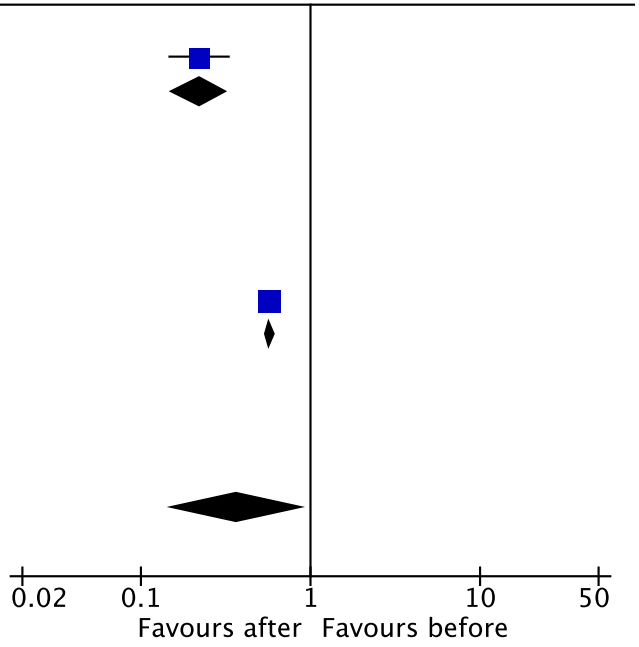
Footnotes

(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

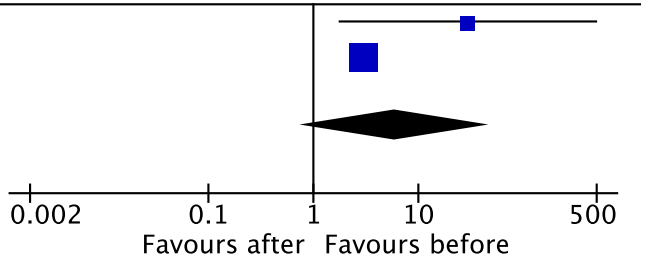
Outcome: *Duration of antibiotic therapy >5 days by study design*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.31.1 Cohort study						
Chu 2023	19	90	92	96	47.8%	0.22 [0.15, 0.33]
Subtotal (95% CI)		**90**		**96**	**47.8%**	**0.22 [0.15, 0.33]**
Total events	19		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.38 (P < 0.00001)						
1.31.2 Quasi-experimental 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 applicable						
Test for overall effect: Z = 14.23 (P < 0.00001)						
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, df = 1 (P < 0.00001); I^2 = 95%						
Test for overall effect: Z = 2.11 (P = 0.03)						
Test for subgroup differences: Chi^2 = 21.21, df = 1 (P < 0.00001), I^2 = 95.3%						



Outcome: *Neonates with antibiotics discontinued after 48 hours*

Study or Subgroup	After Intervention Events	Total	Before Intervention Events	Total	Weight	Risk Ratio 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 = 1.62; Chi^2 = 2.57, df = 1 (P = 0.11); I^2 = 61%						
Test for overall effect: Z = 1.69 (P = 0.09)						



4.1.2. Chlorhexidine Cleansing

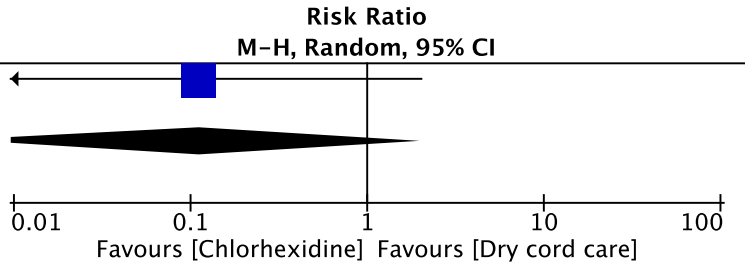
Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

Outcome: *Neonatal mortality*

	Chlorhexidine cleansing		Dry cord care			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Gathwala 2013	0	70	4	70	100.0%	0.11 [0.01, 2.03]
Total (95% CI)		**70**		**70**	**100.0%**	**0.11 [0.01, 2.03]**
Total events	0		4			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

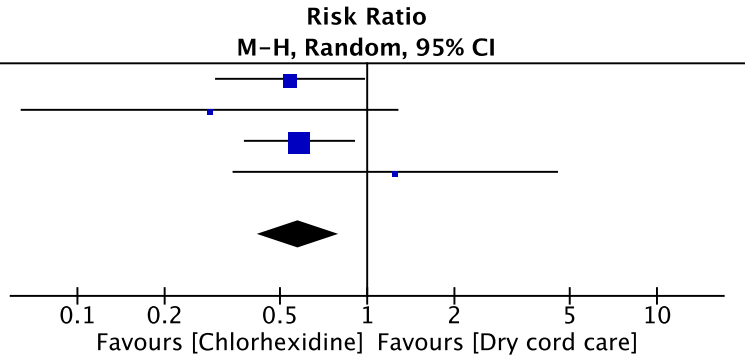


Outcome: *Omphalitis*

	Chlorhexidine cleansing		Dry cord care			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**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			

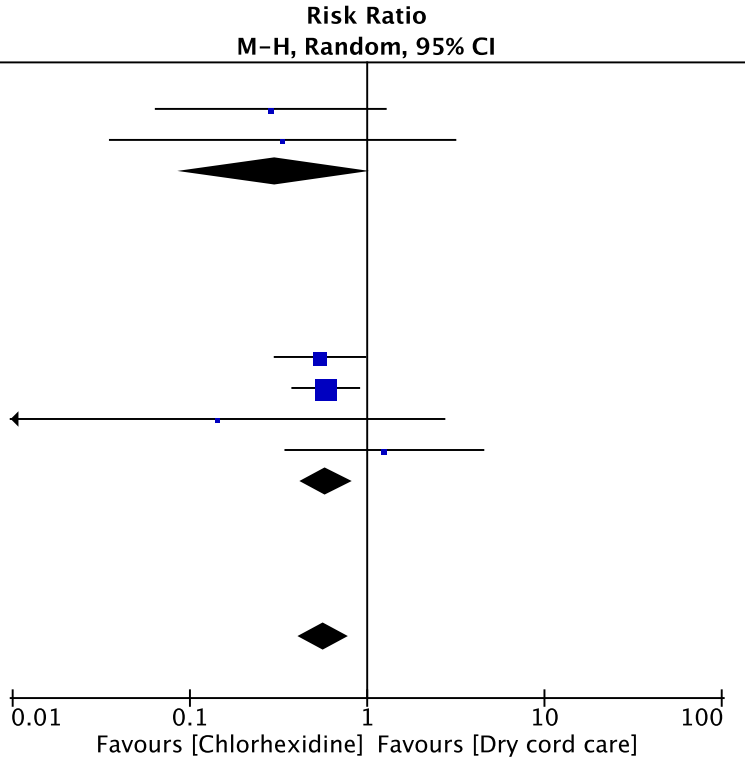
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.29$, df = 3 (P = 0.51); $I^2 = 0\%$

Test for overall effect: Z = 3.26 (P = 0.001)



Outcome: *Omphalitis by cleansing frequency*

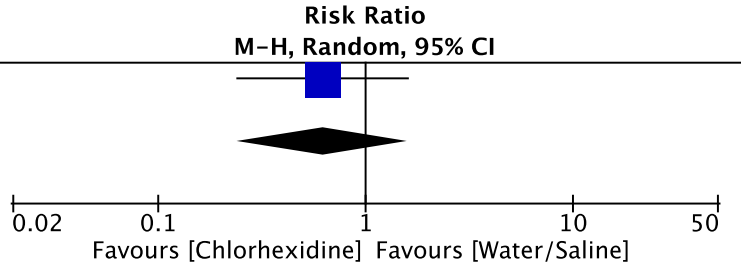
Study or Subgroup	Chlorhexidine cleansing Events	Total	Dry cord care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Single cleansing						
Ishaq 2023	2	32	7	32	4.7%	0.29 [0.06, 1.27]
Ozdemir 2017	1	86	3	86	2.1%	0.33 [0.04, 3.14]
Subtotal (95% CI)		**118**		**118**	**6.8%**	**0.30 [0.09, 1.04]**
Total events	3		10			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 1.90 (P = 0.06)						
1.7.2 Multiple cleansing						
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 = 0.002)						
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: Z = 3.49 (P = 0.0005)						
Test for subgroup differences: $Chi^2 = 1.06$, df = 1 (P = 0.30), $I^2 = 5.7\%$						



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

Outcome: *Neonatal mortality*

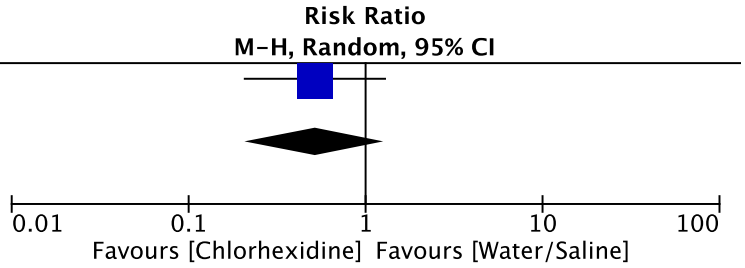
Study or Subgroup	Chlorhexidine cleansing Events	Total	Water/saline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anitha 2022	6	59	10	61	100.0%	0.62 [0.24, 1.60]
Total (95% CI)		**59**		**61**	**100.0%**	**0.62 [0.24, 1.60]**
Total events	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						



Outcome: *Bloodstream infection/sepsis*

Study or Subgroup	Chlorhexidine cleansing Events	Total	Water/saline Events	Total	Weight	Risk Ratio 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 applicable
Test for overall effect: Z = 1.42 (P = 0.16)



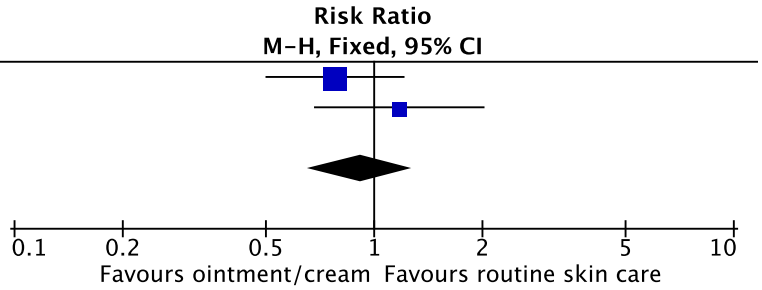
4.1.3. Topical Emollients

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

Outcome: *Invasive infection (any organism)*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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			

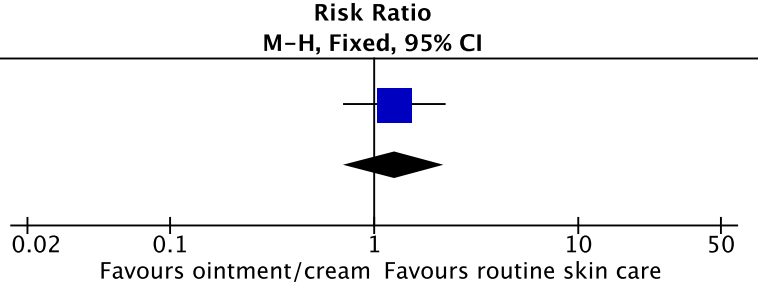
Heterogeneity: $Chi^2 = 1.34$, df = 1 (P = 0.25); $I^2 = 26\%$
Test for overall effect: Z = 0.52 (P = 0.60)



Outcome: *Invasive infection (coagulase negative staphylococci)*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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			

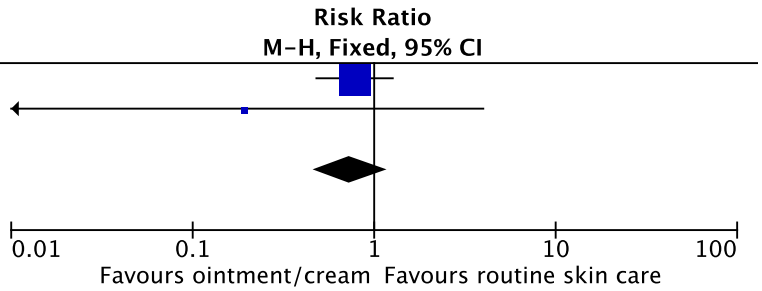
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)



Outcome: *Invasive infection (other bacteria)*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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			

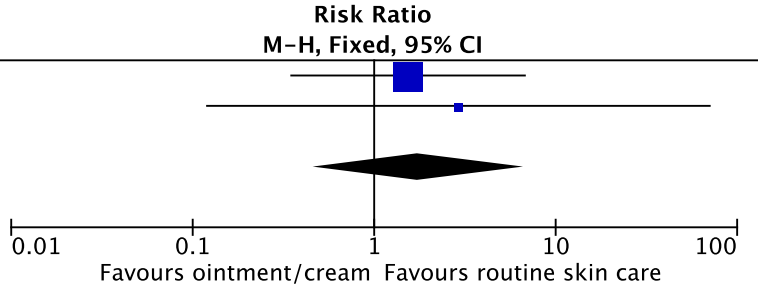
Heterogeneity: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 = 0%
Test for overall effect: Z = 1.26 (P = 0.21)



Outcome: *Invasive infection (fungi)*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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			

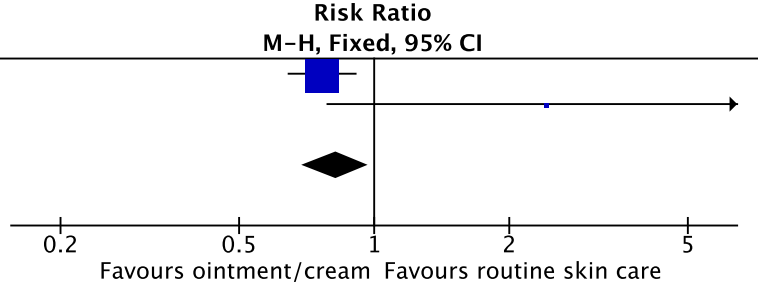
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



Outcome: *All-cause neonatal mortality*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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 = 4.19, df = 1 (P = 0.04); I^2 = 76%
Test for overall effect: Z = 2.25 (P = 0.02)

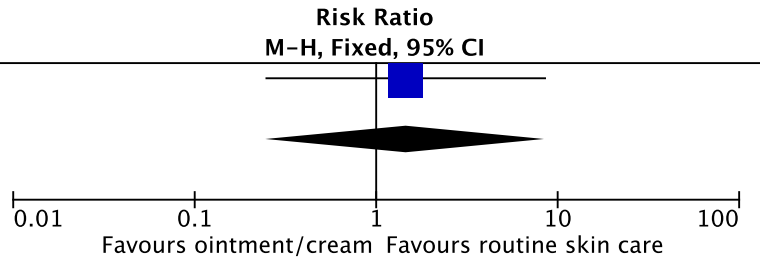


Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 0.42 (P = 0.68)



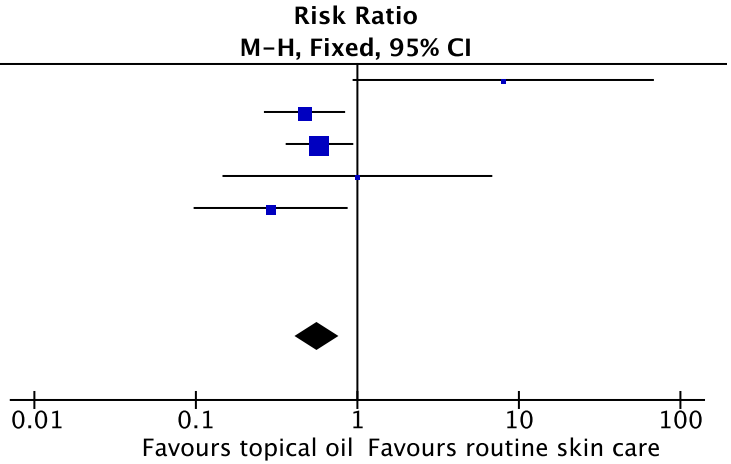
Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: *Invasive infection (any organism)*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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: $Chi^2 = 8.16$, df = 4 (P = 0.09); $I^2 = 51\%$

Test for overall effect: Z = 3.44 (P = 0.0006)

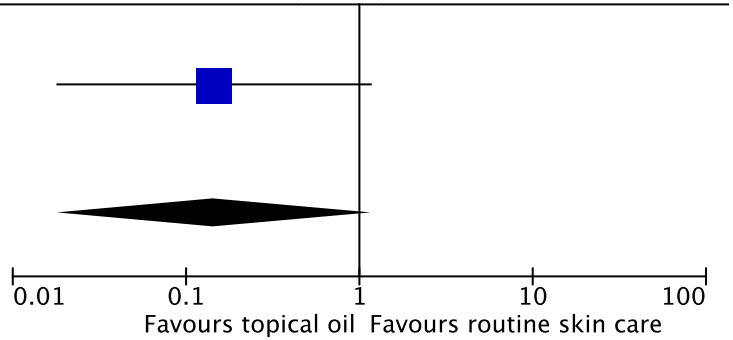


Outcome: *Invasive infection (coagulase negative staphylococci)*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 1.82 (P = 0.07)

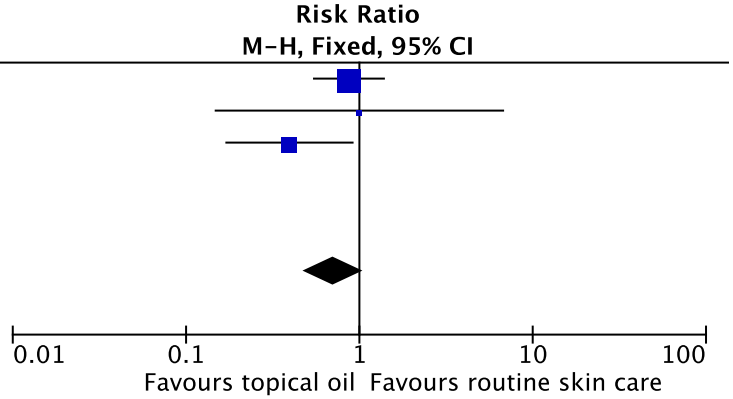


Outcome: *Invasive infection (other bacteria)*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: $Chi^2 = 2.74$, df = 2 (P = 0.25); $I^2 = 27\%$

Test for overall effect: Z = 1.70 (P = 0.09)

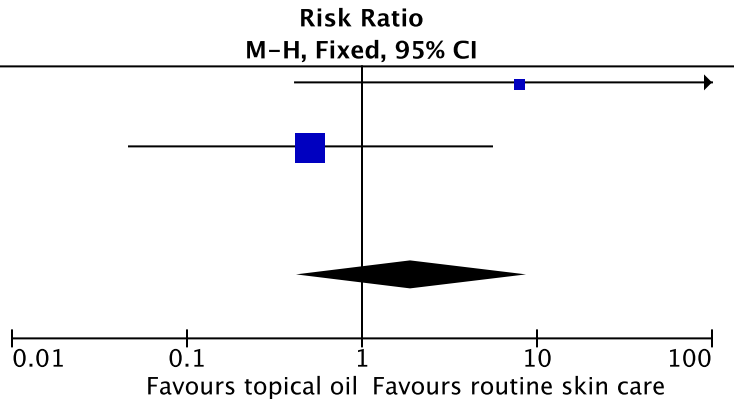


Outcome: *Invasive infection (fungi)*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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: $Chi^2 = 2.08$, df = 1 (P = 0.15); $I^2 = 52\%$

Test for overall effect: Z = 0.85 (P = 0.39)

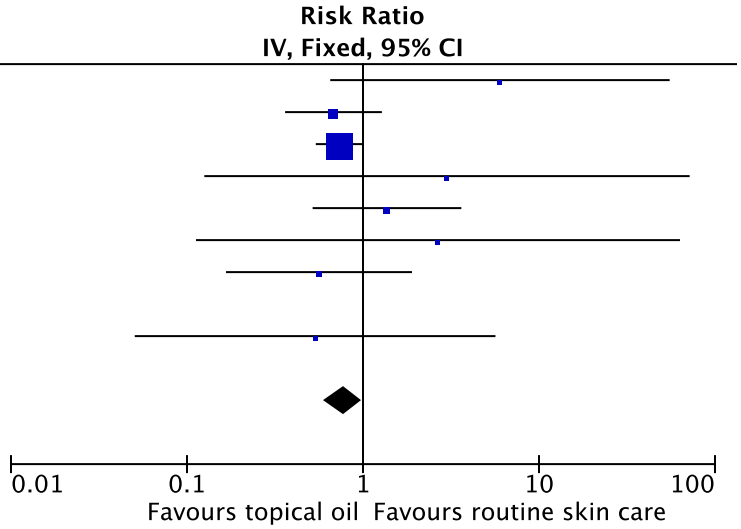


Outcome: *All-cause neonatal mortality*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio 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
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	76		109			

Heterogeneity: $Chi^2 = 6.61$, df = 7 (P = 0.47); $I^2 = 0\%$

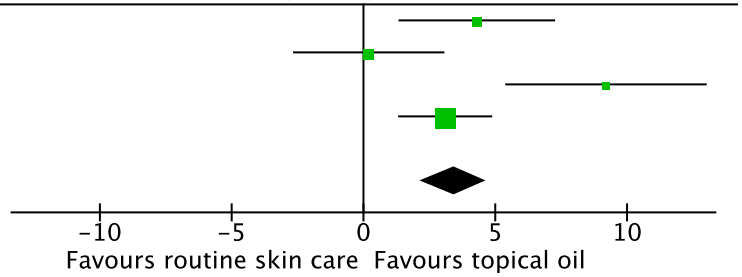
Test for overall effect: Z = 1.99 (P = 0.05)



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

Study or Subgroup	Topical oil Mean	SD	Total	Routine skin care Mean	SD	Total	Weight	Mean Difference 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]**

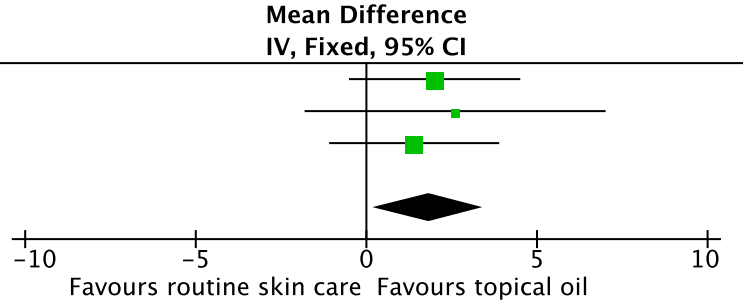
Heterogeneity: Chi^2 = 14.40, df = 3 (P = 0.002); I^2 = 79%
Test for overall effect: Z = 5.36 (P < 0.00001)



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

Study or Subgroup	Topical oil Mean	SD	Total	Routine skin care Mean	SD	Total	Weight	Mean Difference 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]**

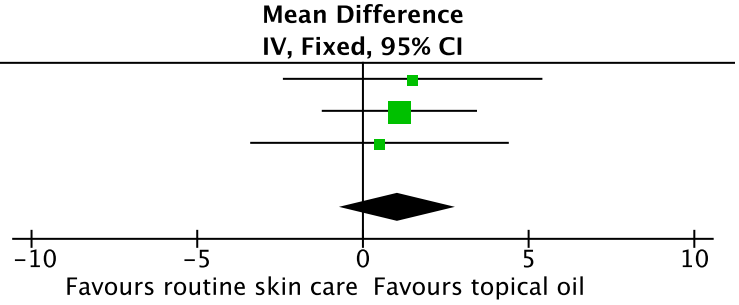
Heterogeneity: Chi^2 = 0.25, df = 2 (P = 0.88); I^2 = 0%
Test for overall effect: Z = 2.20 (P = 0.03)



Outcome: *Change in circumference (mm/week)*

Study or Subgroup	Topical oil Mean	SD	Total	Routine skin care Mean	SD	Total	Weight	Mean Difference 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]**

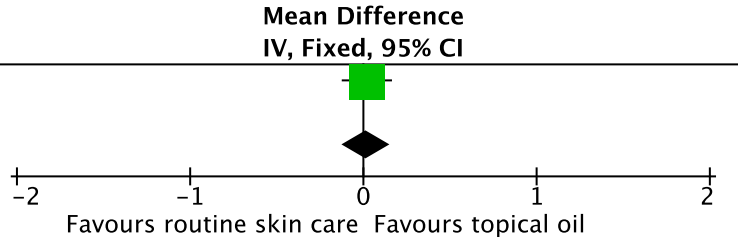
Heterogeneity: Chi^2 = 0.13, df = 2 (P = 0.94); I^2 = 0%
Test for overall effect: Z = 1.17 (P = 0.24)



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

Study or Subgroup	Topical oil Mean	SD	Total	Routine skin care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 0.28 (P = 0.78)

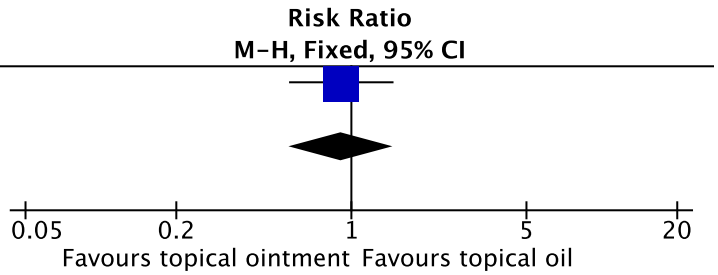


Comparison: Topical ointment/cream versus topical oil in preterm neonates

Outcome: *Invasive infection (any organism)*

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

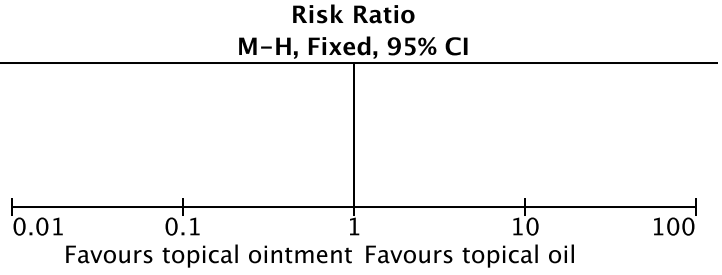
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)



Outcome: *Invasive infection (coagulase negative staphylococci)*

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

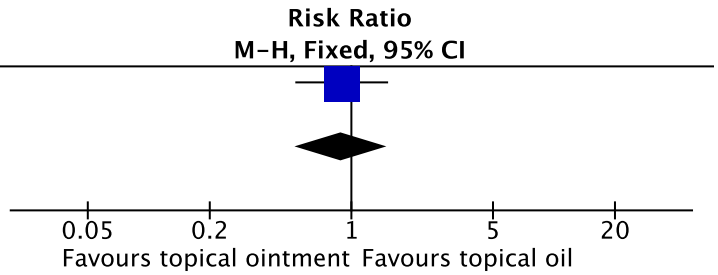
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Outcome: *Invasive infection (other bacteria)*

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

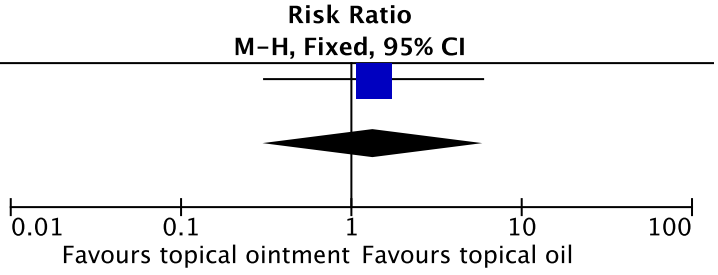
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)



Outcome: *Invasive infection (fungi)*

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

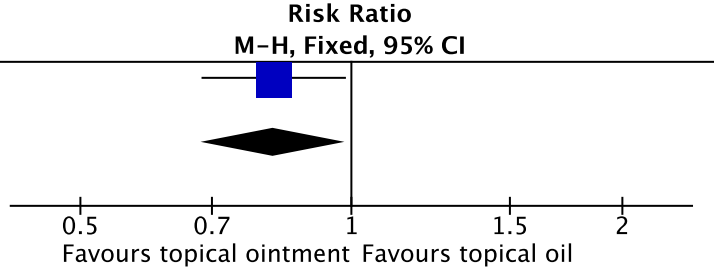
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



Outcome: *All-cause neonatal mortality*

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

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

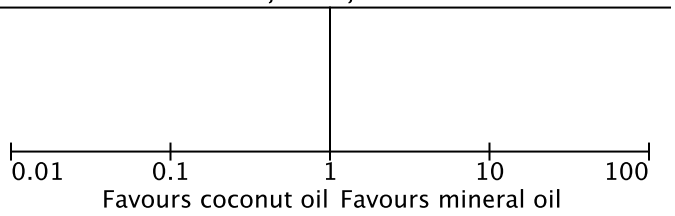


Comparison: One topical oil (or combination) versus another oil (or combination)

Outcome: *Invasive infection*

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

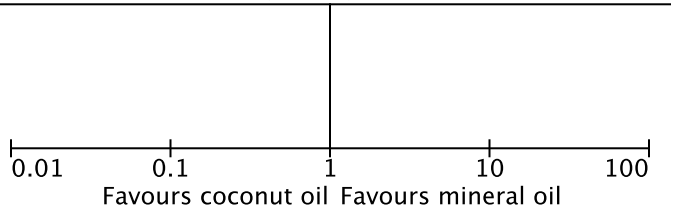
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Outcome: *All-cause mortality*

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

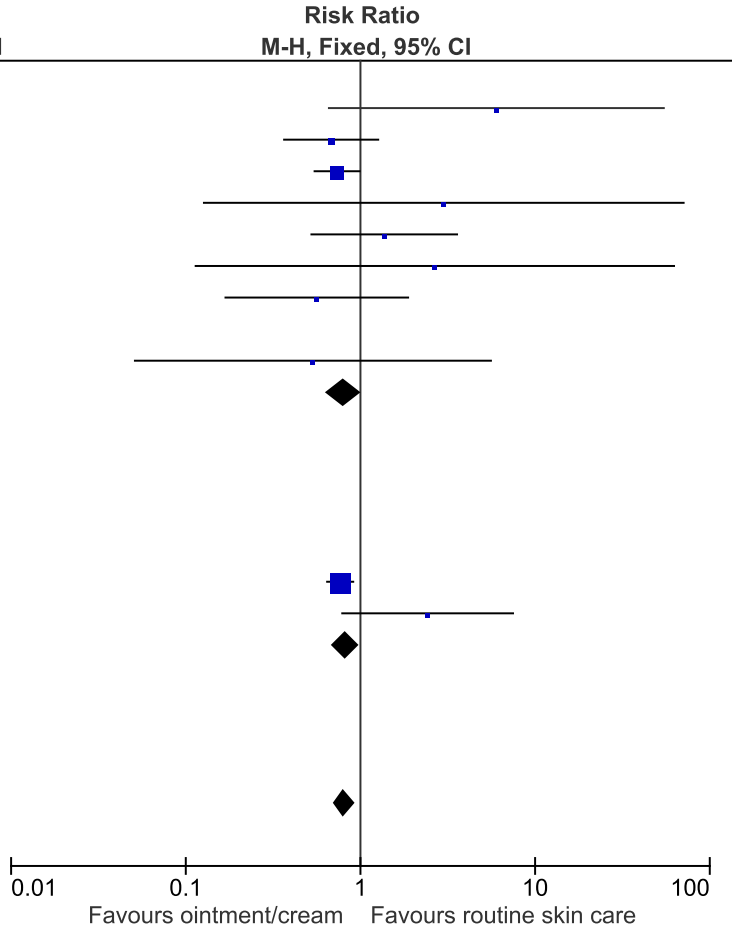
Heterogeneity: Not applicable
Test for overall effect: Not applicable



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

Outcome: *All-cause neonatal mortality*

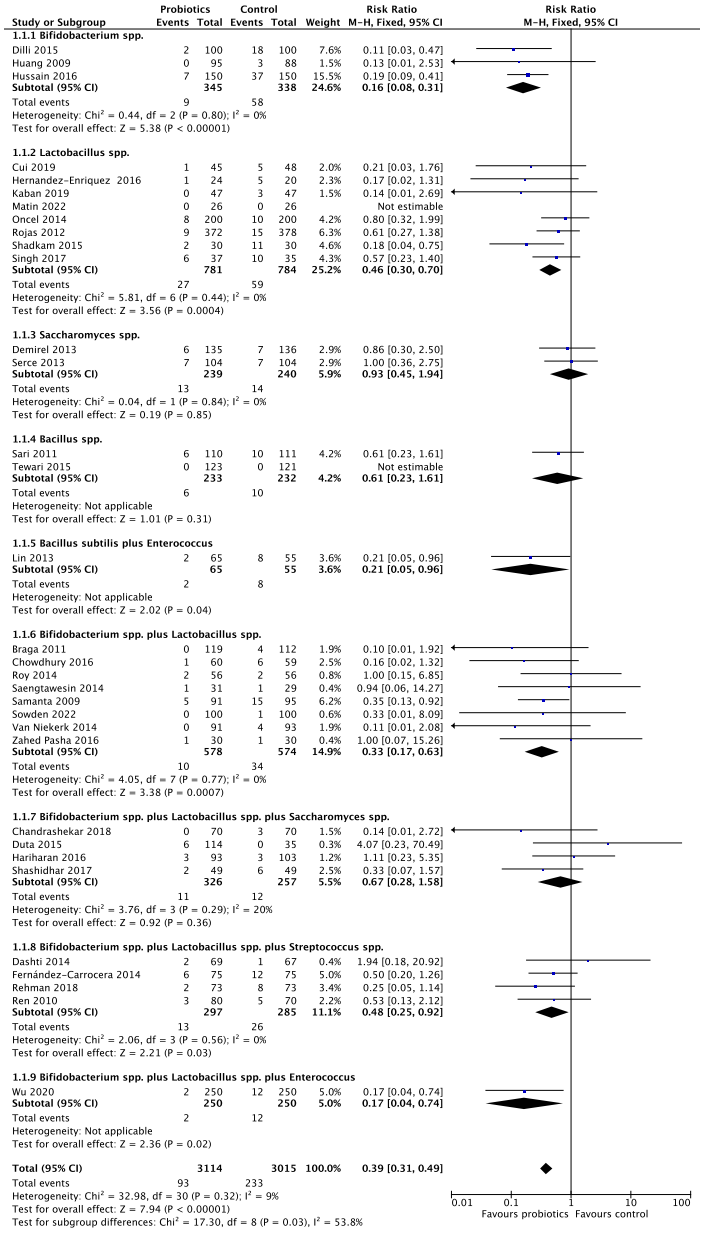
Study or Subgroup	Topical ointment/cream Events	Total	Routine skin care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Topical oil						
Arora 2005	3	23	1	46	0.3%	6.00 [0.66, 54.54]
Darmstadt 2004	12	51	18	52	7.9%	0.68 [0.37, 1.26]
Darmstadt 2005 (2)	46	151	75	181	30.2%	0.74 [0.55, 0.99]
Fallah 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: Chi² = 6.66, df = 7 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.5.2 Topical ointment or 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: Chi² = 4.19, df = 1 (P = 0.04); I² = 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: Chi² = 10.80, df = 9 (P = 0.29); I² = 17%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



4.1.4. Probiotics Supplementation

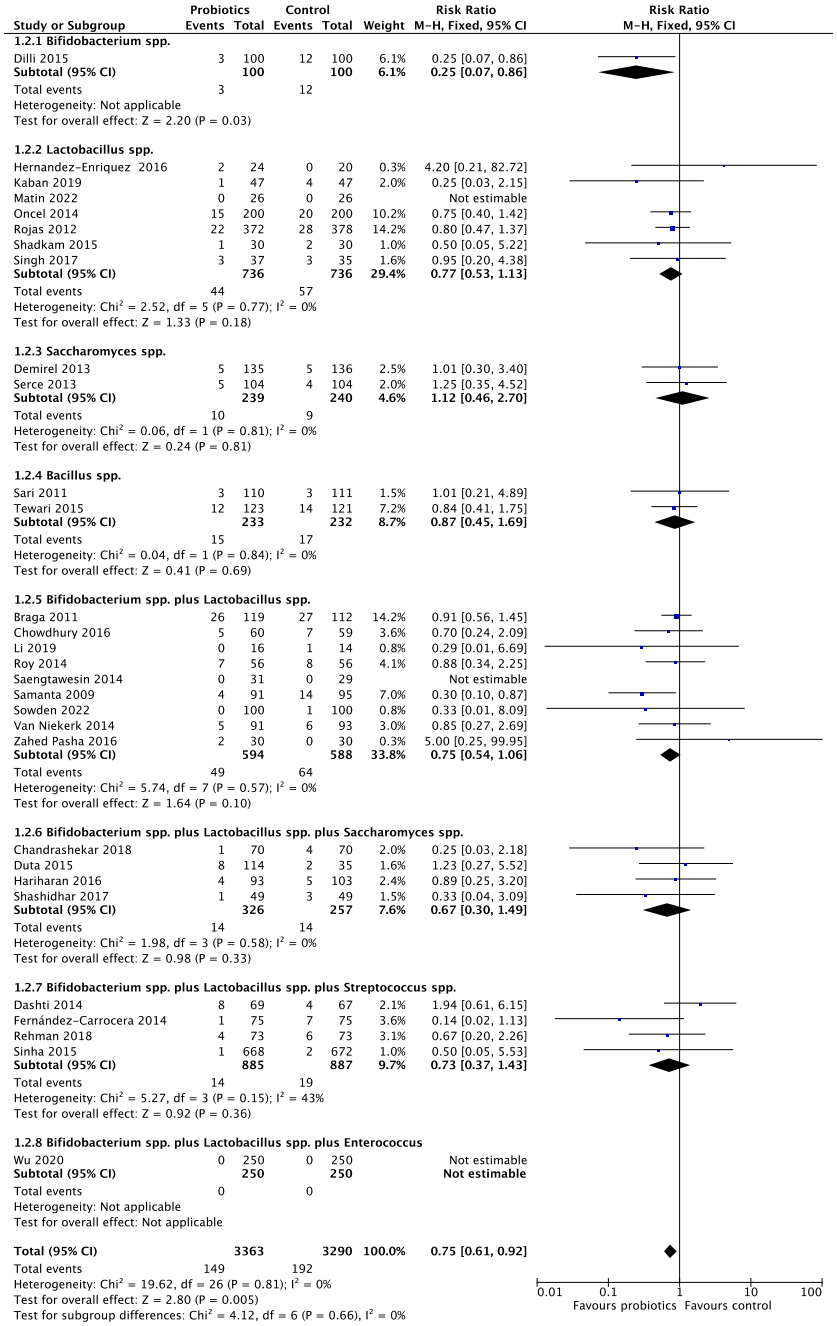
Comparison: Probiotics versus control in preterm newborns by probiotic type

Outcome: *Necrotizing enterocolitis*

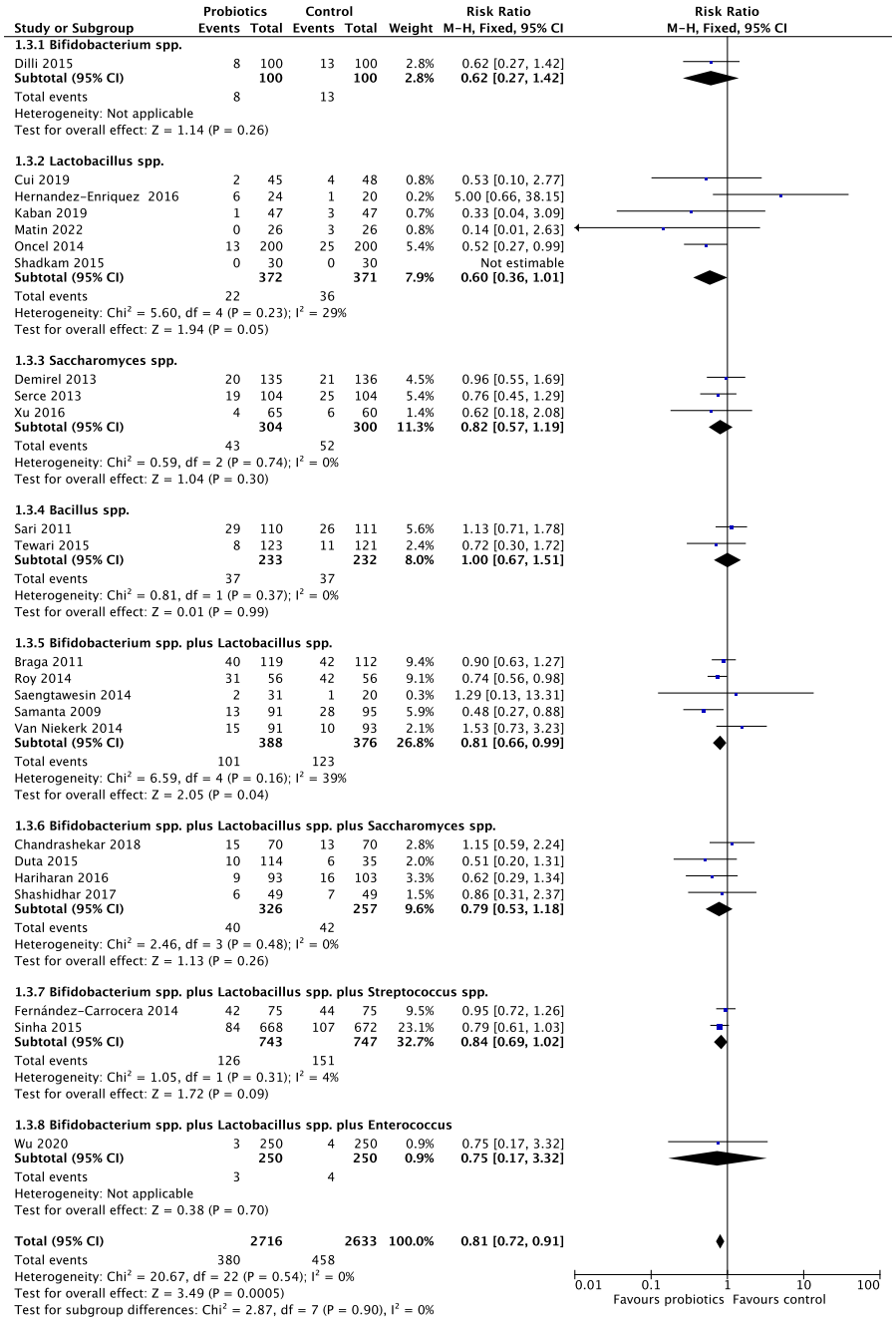


Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *All-cause neonatal mortality*

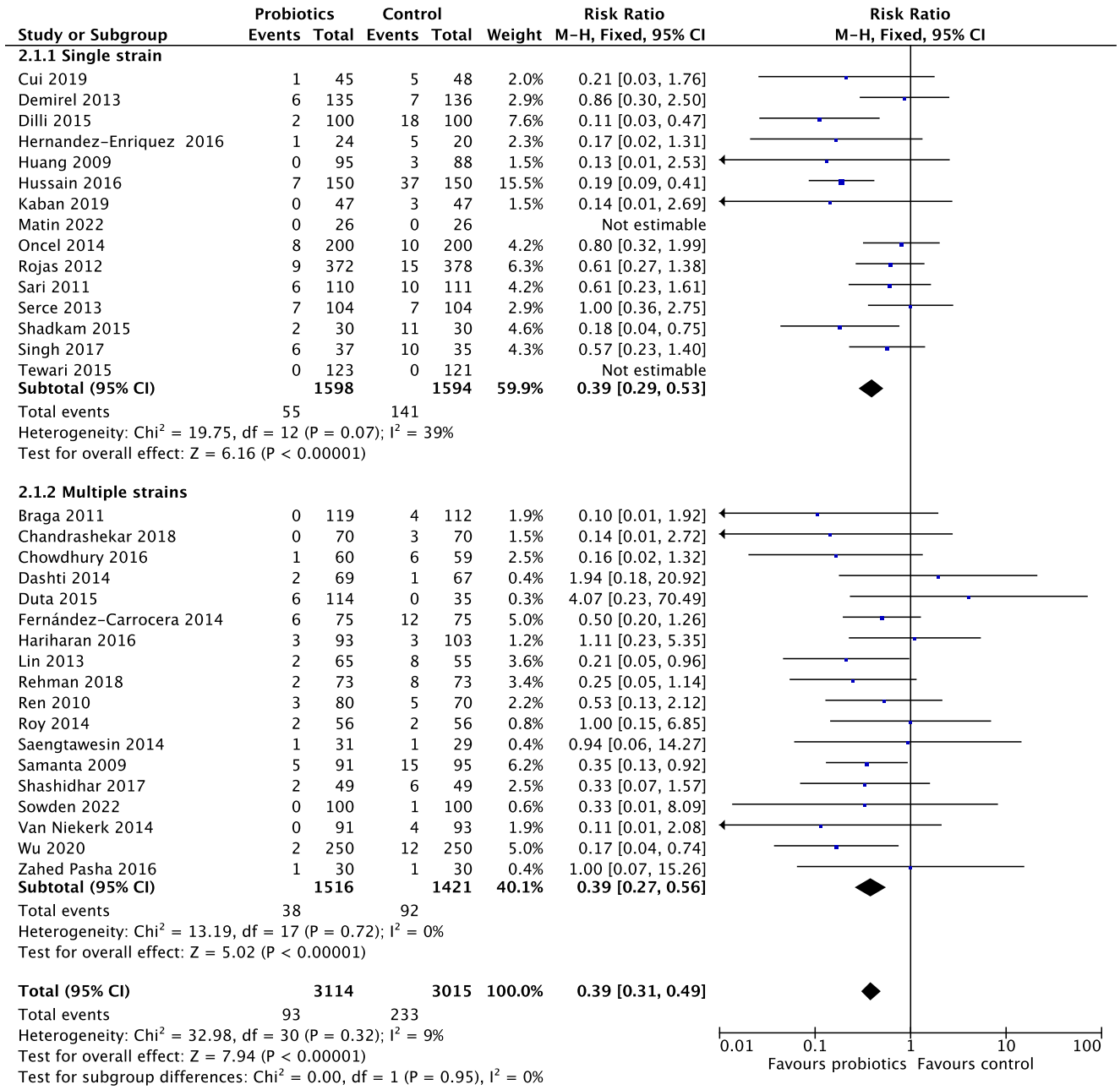


Outcome: *Invasive infection*

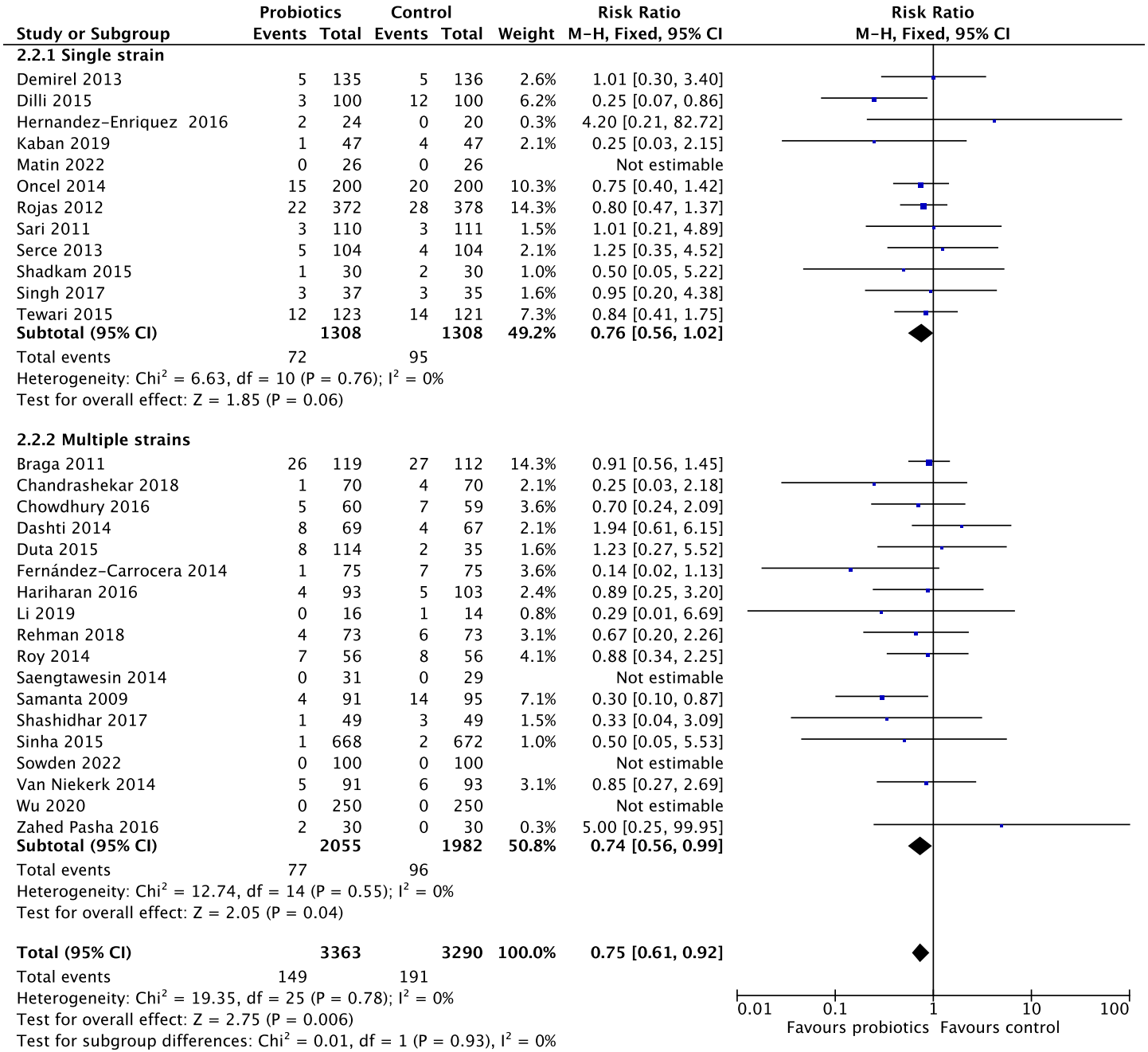


Comparison: Probiotics versus control in preterm newborns by probiotic strain type

Outcome: *Necrotizing enterocolitis*

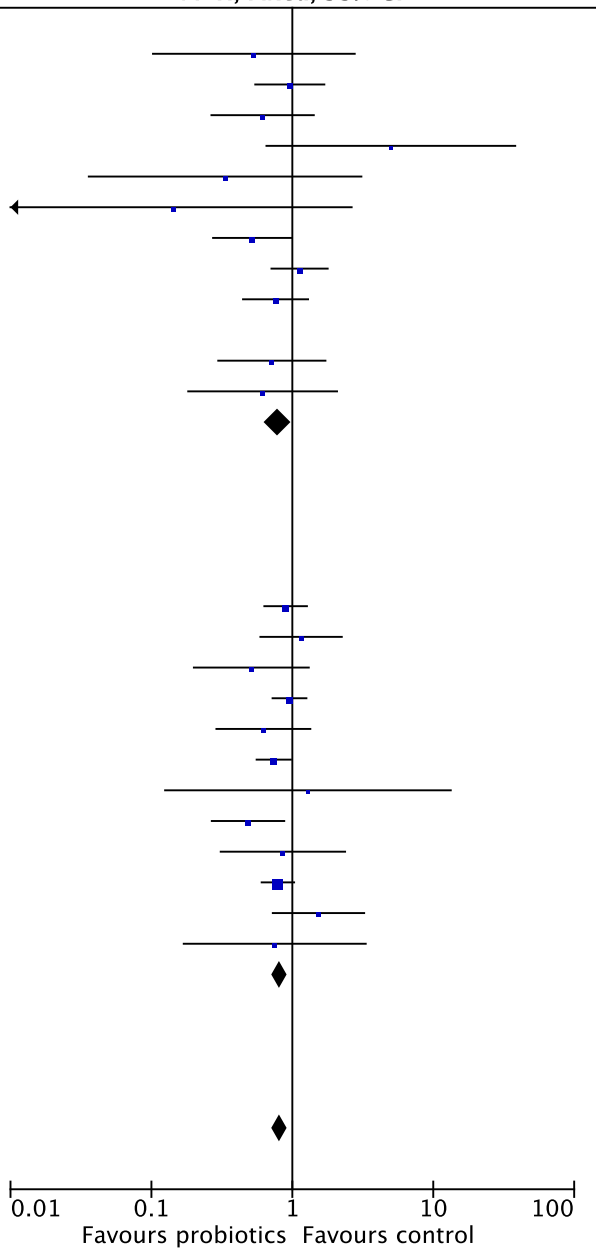


Outcome: *All-cause neonatal mortality*



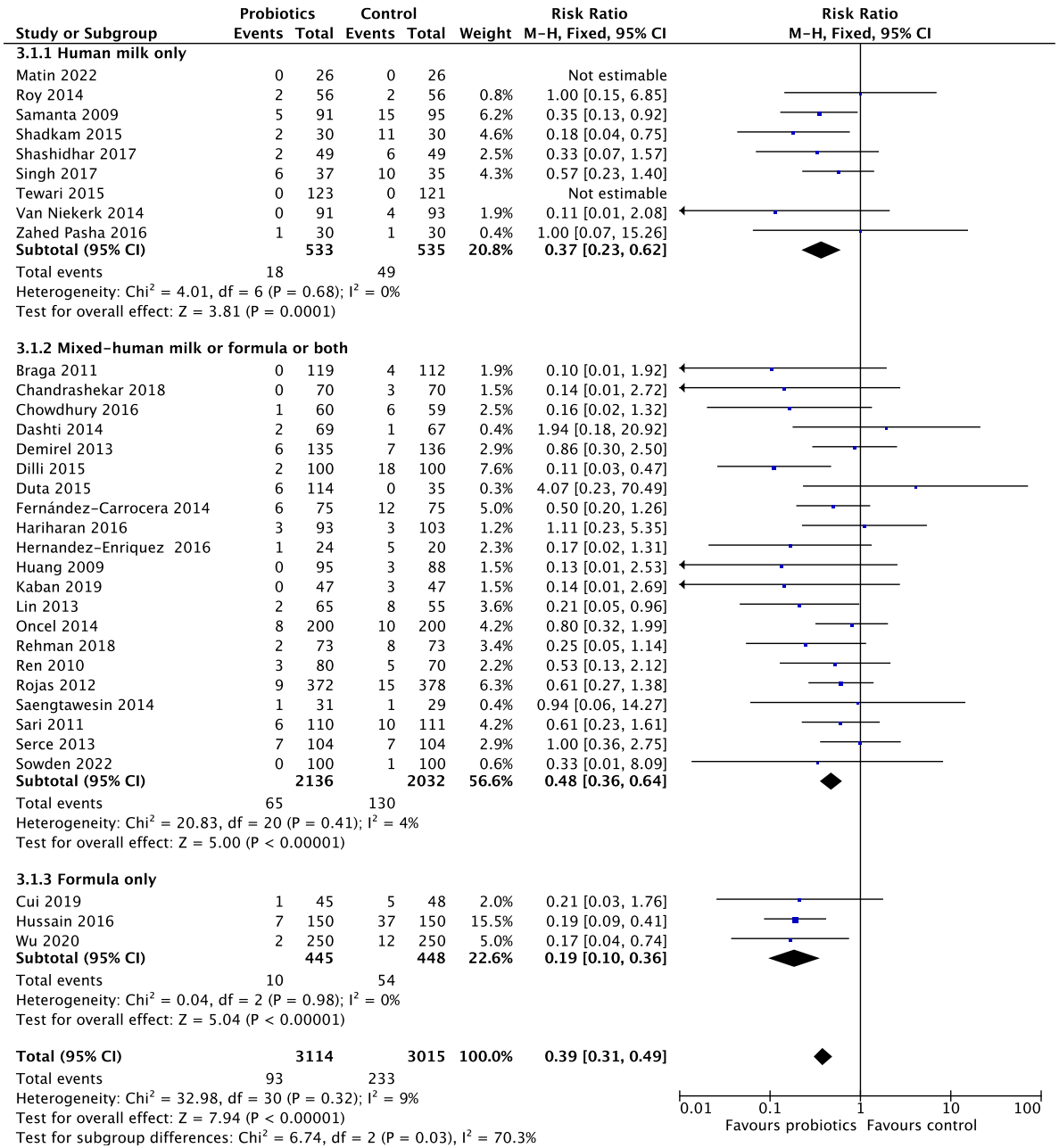
Outcome: *Invasive infection*

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Single strain						
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]
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]
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% CI)		**1009**		**1003**	**30.0%**	**0.79 [0.63, 1.00]**
Total events	110		138			
Heterogeneity: $Chi^2 = 10.22$, df = 10 (P = 0.42); $I^2 = 2\%$						
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% CI)		**1707**		**1630**	**70.0%**	**0.82 [0.71, 0.94]**
Total events	270		320			
Heterogeneity: $Chi^2 = 10.42$, df = 11 (P = 0.49); $I^2 = 0\%$						
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: $Chi^2 = 20.67$, df = 22 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 3.49 (P = 0.0005)						
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.82), $I^2 = 0\%$						

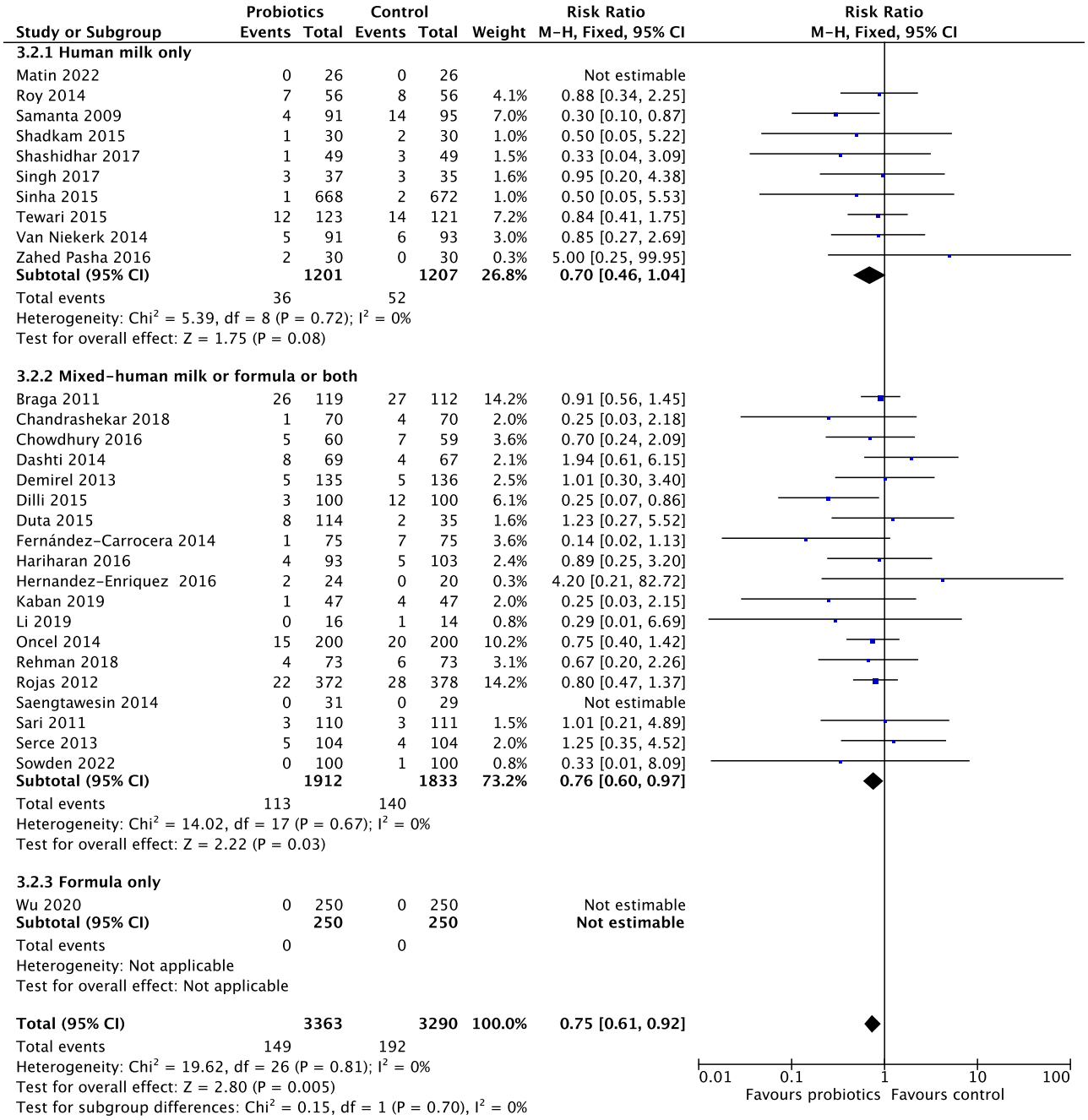


Comparison: Probiotics versus control in preterm newborns by feeding type

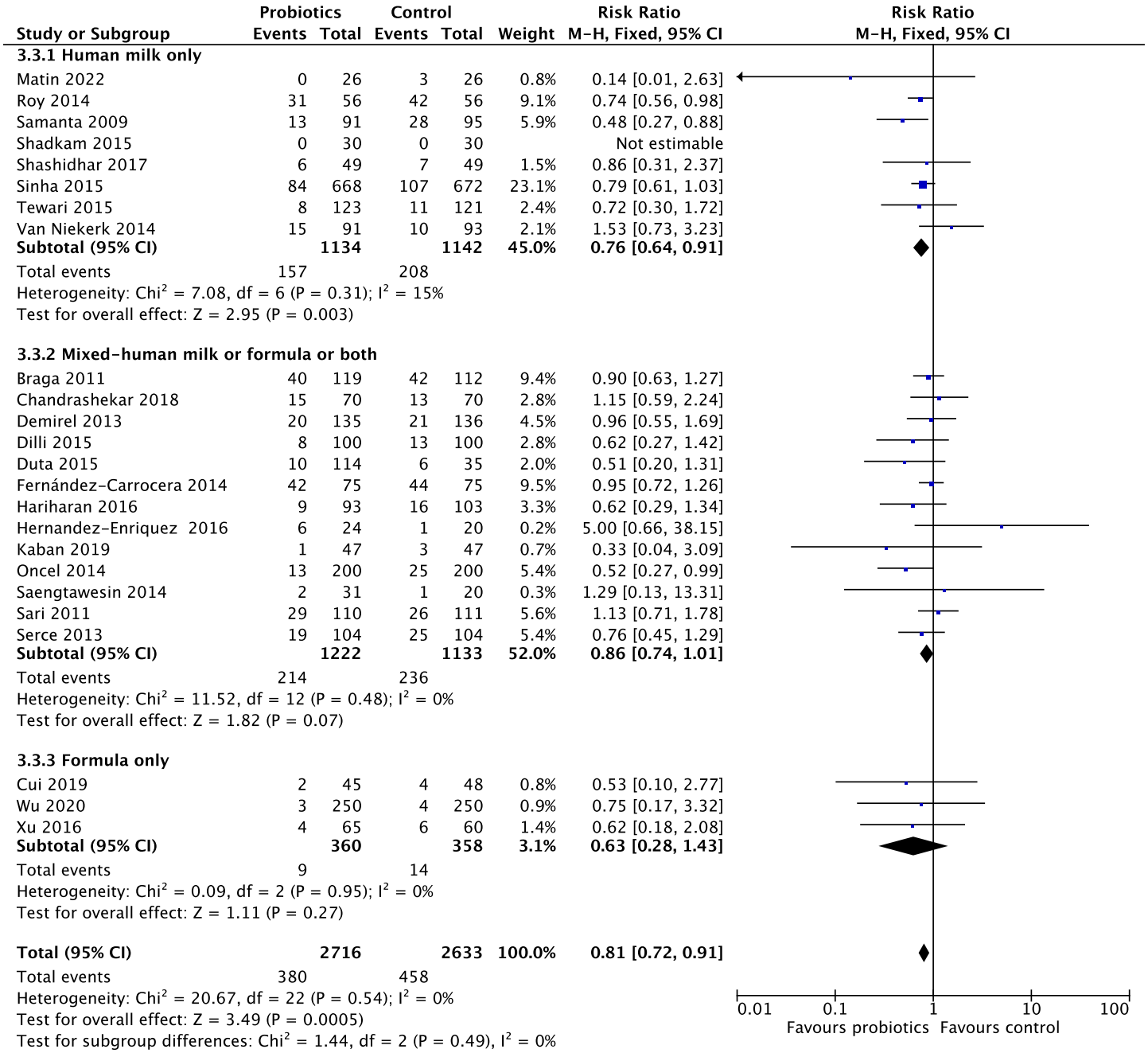
Outcome: *Necrotizing enterocolitis*



Outcome: *All-cause neonatal mortality*

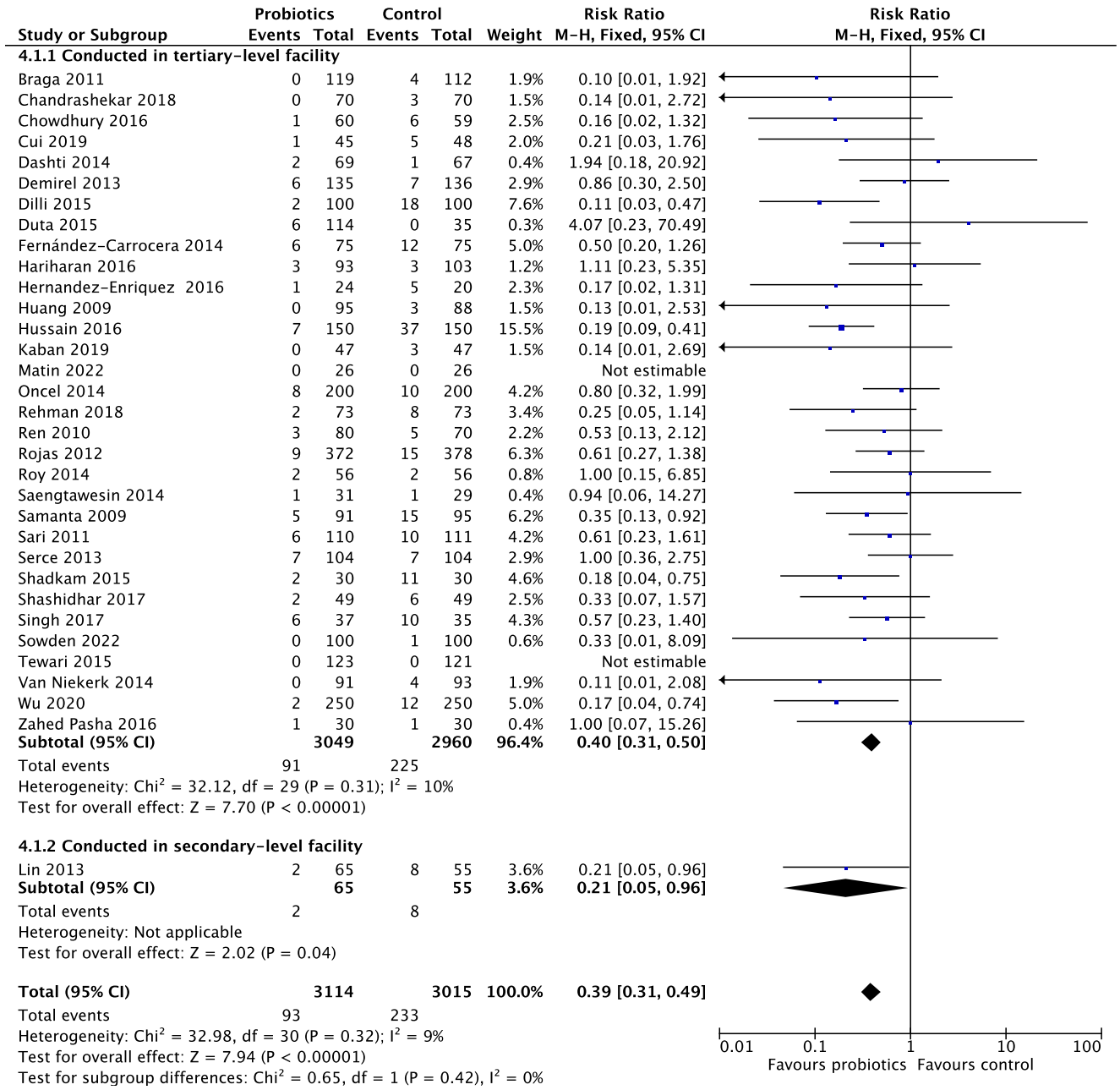


Outcome: *Invasive infection*

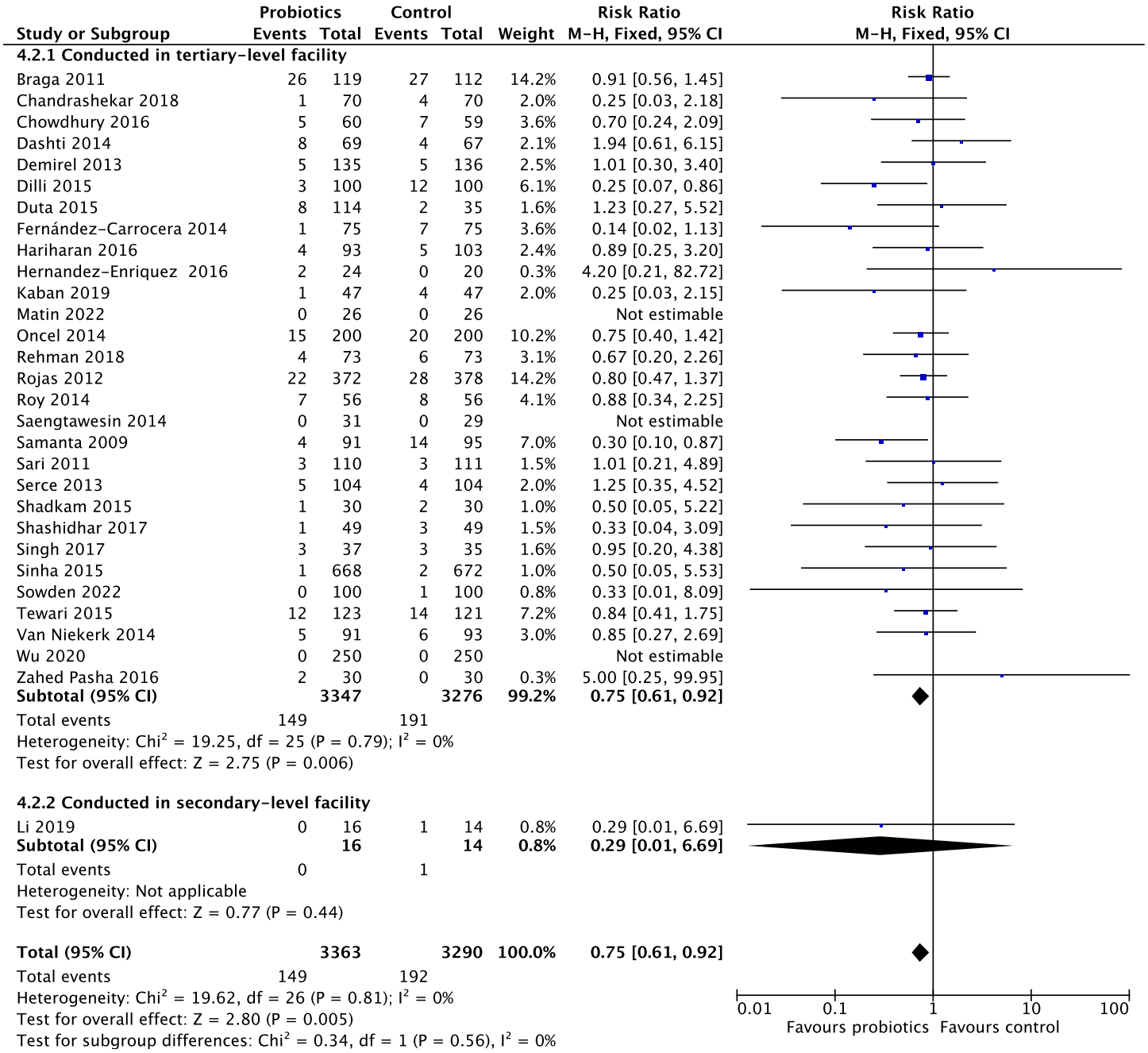


Comparison: Probiotics versus control in preterm newborns by facility level

Outcome: *Necrotizing enterocolitis*

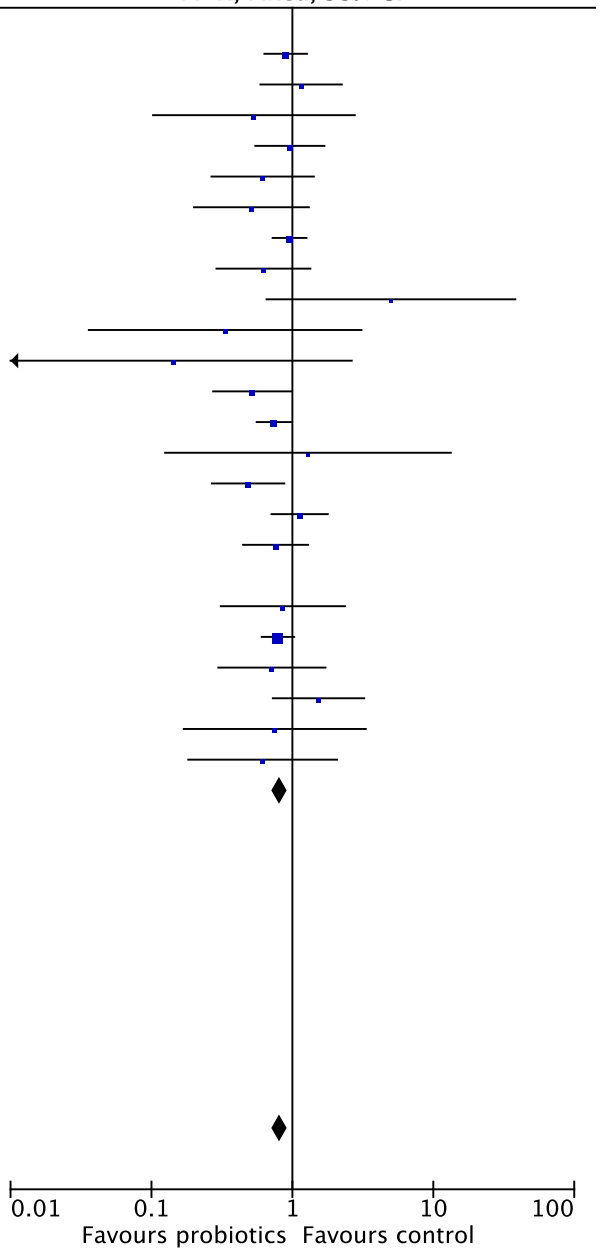


Outcome: *All-cause neonatal mortality*



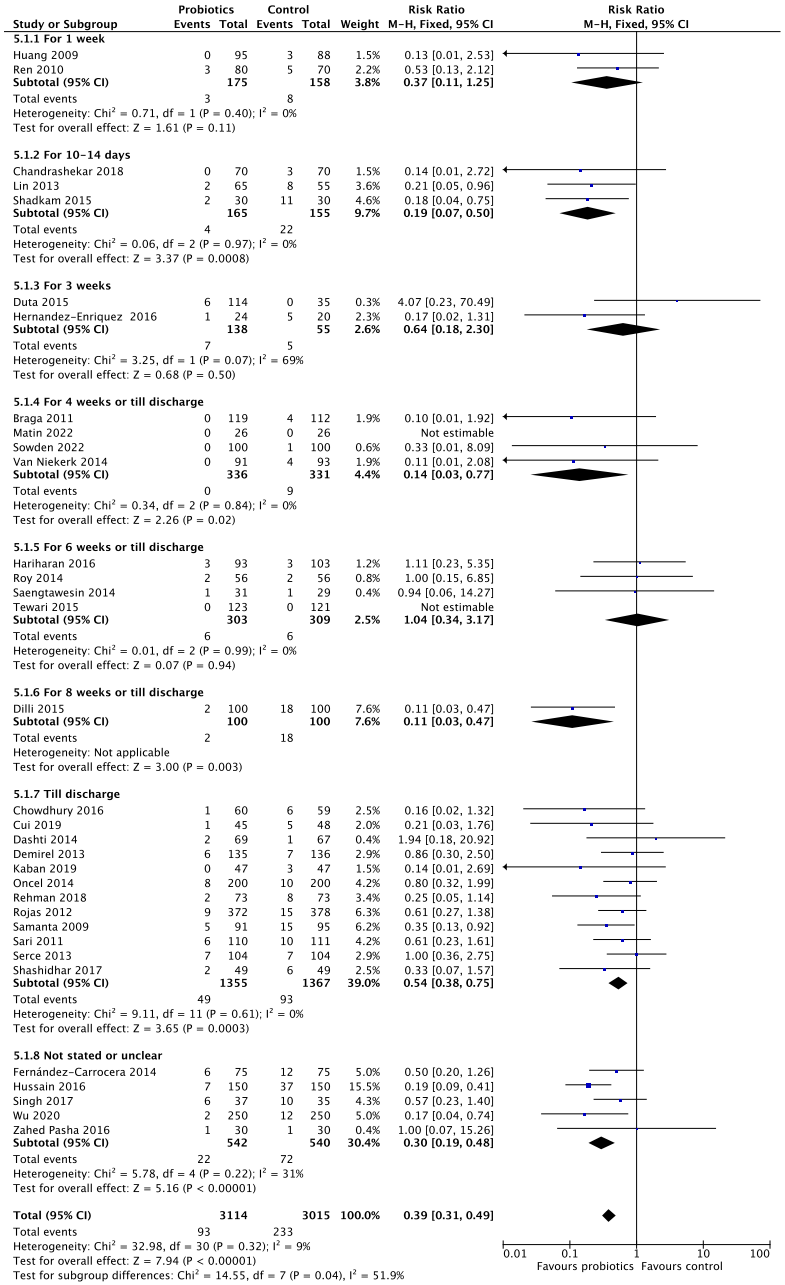
Outcome: *Invasive infection*

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Conducted in tertiary-level facility						
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 = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 3.49 (P = 0.0005)						
4.3.2 Conducted in secondary-level facility						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
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 = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 3.49 (P = 0.0005)						
Test for subgroup differences: Not applicable						



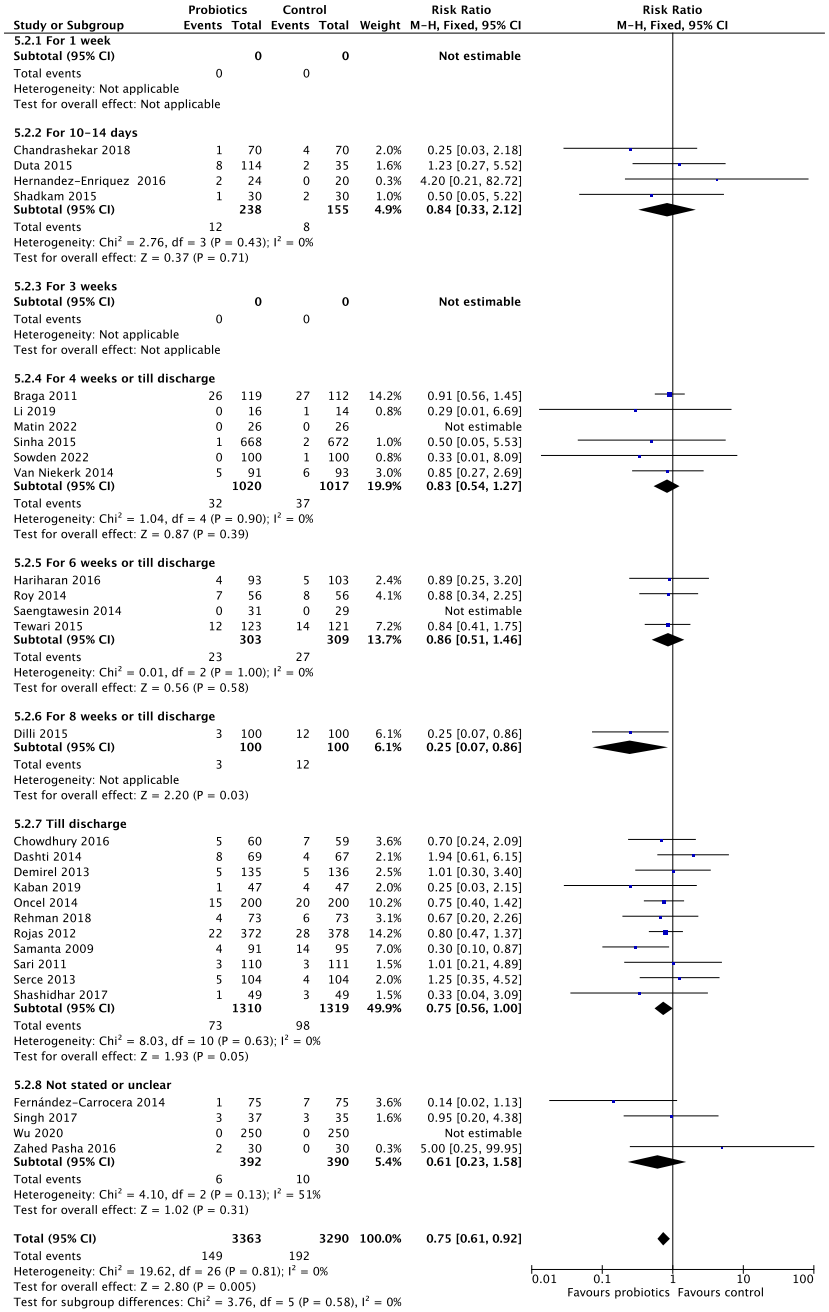
Comparison: Probiotics versus control in preterm newborns by duration of intervention

Outcome: *Necrotizing enterocolitis*



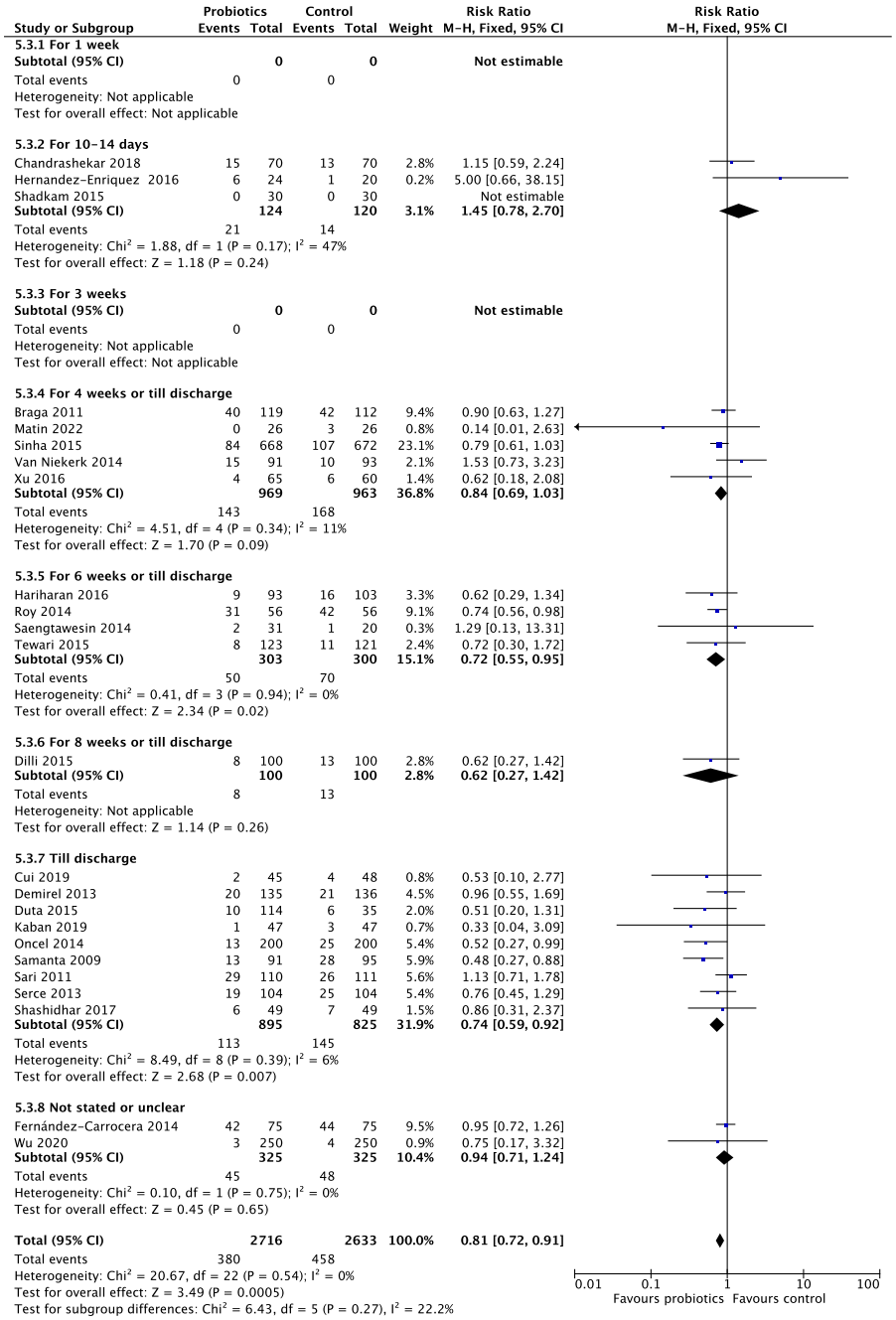
Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *All-cause neonatal mortality*



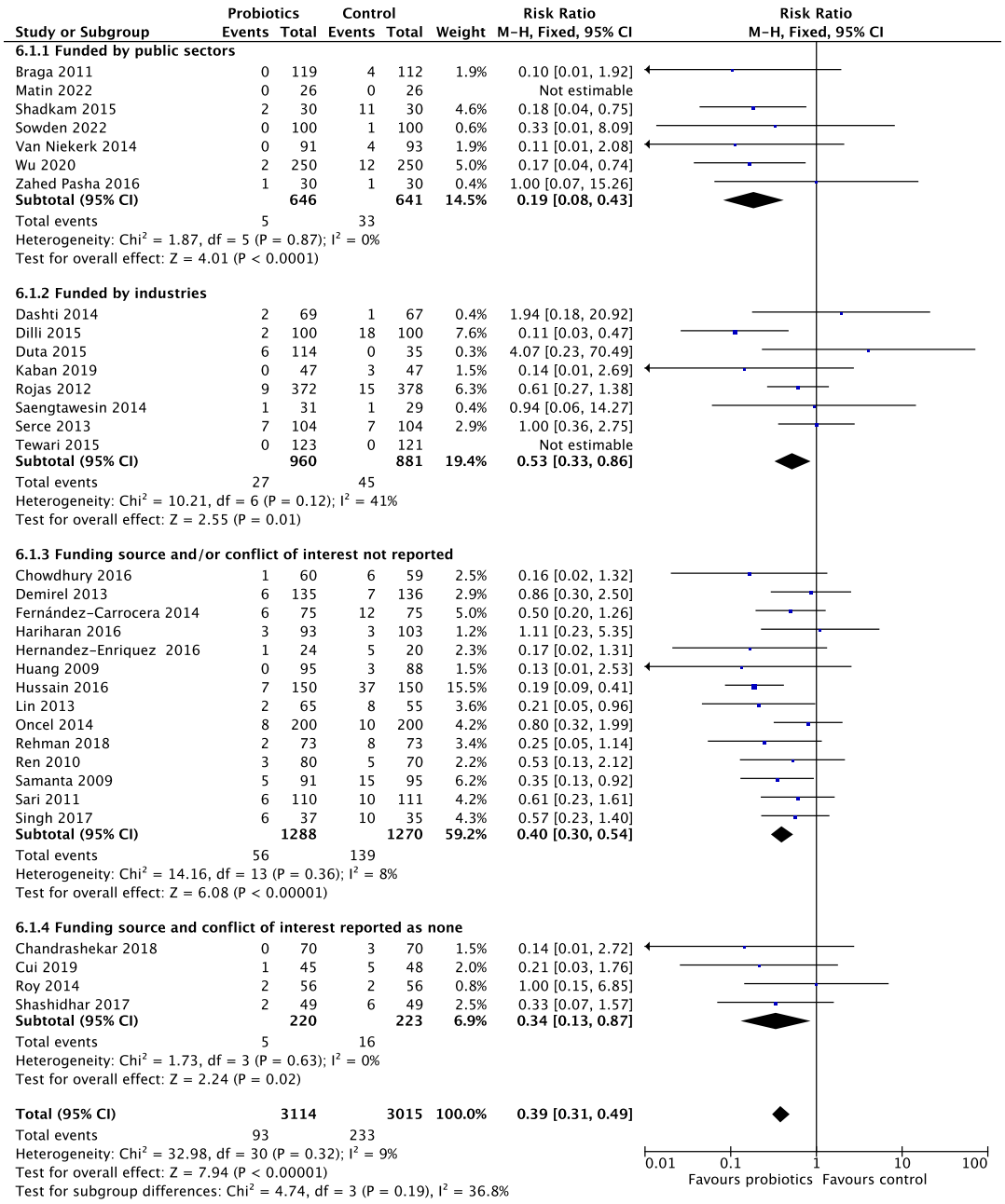
Prevention and Treatment of Neonatal Infections in LMICs

Outcome: *Invasive infection*

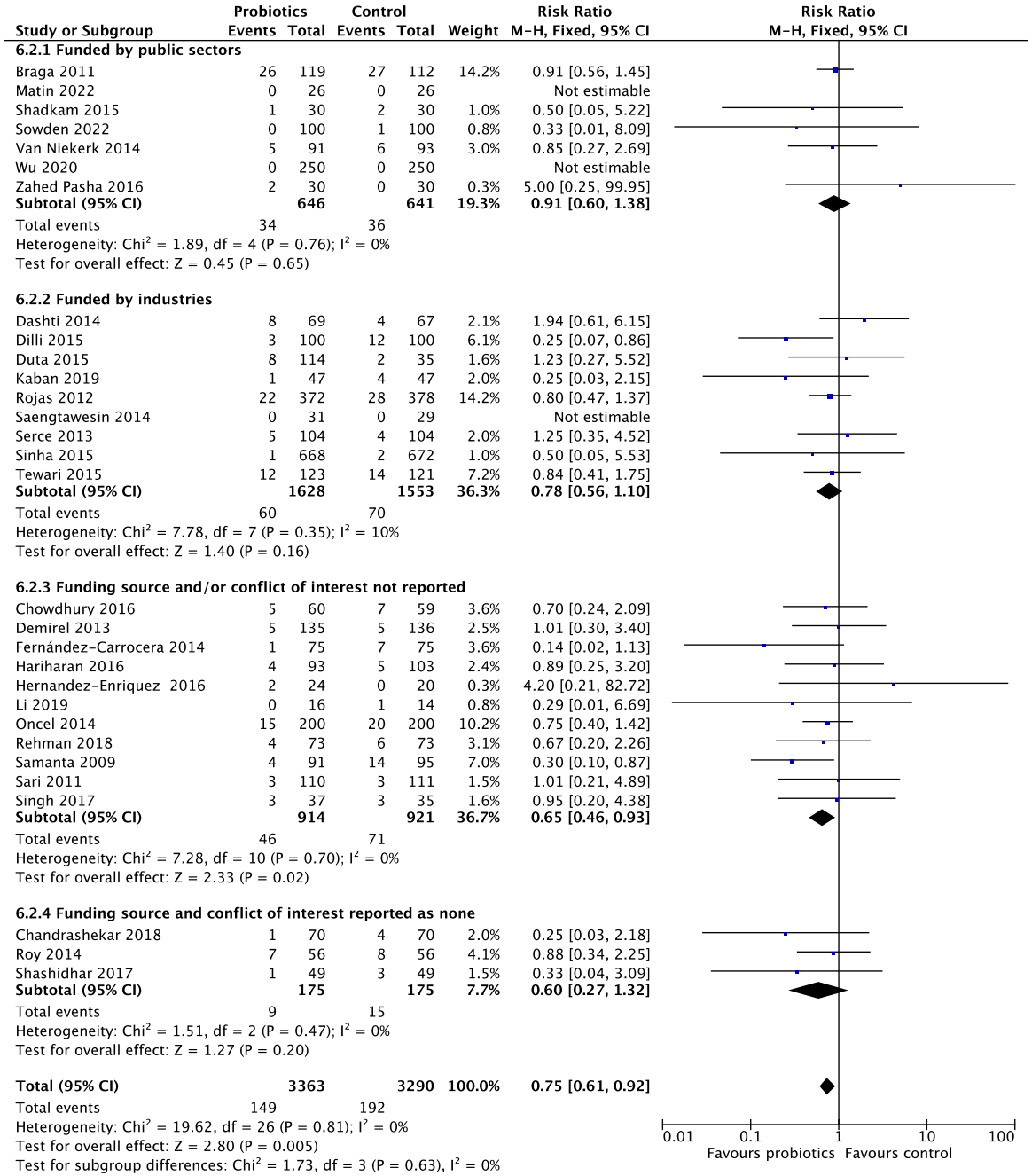


Comparison: Probiotics versus control in preterm newborns by funding source

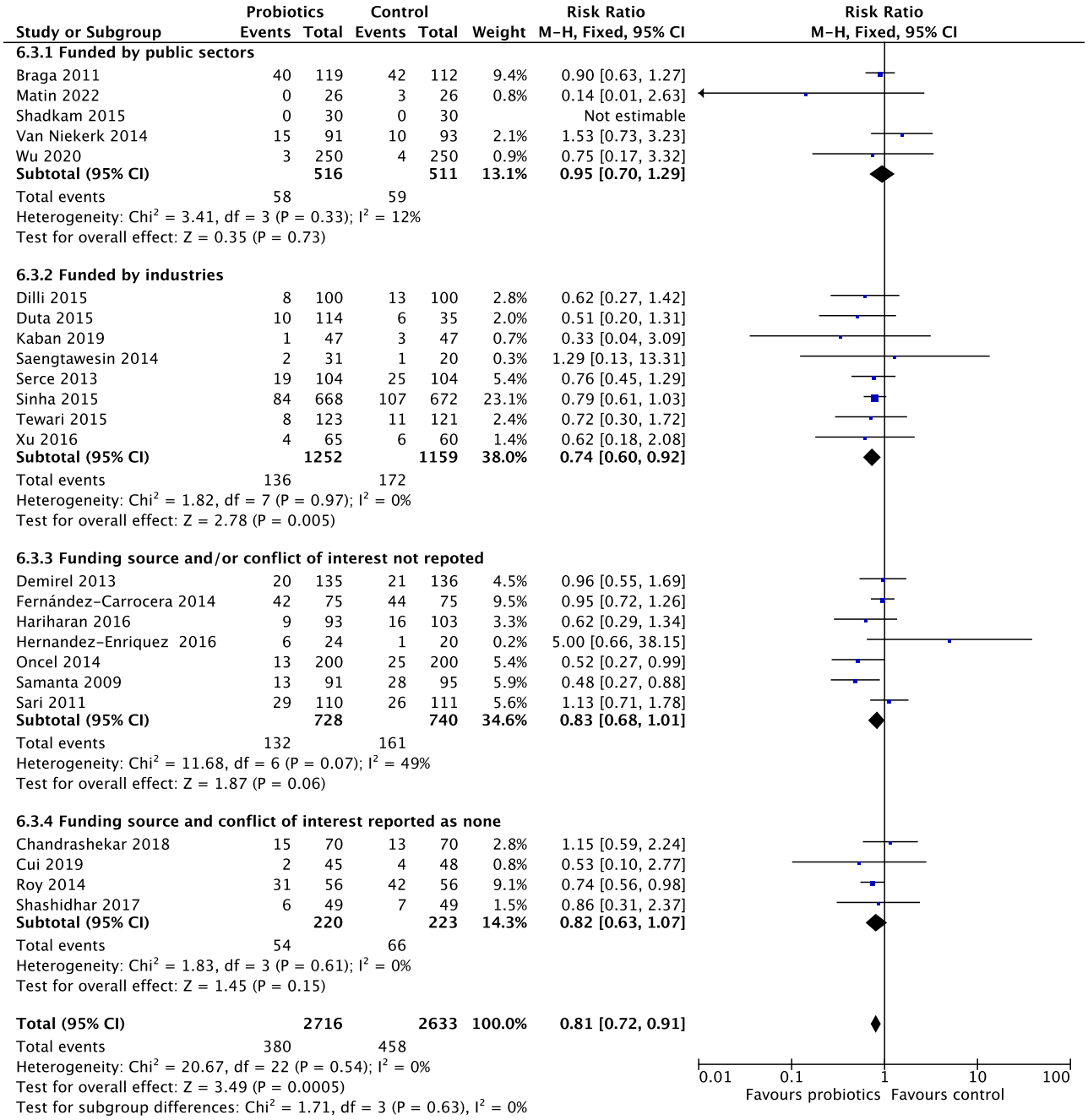
Outcome: *Necrotizing enterocolitis*



Outcome: *All-cause neonatal mortality*

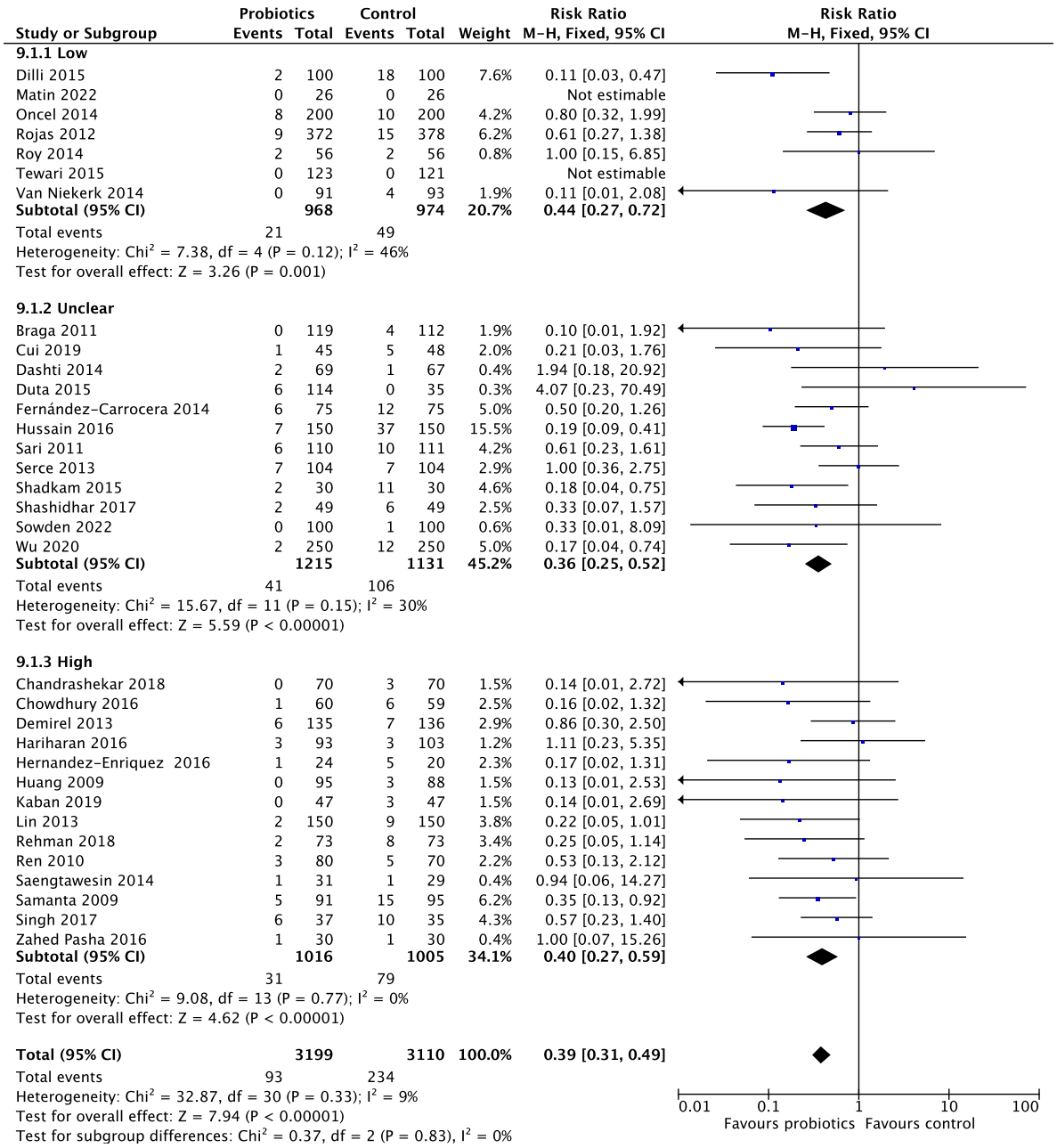


Outcome: *Invasive infection*

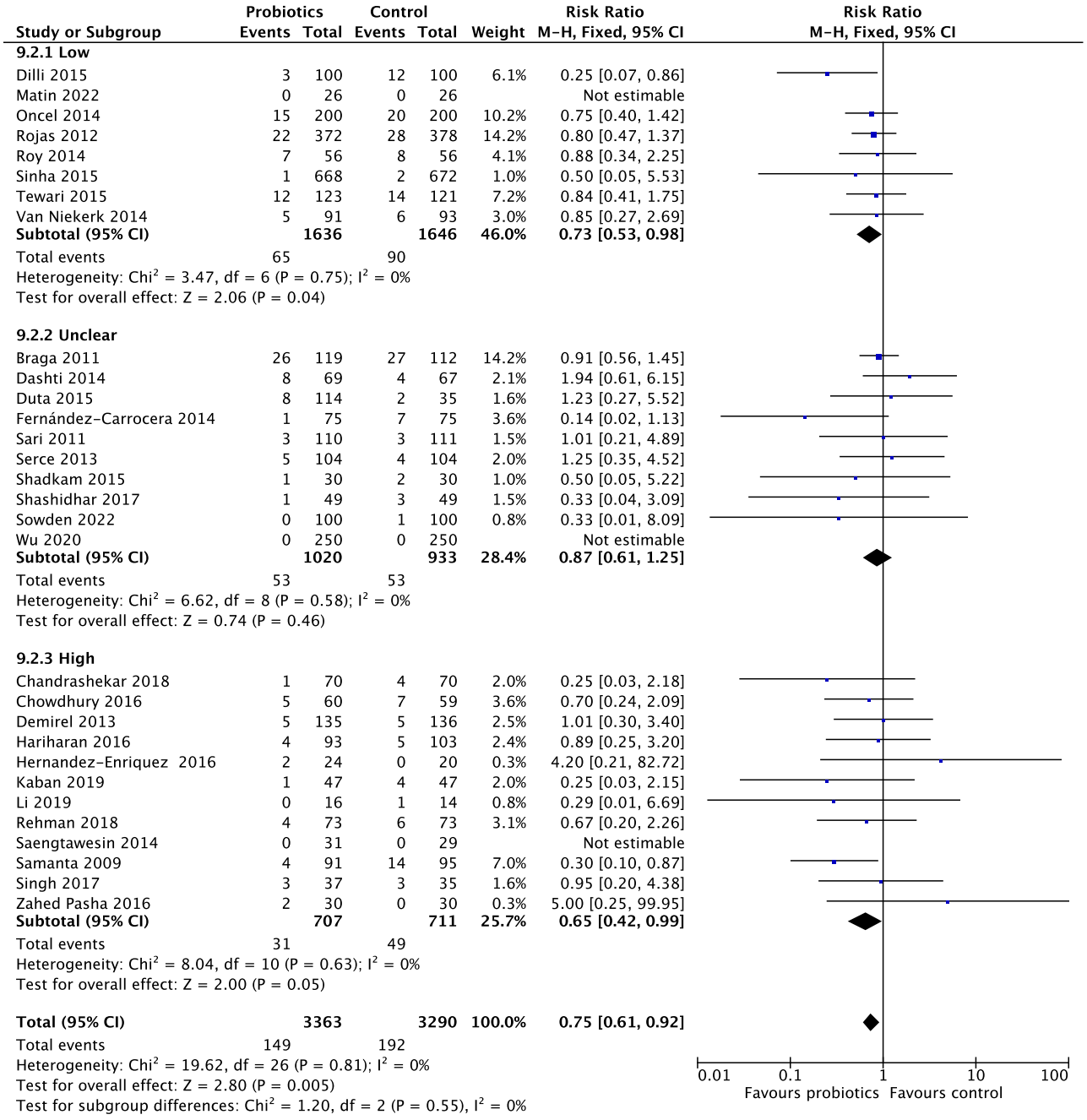


Comparison: Probiotics versus control in preterm newborns by risk of bias

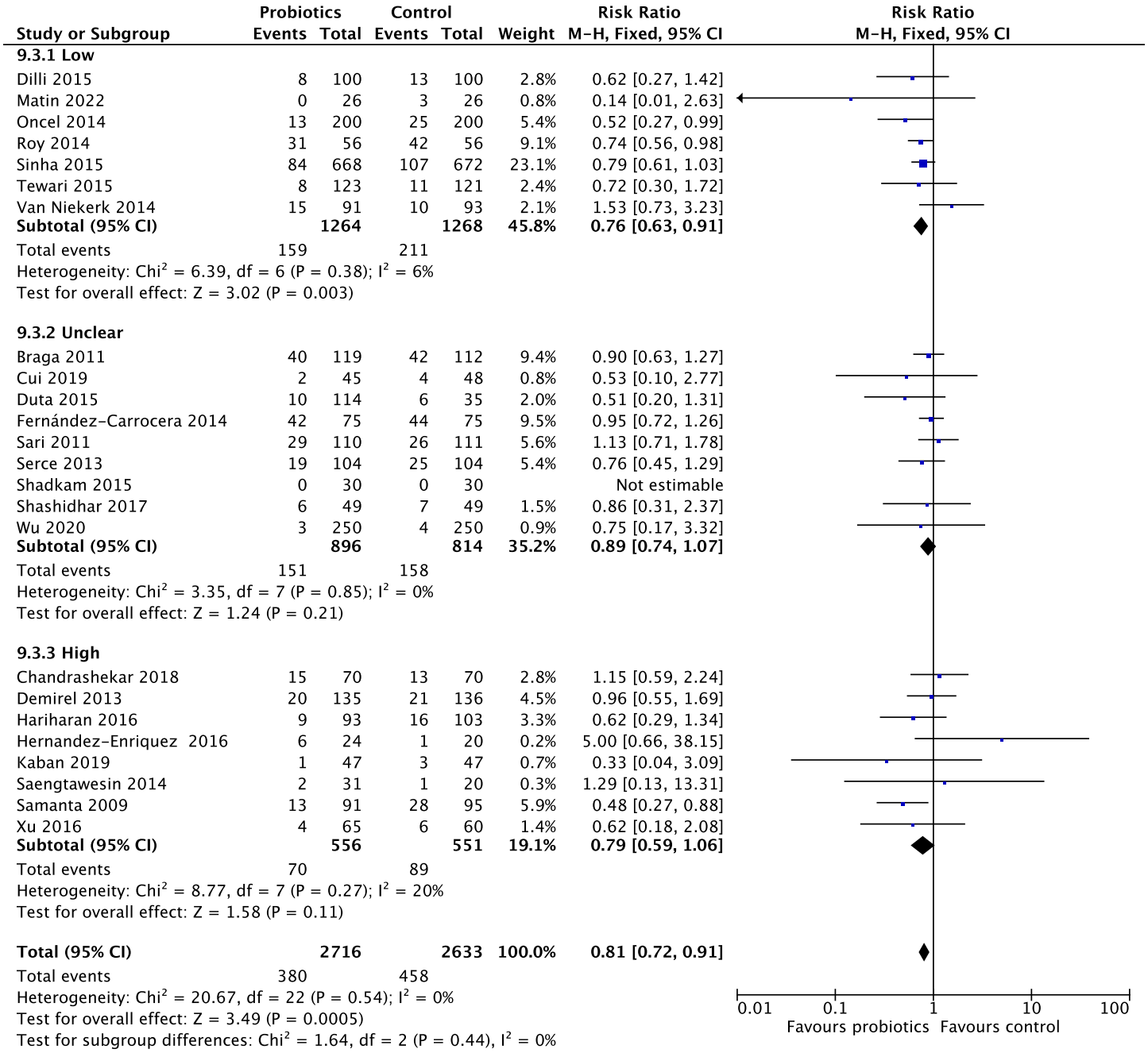
Outcome: *Necrotizing enterocolitis*



Outcome: *All-cause neonatal mortality*



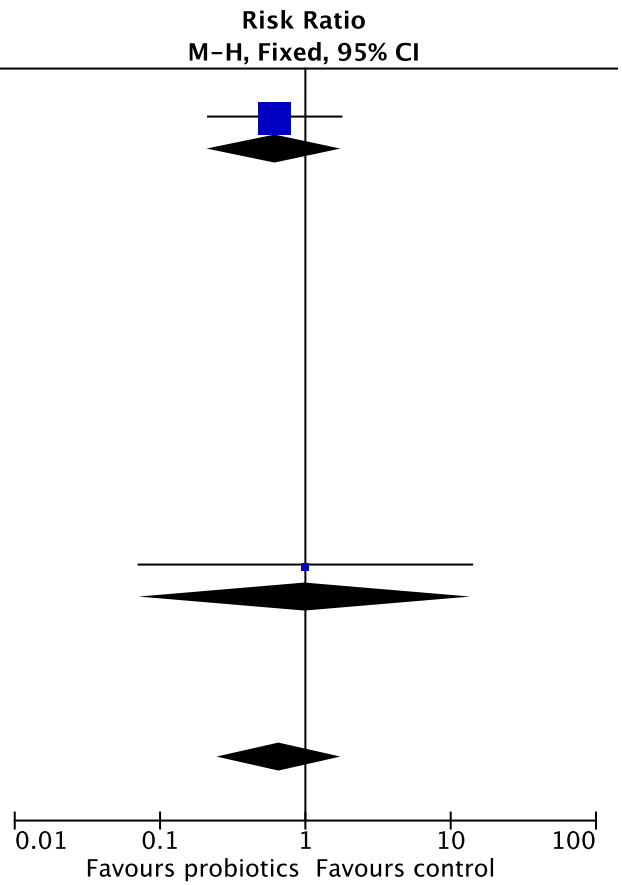
Outcome: *Invasive infection*



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

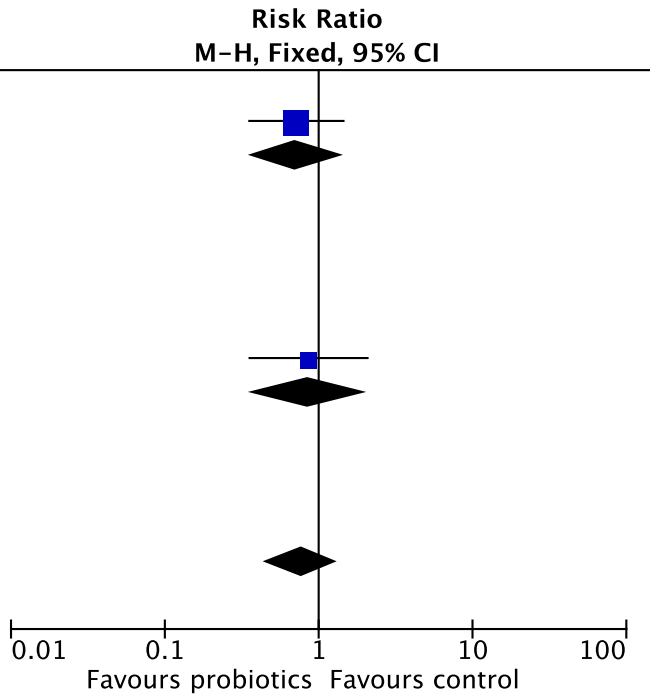
Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Lactobacillus spp.						
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 applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.1.2 Bacillus clausii						
Tewari 2015	0	61	0	59		Not estimable
Subtotal (95% CI)		**61**		**59**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.3 Bifidobacterium spp. plus Lactobacillus 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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
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: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%						



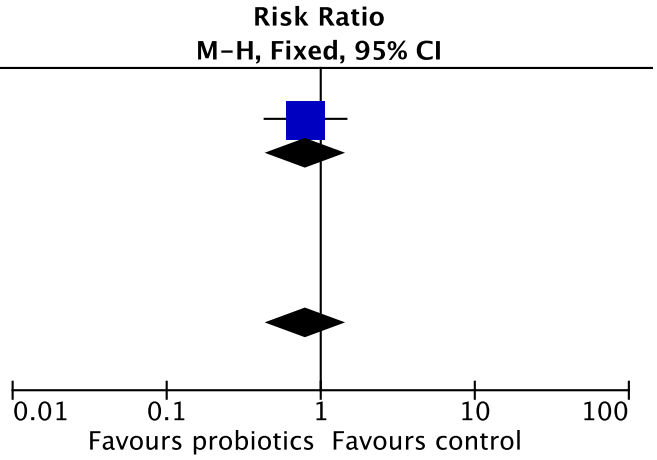
Outcome: *All-cause mortality*

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Lactobacillus spp.						
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 applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.2.2 Bacillus clausii						
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 applicable						
Test for overall effect: Z = 0.34 (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%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 = 0%						



Outcome: *Invasive infection*

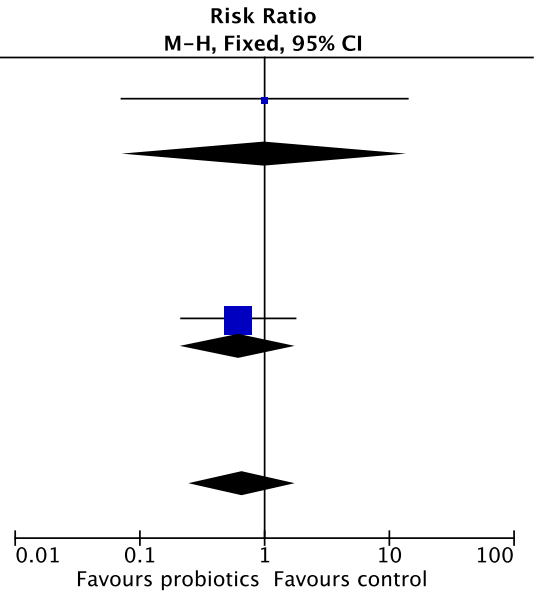
Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Bacillus clausii						
Tewari 2015	14	61	17	59	100.0%	0.80 [0.43, 1.47]
Subtotal (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Total (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Not applicable						



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

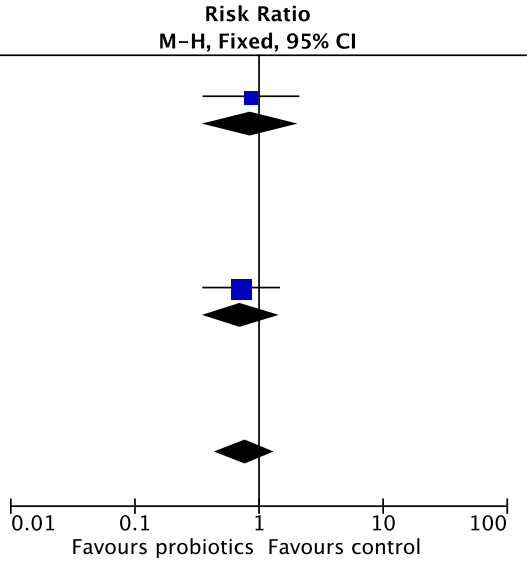
Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Human milk only						
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
7.1.2 Mixed- human milk or formula or both						
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 applicable						
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%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%						



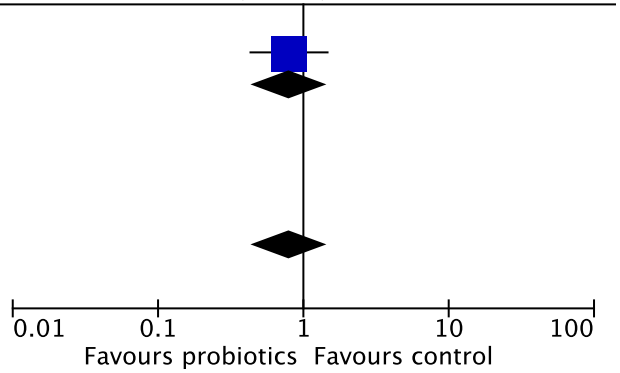
Outcome: *All-cause neonatal mortality*

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Human milk only						
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 applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
7.2.2 Mixed- human milk or formula or both						
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 applicable						
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	19		26			
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 = 0%						



Outcome: *Invasive infection*

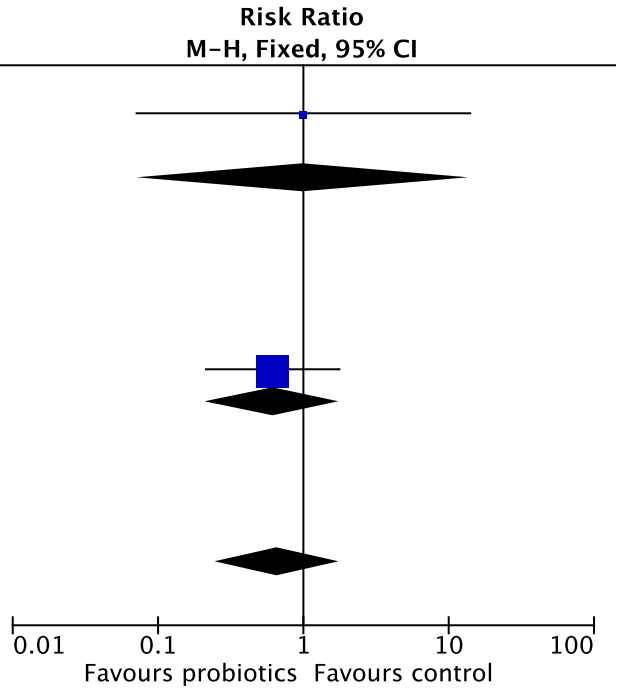
Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Human milk only						
Tewari 2015	14	61	17	59	100.0%	0.80 [0.43, 1.47]
Subtotal (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Total (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Not applicable						



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

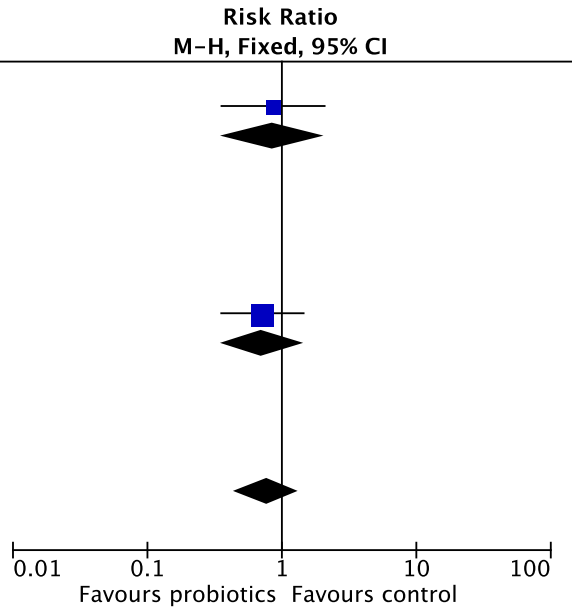
Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 For 6 weeks or till discharge						
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 applicable						
Test for overall effect: Z = 0.00 (P = 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 applicable						
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%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%						



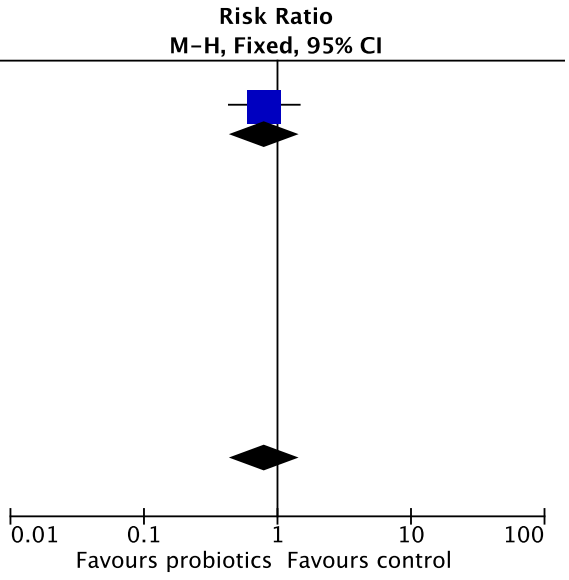
Outcome: *All-cause neonatal mortality*

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 For 6 weeks or till discharge						
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 applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
8.2.2 Till discharge						
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 applicable						
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	19		26			
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 = 0%						



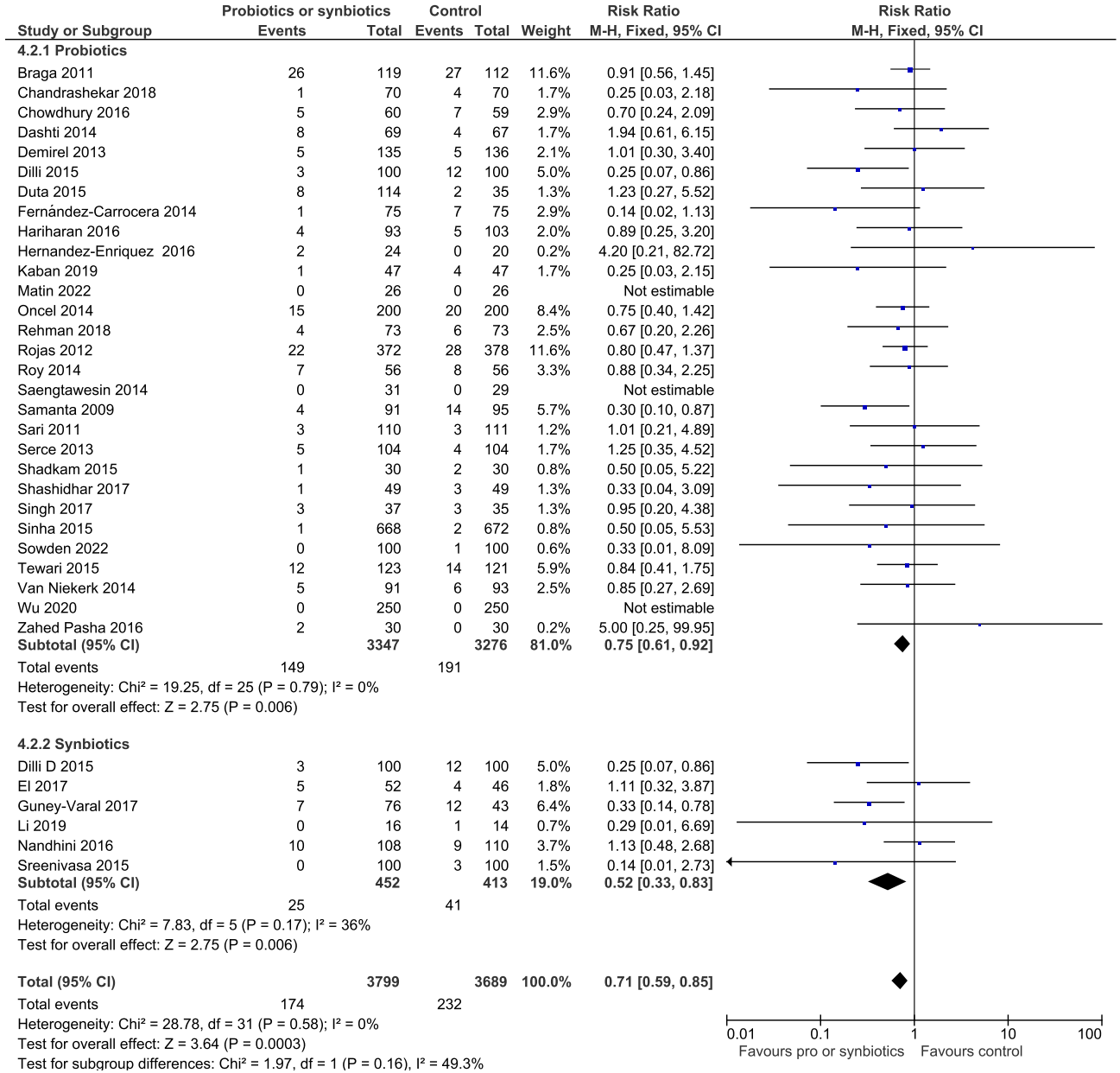
Outcome: *Invasive infection*

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 For 6 weeks or till discharge						
Tewari 2015	14	61	17	59	100.0%	0.80 [0.43, 1.47]
Subtotal (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
8.3.2 Till discharge						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**61**		**59**	**100.0%**	**0.80 [0.43, 1.47]**
Total events	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Not applicable						



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*

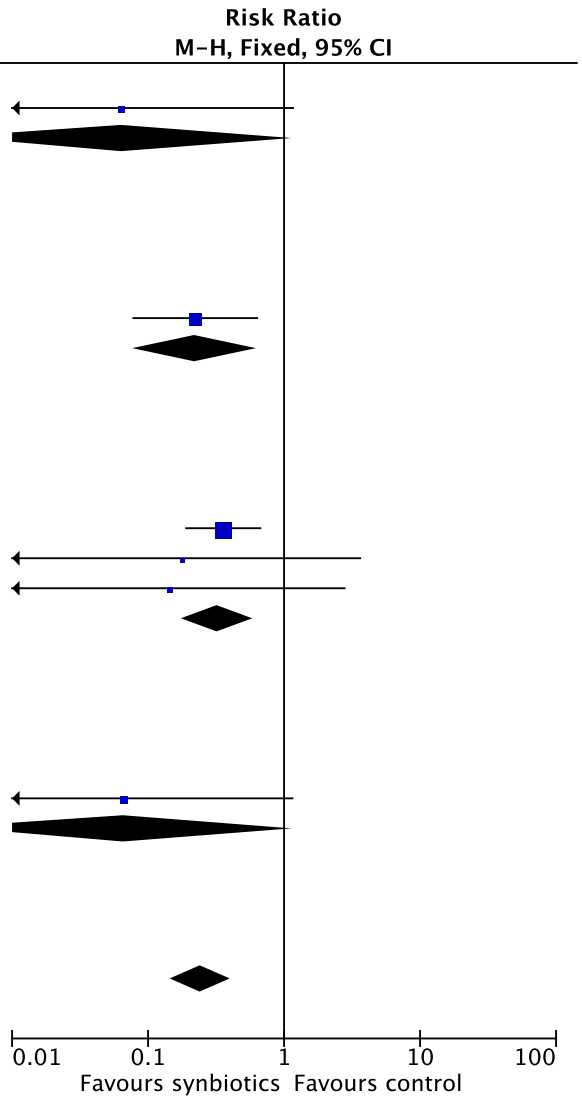


4.1.5. Synbiotics Supplementation

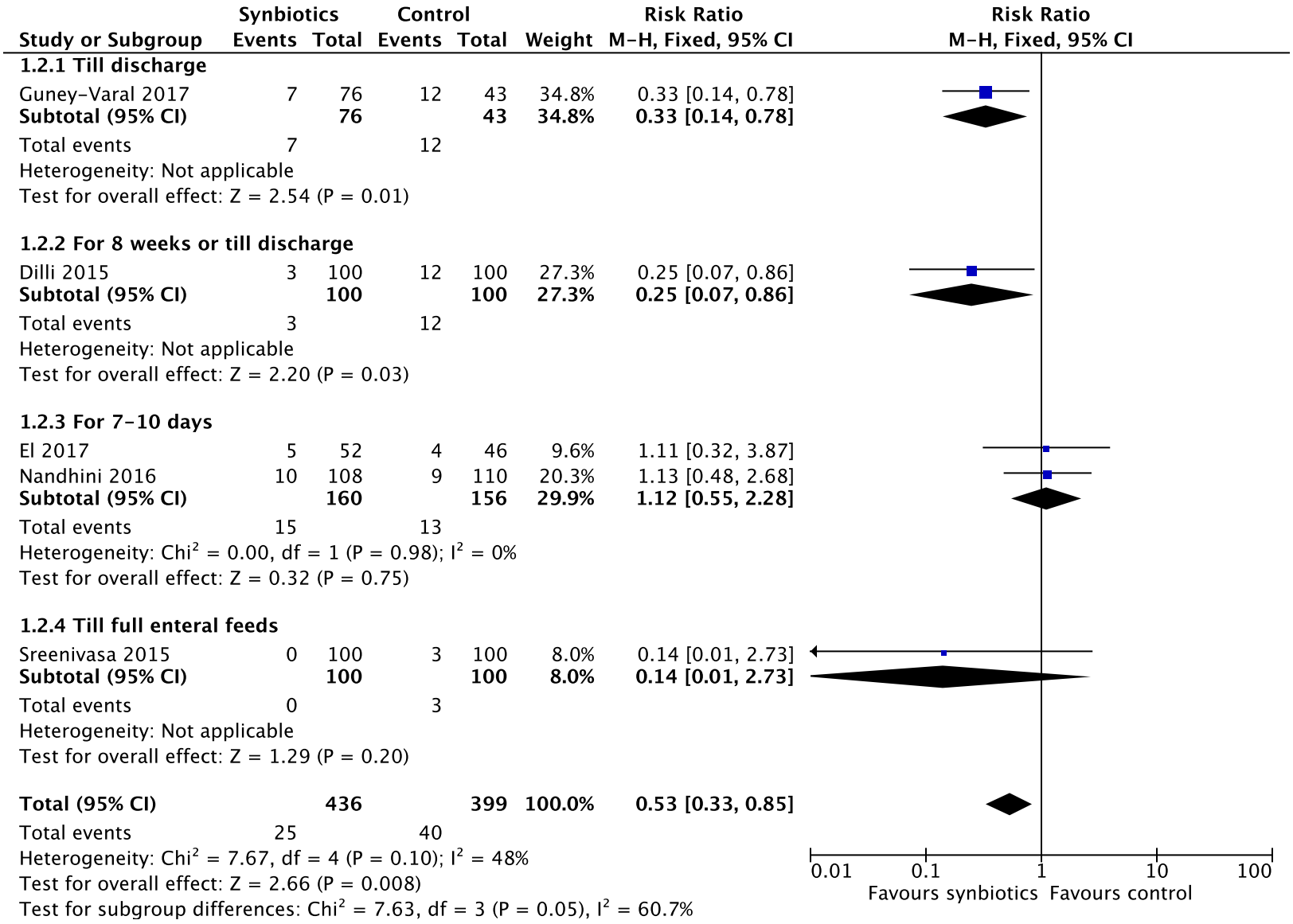
Comparison: Synbiotics versus control in preterm or LBW infants by the duration of intervention

Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Synbiotics Events	Synbiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Till discharge						
Guney-Varal 2017	0	70	4	40	8.7%	0.06 [0.00, 1.16]
Subtotal (95% CI)		**70**		**40**	**8.7%**	**0.06 [0.00, 1.16]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.1.2 For 8 weeks or till discharge						
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 applicable						
Test for overall effect: Z = 2.81 (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	110	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: $Chi^2 = 0.53$, df = 2 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 3.68 (P = 0.0002)						
1.1.4 Till full enteral feeds						
Sreenivasa 2015	0	100	7	100	11.5%	0.07 [0.00, 1.15]
Subtotal (95% CI)		**100**		**100**	**11.5%**	**0.07 [0.00, 1.15]**
Total events	0		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 5.50 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 2.33$, df = 3 (P = 0.51), $I^2 = 0\%$						

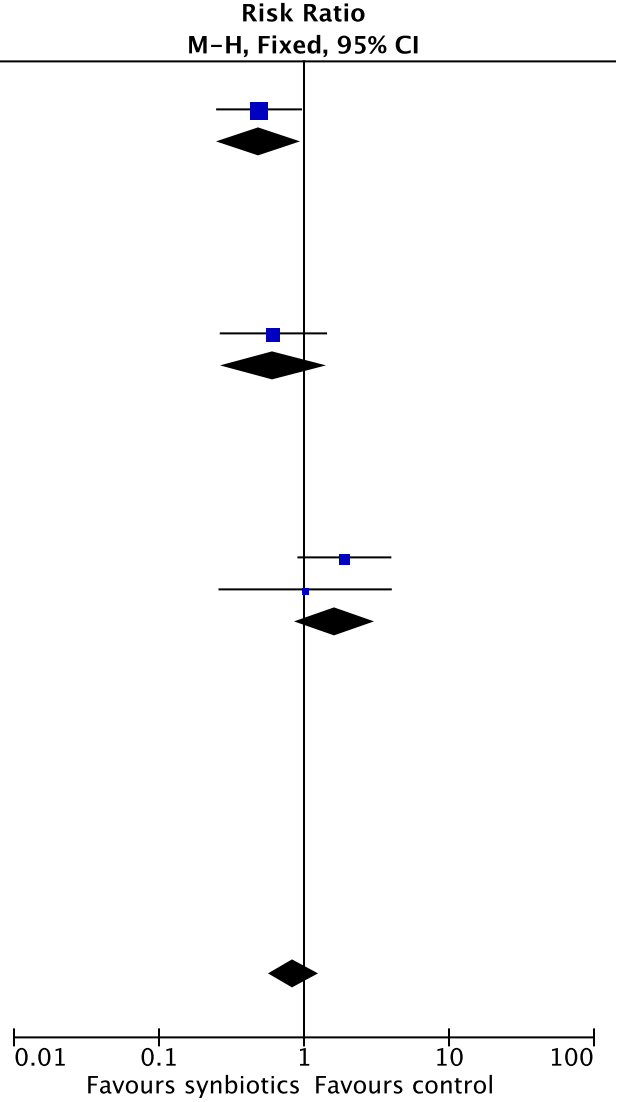


Outcome: *All-cause mortality till discharge*



Outcome: *Invasive infection*

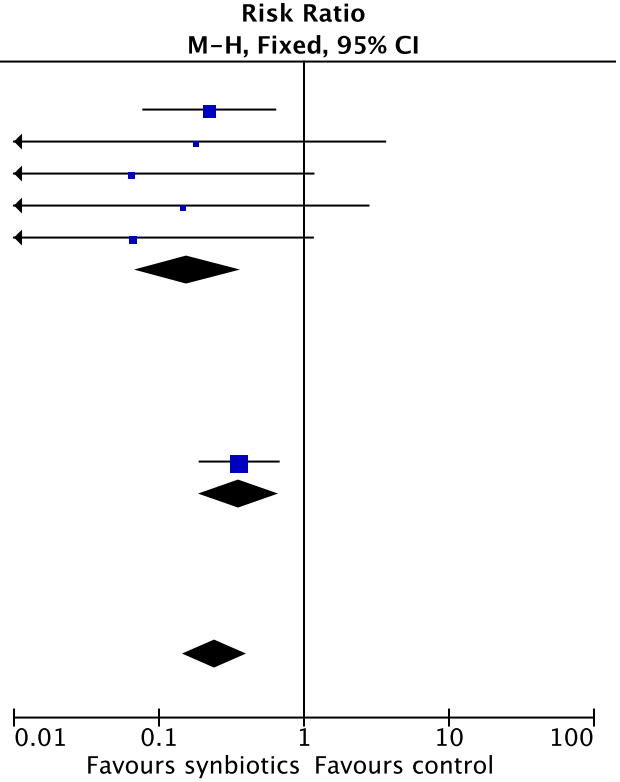
Study or Subgroup	Synbiotics Events	Synbiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Till discharge						
Guney-Varal 2017	12	70	14	40	41.2%	0.49 [0.25, 0.95]
Subtotal (95% CI)		**70**		**40**	**41.2%**	**0.49 [0.25, 0.95]**
Total events	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.3.2 For 8 weeks or till discharge						
Dilli 2015	8	100	13	100	30.1%	0.62 [0.27, 1.42]
Subtotal (95% CI)		**100**		**100**	**30.1%**	**0.62 [0.27, 1.42]**
Total events	8		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (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 = 0.63, df = 1 (P = 0.43); I^2 = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
1.3.4 Till full enteral feeds						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
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 = 0.81 (P = 0.42)						
Test for subgroup differences: Chi^2 = 7.09, df = 2 (P = 0.03), I^2 = 71.8%						



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

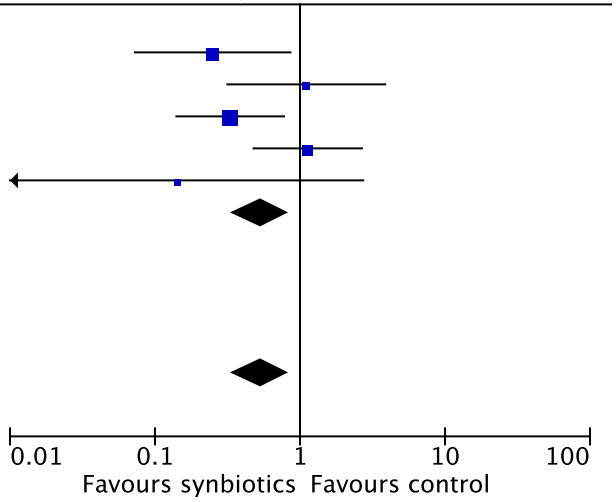
Outcome: *Necrotizing enterocolitis*

Study or Subgroup	Synbiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Not stated or reported as none						
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%	0.15 [0.01, 2.78]
Sreenivasa 2015	0	100	7	100	11.5%	0.07 [0.00, 1.15]
Subtotal (95% CI)		**425**		**392**	**57.1%**	**0.16 [0.07, 0.36]**
Total events	4		34			
Heterogeneity: $Chi^2 = 1.15$, df = 4 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 4.33 (P < 0.0001)						
3.1.2 Funded by public sectors or universities						
Amini 2017	10	60	28	60	42.9%	0.36 [0.19, 0.67]
Subtotal (95% CI)		**60**		**60**	**42.9%**	**0.36 [0.19, 0.67]**
Total events	10		28			
Heterogeneity: Not applicable						
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); $I^2 = 0\%$						
Test for overall effect: Z = 5.50 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 2.38$, df = 1 (P = 0.12), $I^2 = 58.0\%$						



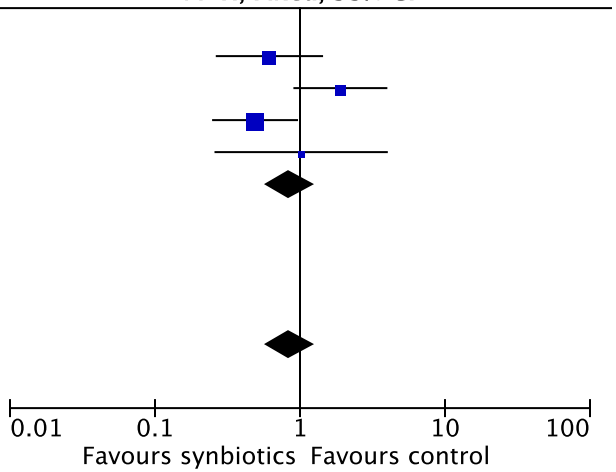
Outcome: *All-cause neonatal mortality*

Study or Subgroup	Synbiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Not stated or reported as none						
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 (P = 0.008)						
Total (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 (P = 0.008)						
Test for subgroup differences: Not applicable						



Outcome: *Invasive infection*

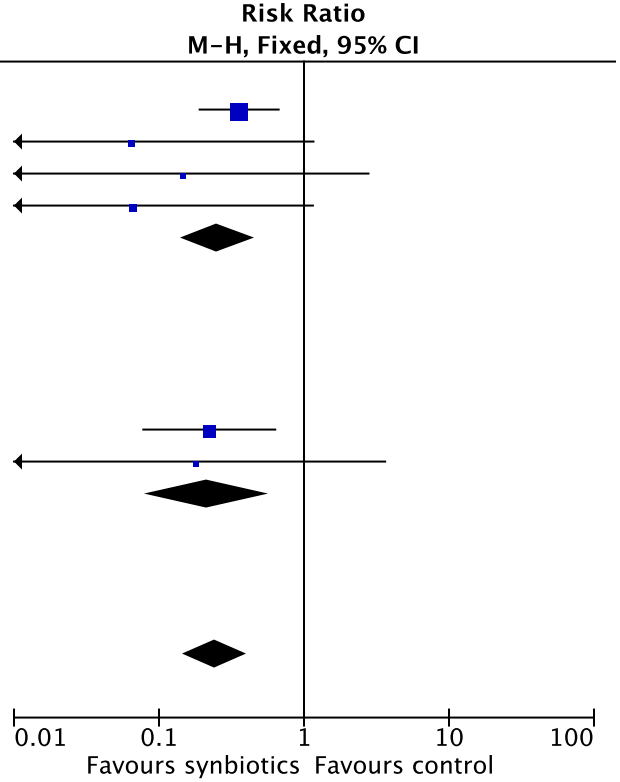
Study or Subgroup	Synbiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Not stated or reported as none						
Dilli 2015	8	100	13	100	30.1%	0.62 [0.27, 1.42]
El 2017	17	47	8	42	19.5%	1.90 [0.92, 3.94]
Guney-Varal 2017	12	70	14	40	41.2%	0.49 [0.25, 0.95]
Nandhini 2016	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 = 0.81 (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 = 0.81 (P = 0.42)						
Test for subgroup differences: Not applicable						



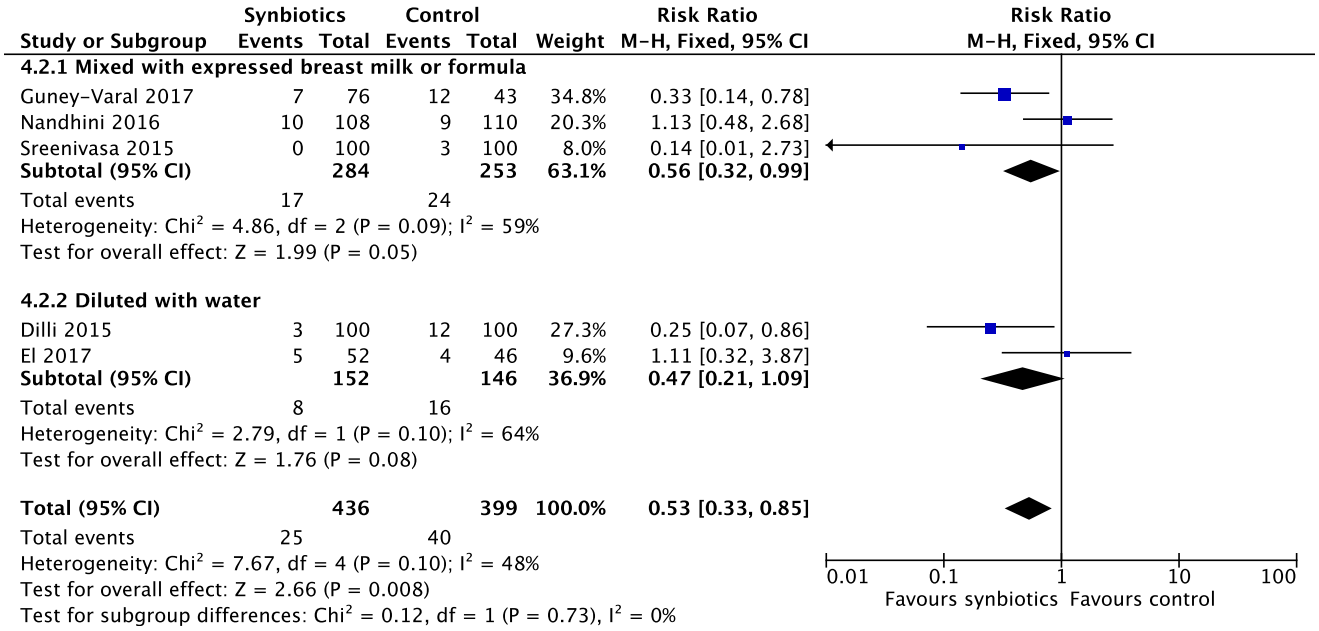
Comparison: Synbiotics versus control in preterm or LBW infants by synbiotics' volume

Outcome: *Necrotizing enterocolitis*

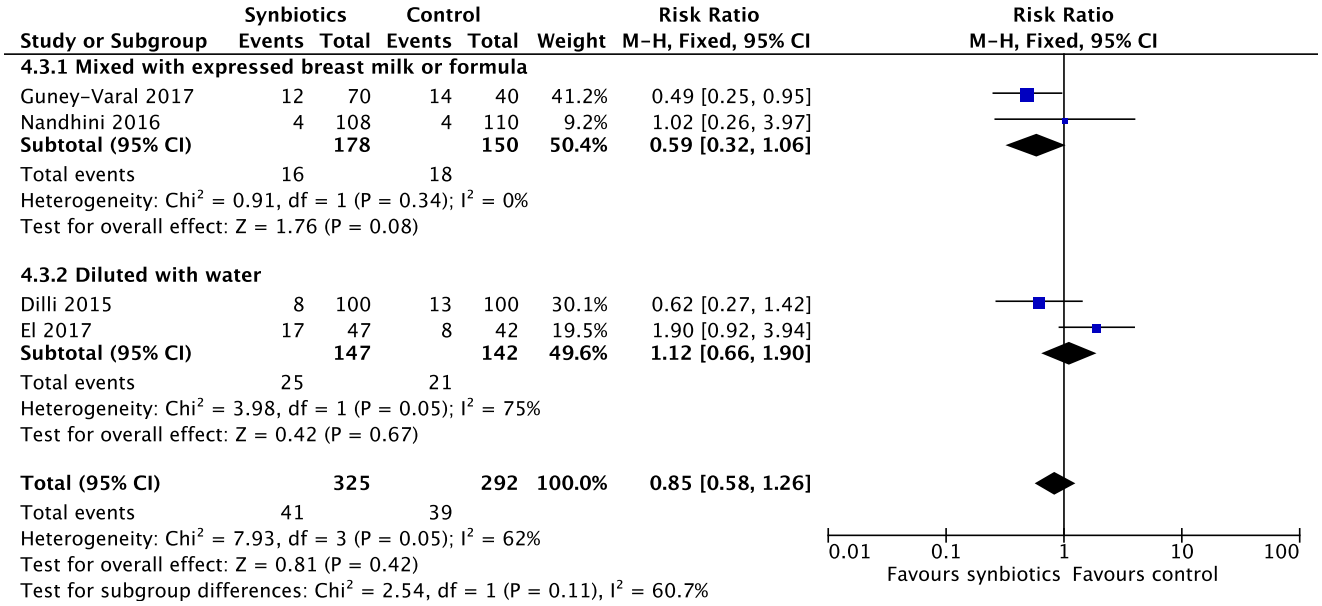
Study or Subgroup	Synbiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Mixed with expressed breast milk or formula						
Amini 2017	10	60	28	60	42.9%	0.36 [0.19, 0.67]
Guney-Varal 2017	0	70	4	40	8.7%	0.06 [0.00, 1.16]
Nandhini 2016	0	108	3	110	5.3%	0.15 [0.01, 2.78]
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 water						
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]
Subtotal (95% CI)		**147**		**142**	**31.6%**	**0.22 [0.08, 0.58]**
Total events	4		20			
Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 3.03 (P = 0.002)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 5.50 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0\%$						



Outcome: *All-cause neonatal mortality*



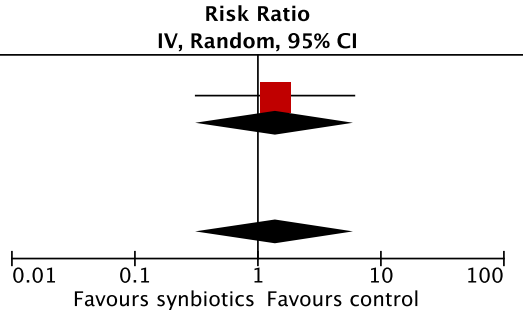
Outcome: *Invasive infection*



Comparison: Synbiotics versus control in term newborns by facility level

Outcome: *All-cause neonatal mortality*

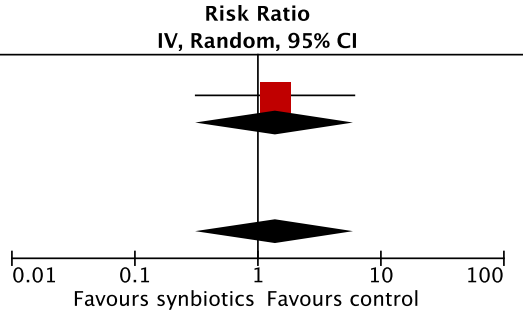
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Conducted in tertiary-level facility				
Cooper 2016	0.3209	0.7575	100.0%	1.38 [0.31, 6.08]
Subtotal (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Total (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Test for subgroup differences: Not applicable				



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

Outcome: *All-cause neonatal mortality*

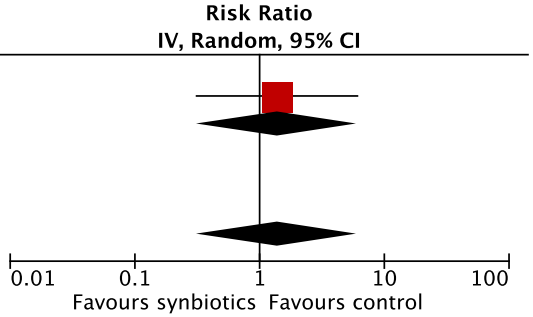
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 For 6 months				
Cooper 2016	0.3209	0.7575	100.0%	1.38 [0.31, 6.08]
Subtotal (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Total (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Test for subgroup differences: Not applicable				



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
6.1.1 Funded by industry				
Cooper 2016	0.3209	0.7575	100.0%	1.38 [0.31, 6.08]
Subtotal (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Total (95% CI)			**100.0%**	**1.38 [0.31, 6.08]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				
Test for subgroup differences: Not applicable				



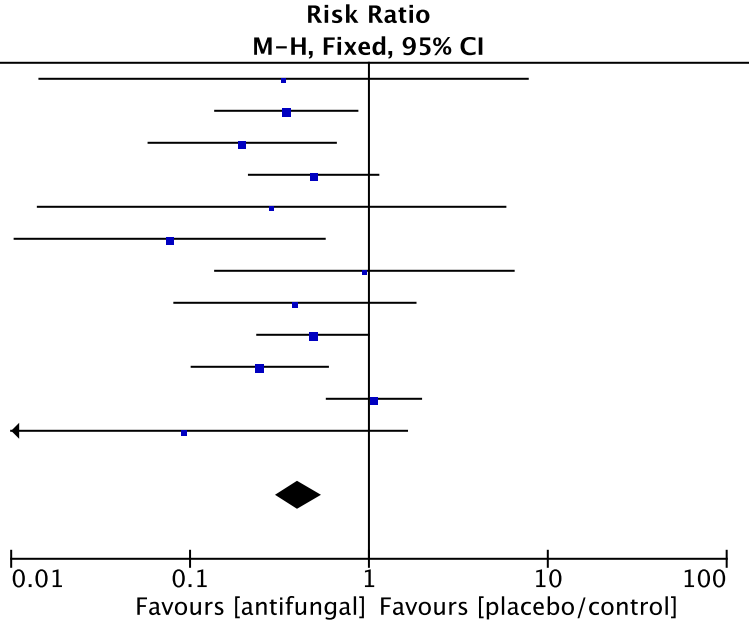
4.1.6. Prophylactic Systemic Antifungal Agents

Outcome: *Invasive fungal infections (Total)*

Study or Subgroup	Systemic antifungal Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arrieta 2010	0	20	1	20	1.2%	0.33 [0.01, 7.72]
Autmizquine 2018	6	188	16	173	13.2%	0.35 [0.14, 0.86]
Aydemir 2011a	3	93	15	91	12.0%	0.20 [0.06, 0.65]
Benjamin 2014	8	188	15	173	12.4%	0.49 [0.21, 1.13]
Cabrera 2002	0	6	1	5	1.3%	0.29 [0.01, 5.79]
Kaufman 2001	1	50	13	50	10.3%	0.08 [0.01, 0.57]
Kicklighter 2001	2	53	2	50	1.6%	0.94 [0.14, 6.44]
Kim 2010	2	28	5	27	4.0%	0.39 [0.08, 1.82]
Kirpal 2015	8	38	16	37	12.9%	0.49 [0.24, 1.00]
Manzoni 2007a	7	216	14	106	14.9%	0.25 [0.10, 0.59]
Parikh 2007	16	60	15	60	11.9%	1.07 [0.58, 1.96]
Rundjan 2020	0	47	5	48	4.3%	0.09 [0.01, 1.63]
Total (95% CI)		**987**		**840**	**100.0%**	**0.41 [0.30, 0.55]**
Total events	53		118			

Heterogeneity: $Chi^2 = 17.47$, df = 11 (P = 0.09); $I^2 = 37\%$

Test for overall effect: Z = 5.91 (P < 0.00001)

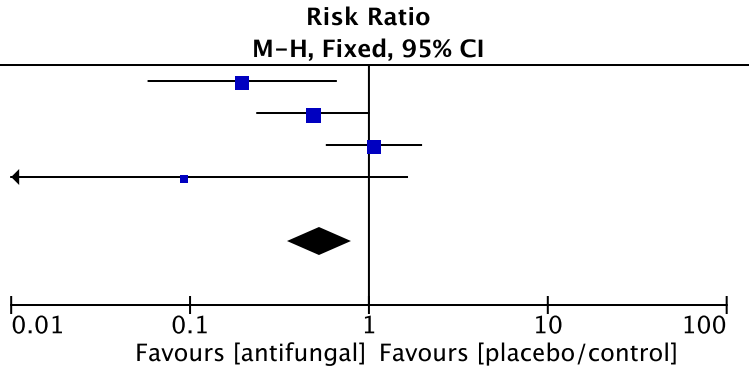


Outcome: *Invasive fungal infections (LMICs only)*

Study or Subgroup	Systemic antifungal Events	Total	Placebo/control Events	Total	Weight	Risk Ratio 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); $I^2 = 67\%$

Test for overall effect: Z = 3.03 (P = 0.002)

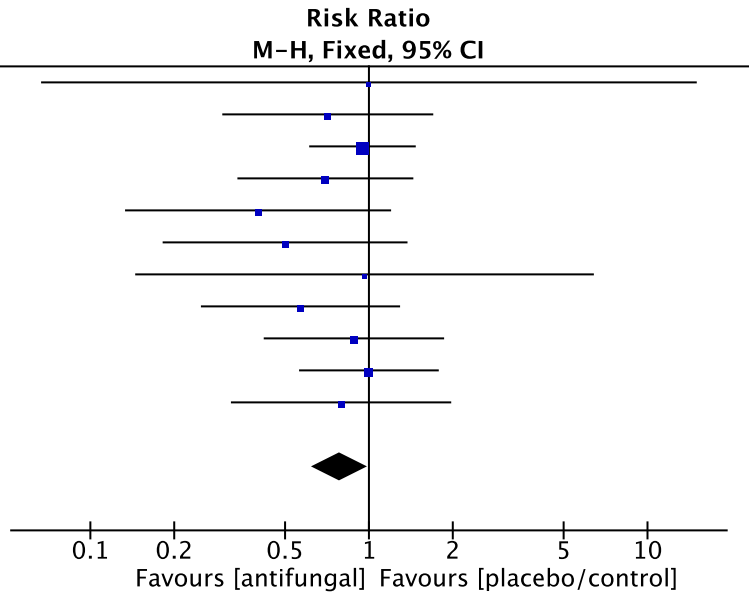


Outcome: *Neonatal mortality prior to hospital discharge (Total)*

Study or Subgroup	Systemic antifungal Events	Total	Placebo/control Events	Total	Weight	Risk Ratio 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); $I^2 = 0\%$

Test for overall effect: Z = 2.06 (P = 0.04)

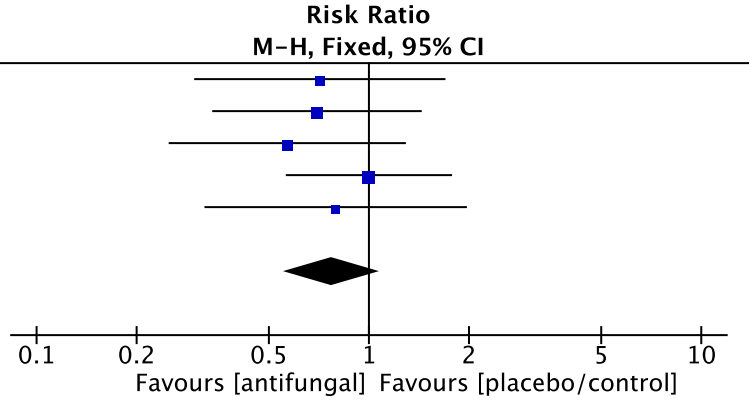


Outcome: *Neonatal mortality prior to hospital discharge (LMICs only)*

Study or Subgroup	Systemic antifungal Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% 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); $I^2 = 0\%$

Test for overall effect: Z = 1.55 (P = 0.12)



4.2 Mixed Level Forest Plots

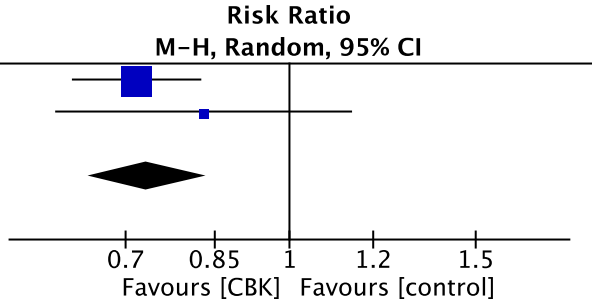
4.2.1. Clean Birth Kits

Outcome: *Neonatal mortality*

Study or Subgroup	CBK Events	CBK Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Jokhio 2005	340	9710	439	8989	84.3%	0.72 [0.62, 0.82]
Pell 2019	65	2557	82	2676	15.7%	0.83 [0.60, 1.14]
Total (95% CI)		**12267**		**11665**	**100.0%**	**0.73 [0.65, 0.83]**
Total events	405		521			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$

Test for overall effect: Z = 4.77 (P < 0.00001)

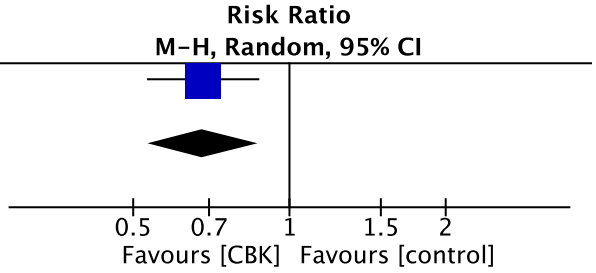


Outcome: *Any omphalitis*

Study or Subgroup	CBK Events	CBK Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Pell 2019	101	2557	155	2676	100.0%	0.68 [0.53, 0.87]
Total (95% CI)		**2557**		**2676**	**100.0%**	**0.68 [0.53, 0.87]**
Total events	101		155			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.07 (P = 0.002)



4.2.2. Chlorhexidine Cleansing

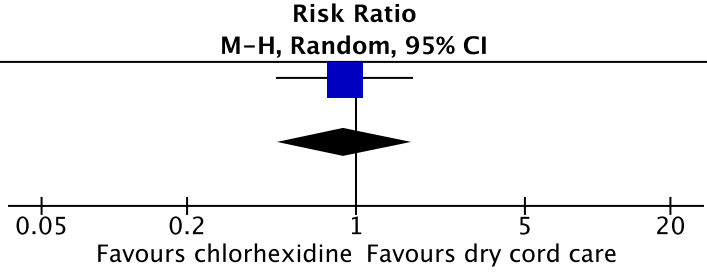
Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

Outcome: *Neonatal mortality*

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Total	Dry cord care Events	Dry cord care Total	Weight	Risk Ratio M-H, Random, 95% 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 applicable

Test for overall effect: Z = 0.33 (P = 0.74)

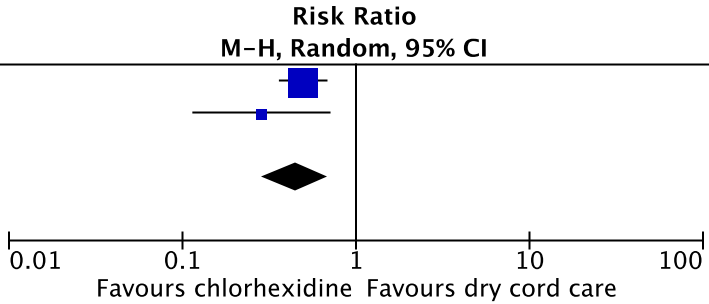


Outcome: *Omphalitis*

Study or Subgroup	Chlorhexidine Events	Total	Dry cord care Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.04$; $Chi^2 = 1.30$, df = 1 (P = 0.26); $I^2 = 23\%$

Test for overall effect: Z = 3.68 (P = 0.0002)



Outcome: *Omphalitis by cleansing frequency*

Study or Subgroup	Chlorhexidine Events	Total	Dry cord care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Multiple cleansing						
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]
Subtotal (95% CI)		**563**		**568**	**100.0%**	**0.45 [0.29, 0.69]**
Total events	57		124			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.30$, df = 1 (P = 0.26); $I^2 = 23\%$

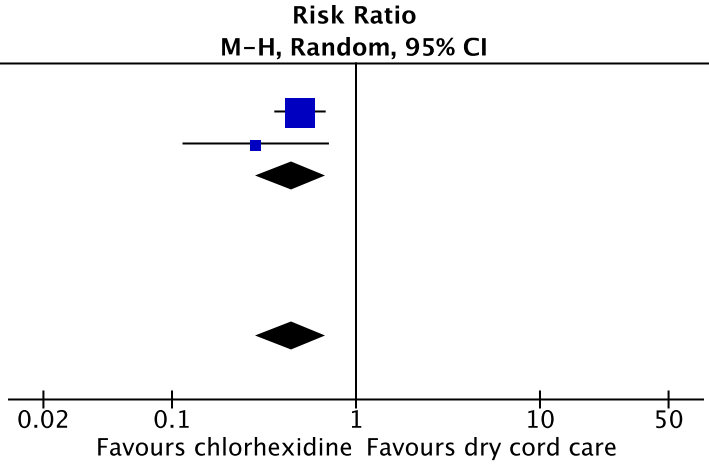
Test for overall effect: Z = 3.68 (P = 0.0002)

Total (95% CI)		**563**		**568**	**100.0%**	**0.45 [0.29, 0.69]**
Total events	57		124			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.30$, df = 1 (P = 0.26); $I^2 = 23\%$

Test for overall effect: Z = 3.68 (P = 0.0002)

Test for subgroup differences: Not applicable

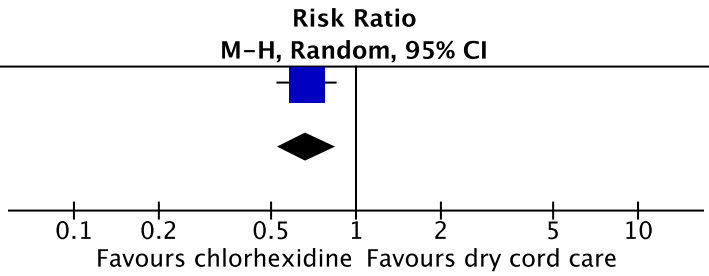


Outcome: *Bloodstream infection/sepsis*

Study or Subgroup	Chlorhexidine Events	Total	Dry cord care Events	Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 3.34 (P = 0.0009)



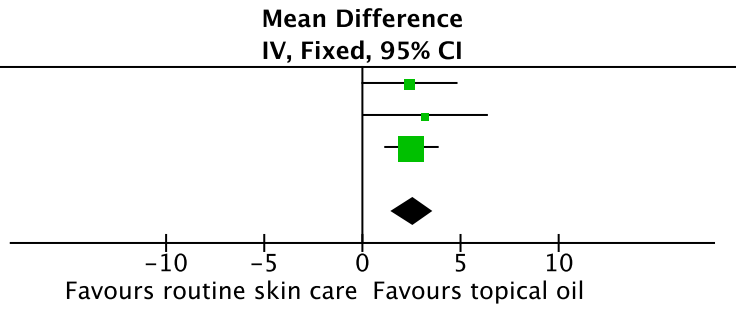
4.2.3. Topical Emollients

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
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**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]**

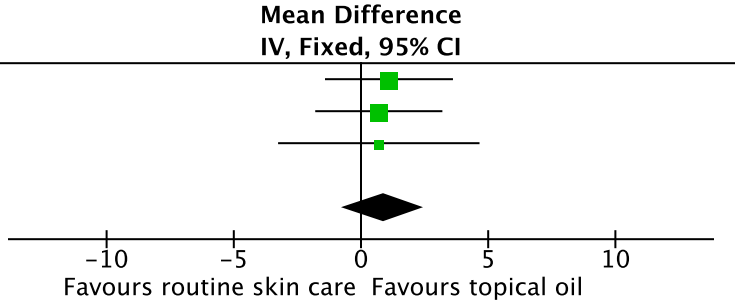
Heterogeneity: Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)



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

	Topical oil			Routine skin care				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**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]**

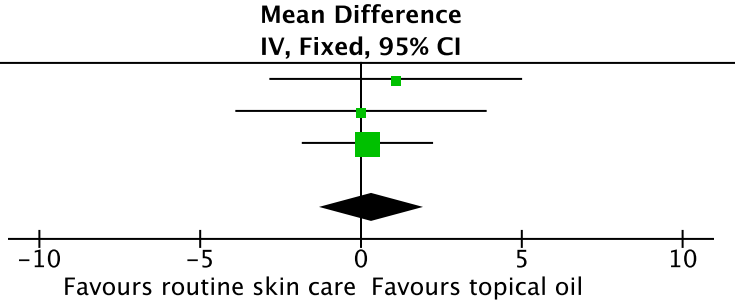
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)



Outcome: *Change in circumference (mm/week)*

	Topical oil			Routine skin care				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**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]**

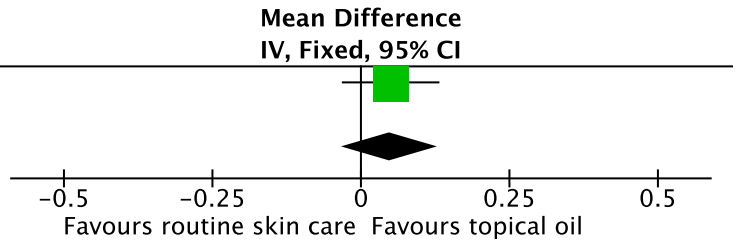
Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)



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

Study or Subgroup	Topical oil Mean	SD	Total	Routine skin care Mean	SD	Total	Weight	Mean Difference 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 applicable
Test for overall effect: Z = 1.22 (P = 0.22)

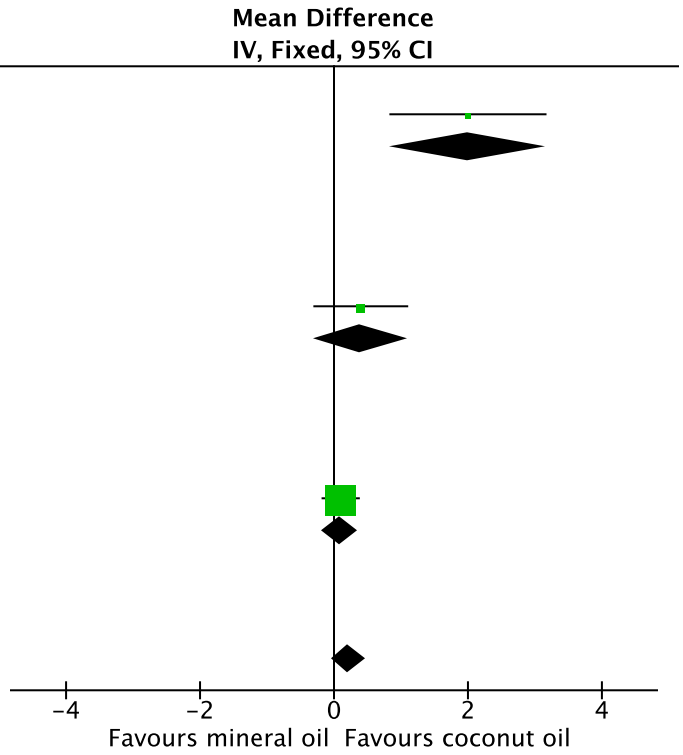


Comparison: One topical oil (or combination) versus another oil (or combination)

Outcome: *Growth*

Study or Subgroup	Coconut oil Mean	SD	Total	Mineral oil Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 Rate of weight gain (g/kg/day)								
Sankaranarayanan 2005	11	2.6	32	9	2.1	32	4.5%	2.00 [0.84, 3.16]
Subtotal (95% CI)			**32**			**32**	**4.5%**	**2.00 [0.84, 3.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.39 (P = 0.0007)								
4.1.2 Change in crown-heel length (mm/week)								
Sankaranarayanan 2005	6.3	1.2	32	5.9	1.6	32	12.6%	0.40 [-0.29, 1.09]
Subtotal (95% CI)			**32**			**32**	**12.6%**	**0.40 [-0.29, 1.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								
4.1.3 Change in head circumference (mm/week)								
Sankaranarayanan 2005	4.9	0.5	32	4.8	0.6	32	82.8%	0.10 [-0.17, 0.37]
Subtotal (95% CI)			**32**			**32**	**82.8%**	**0.10 [-0.17, 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
Total (95% CI)			**96**			**96**	**100.0%**	**0.22 [-0.02, 0.47]**

Heterogeneity: $Chi^2 = 10.09$, df = 2 (P = 0.006); $I^2 = 80\%$
Test for overall effect: Z = 1.78 (P = 0.07)
Test for subgroup differences: $Chi^2 = 10.09$, df = 2 (P = 0.006), $I^2 = 80.2\%$



4.2.4. Mixed Setting Antibiotic Delivery for PSBIs

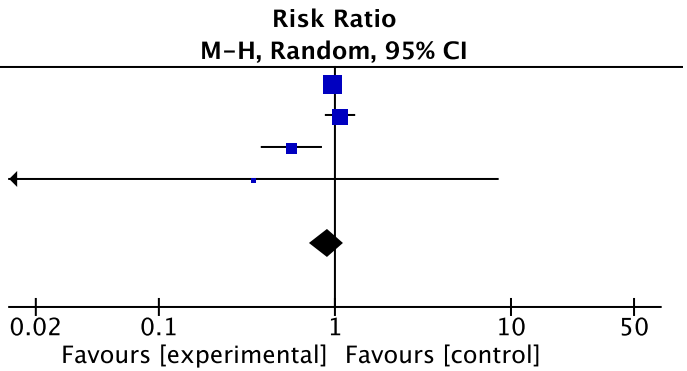
Comparison: Home-based & primary facility-based antibiotic delivery versus standard care (i.e., hospital referral)

Outcome: *All-cause neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhandari 2012	1244	29667	1326	30813	45.3%	0.97 [0.90, 1.05]
Degefie 2017	236	9744	204	9003	35.4%	1.07 [0.89, 1.29]
Gill 2011	43	1889	59	1466	18.8%	0.57 [0.38, 0.83]
Nisar 2021	0	590	1	607	0.4%	0.34 [0.01, 8.40]
Total (95% CI)		**41890**		**41889**	**100.0%**	**0.90 [0.73, 1.12]**
Total events	1523		1590			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.94$, df = 3 (P = 0.03); $I^2 = 66\%$

Test for overall effect: Z = 0.91 (P = 0.36)

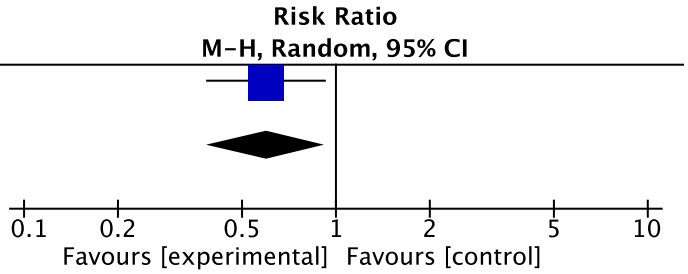


Outcome: *Early neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 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 applicable

Test for overall effect: Z = 2.33 (P = 0.02)

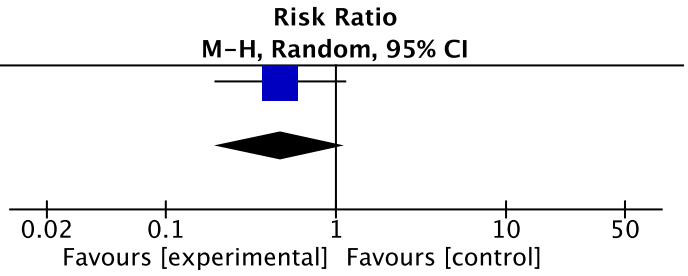


Outcome: *Late neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 1.68 (P = 0.09)

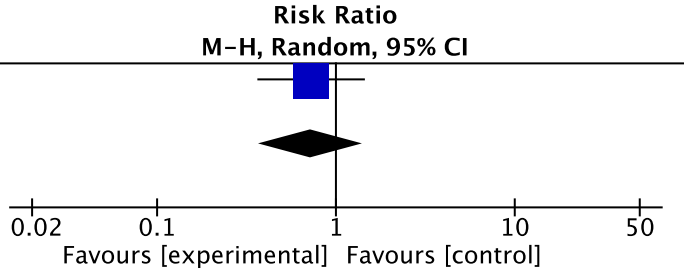


Outcome: *Sepsis-specific neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 0.92 (P = 0.36)



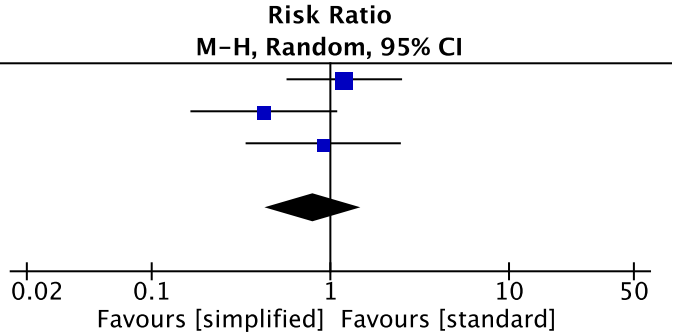
Comparison: Simplified antibiotic regimens versus standard antibiotic regimens

Outcome: *All-cause neonatal mortality*

Study or Subgroup	Simplified regimen Events	Simplified regimen Total	Standard regimen Events	Standard regimen Total	Weight	Risk Ratio 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: $Tau^2 = 0.10$; $Chi^2 = 2.99$, df = 2 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 0.67 (P = 0.50)

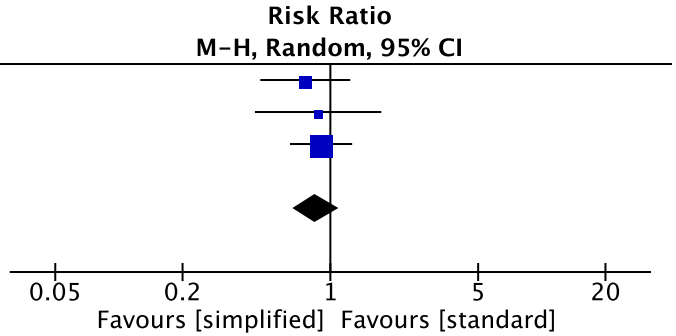


Outcome: *Treatment failure*

Study or Subgroup	Simplified regimen Events	Simplified regimen Total	Standard regimen Events	Standard regimen Total	Weight	Risk Ratio 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); $I^2 = 0\%$

Test for overall effect: Z = 1.19 (P = 0.23)

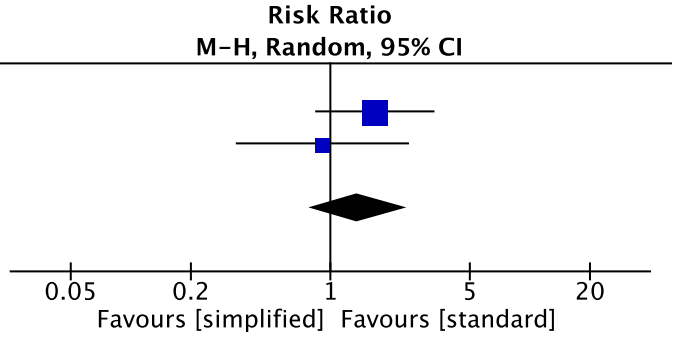


Outcome: *Adverse effects*

Study or Subgroup	Simplified regimen Events	Total	Standard regimen Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.00$; $Chi^2 = 0.98$, df = 1 (P = 0.32); $I^2 = 0\%$

Test for overall effect: Z = 1.12 (P = 0.26)



4.3 Community Level Forest Plots

4.3.1. Chlorhexidine Cleansing

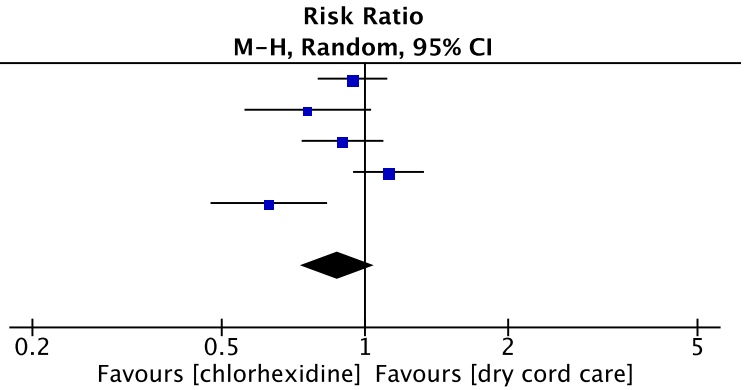
Comparison: Chlorhexidine umbilical cord cleansing versus dry cord care

Outcome: *Neonatal mortality*

Study or Subgroup	Chlorhexidine cleansing Events	Total	Dry cord care Events	Total	Weight	Risk Ratio 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: $Tau^2 = 0.03$; $Chi^2 = 14.38$, df = 4 (P = 0.006); $I^2 = 72\%$

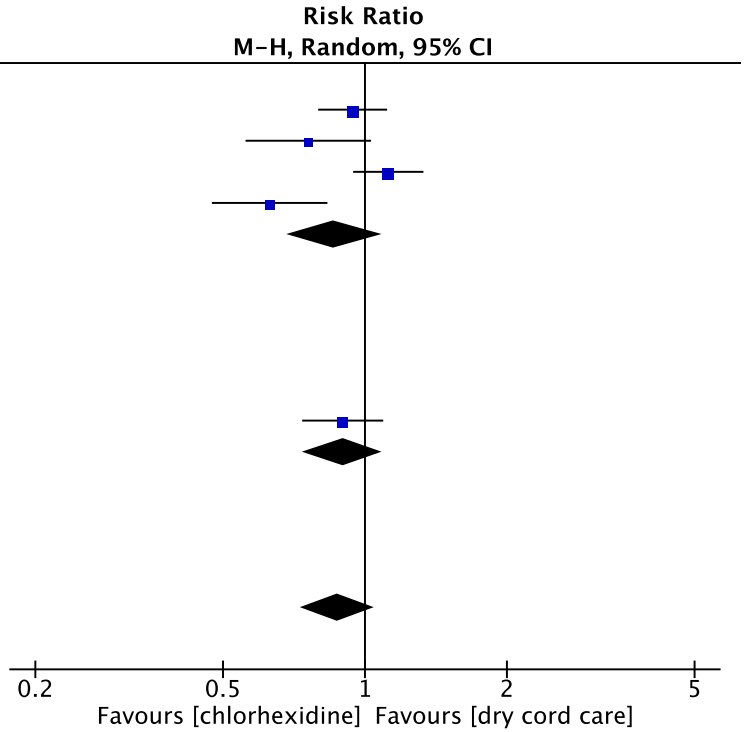
Test for overall effect: Z = 1.47 (P = 0.14)



Subgroup Analysis: Chlorhexidine alone versus chlorhexidine in clean birth kits

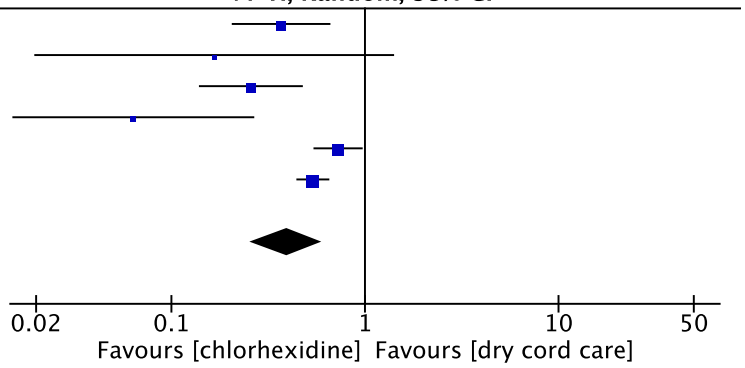
Outcome: *Neonatal mortality*

Study or Subgroup	Chlorhexidine cleansing Events	Total	Dry cord care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Chlorhexidine in 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: Tau² = 0.04; Chi² = 14.29, df = 3 (P = 0.003); I² = 79%						
Test for overall effect: Z = 1.24 (P = 0.22)						
4.2.2 Chlorhexidine alone						
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 applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)		**55254**		**56813**	**100.0%**	**0.88 [0.73, 1.05]**
Total events	897		991			
Heterogeneity: Tau² = 0.03; Chi² = 14.38, df = 4 (P = 0.006); I² = 72%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%						



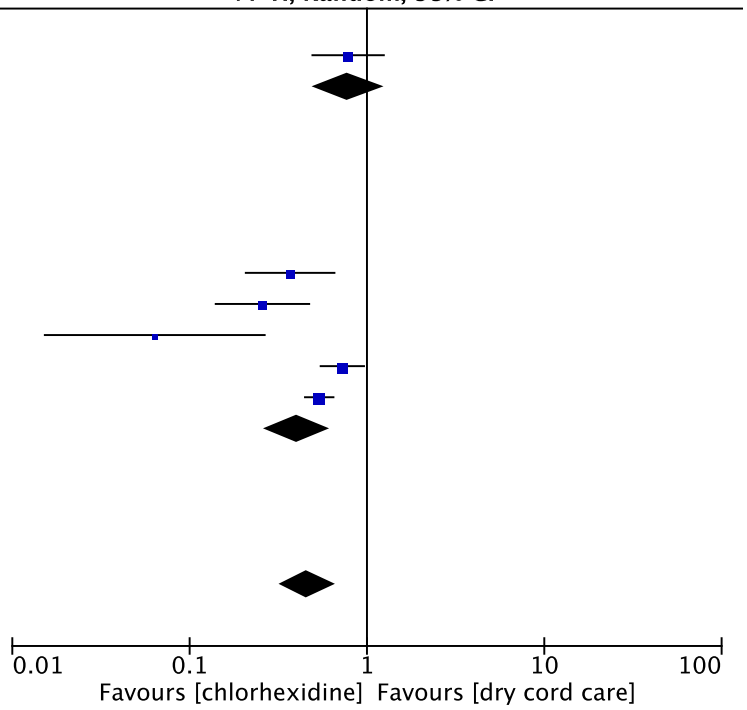
Outcome: *Omphalitis*

Study or Subgroup	Chlorhexidine cleansing Events	Total	Dry cord care Events	Total	Weight	Risk Ratio 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: Tau² = 0.16; Chi² = 21.84, df = 5 (P = 0.0006); I² = 77%						
Test for overall effect: Z = 4.32 (P < 0.0001)						

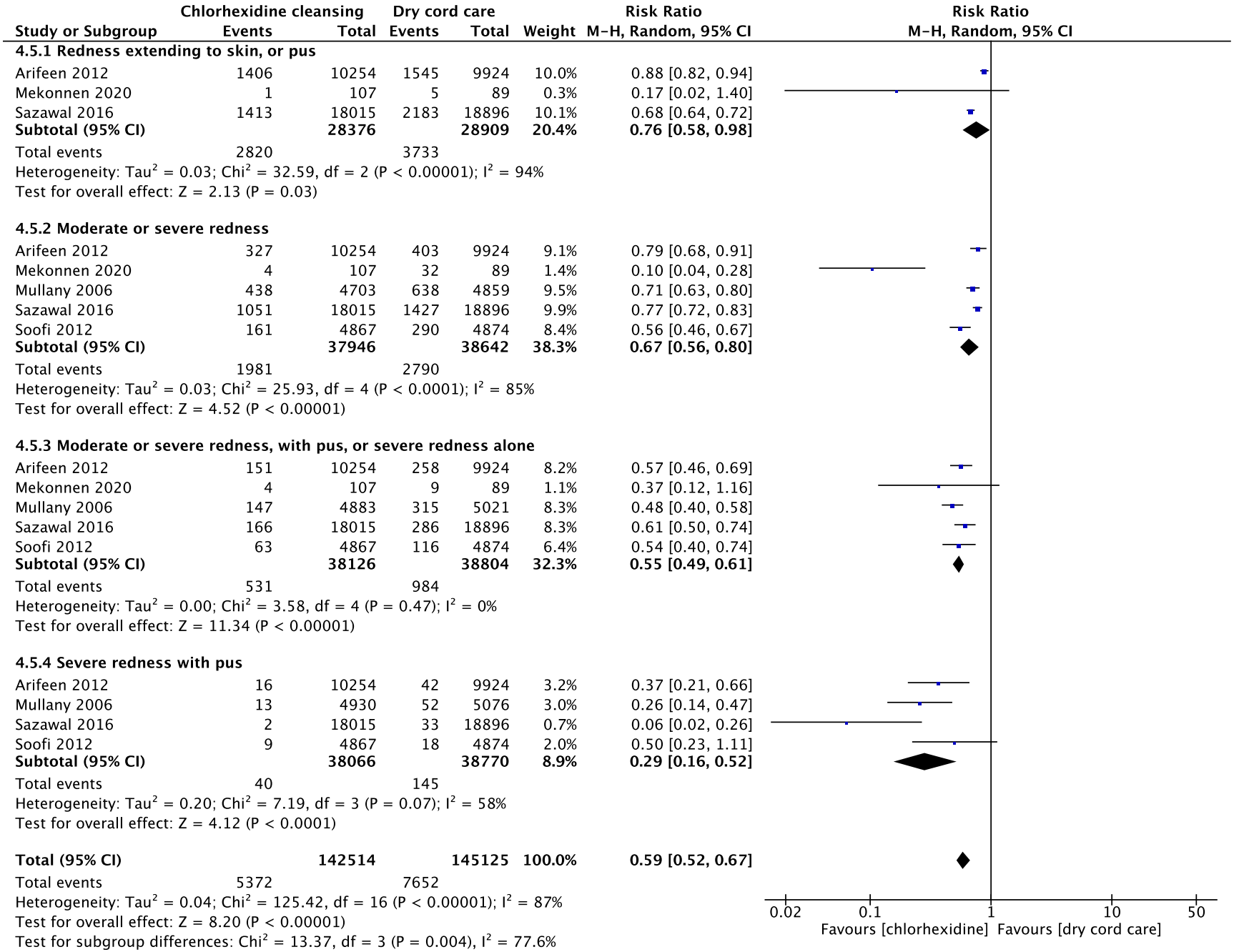


Outcome: *Omphalitis by cleansing frequency*

Study or Subgroup	Chlorhexidine cleansing Events	Total	Dry cord care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Single cleansing						
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 applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.4.2 Multiple cleansing						
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: $Tau^2 = 0.16$; $Chi^2 = 20.67$, df = 4 (P = 0.0004); $I^2 = 81\%$						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Total (95% CI)		**65930**		**68040**	**100.0%**	**0.46 [0.32, 0.67]**
Total events	310		596			
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 23.06$, df = 5 (P = 0.0003); $I^2 = 78\%$						
Test for overall effect: Z = 4.06 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 4.14$, df = 1 (P = 0.04), $I^2 = 75.9\%$						



Outcome: *Omphalitis by severity*



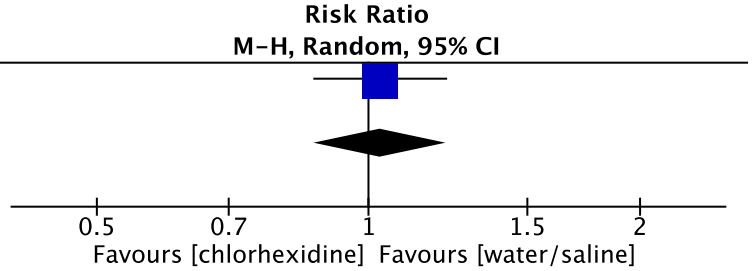
Comparison: Chlorhexidine whole-body cleansing versus water/saline

Outcome: *Neonatal mortality*

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Total	Water/Saline Events	Water/Saline Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 0.35 (P = 0.73)



4.3.2. Topical Emollients

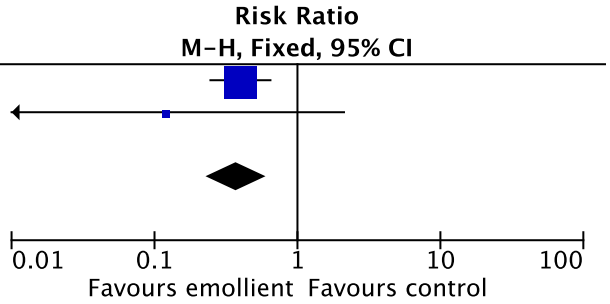
Comparison: Topical emollient versus routine skin care in term neonates

Outcome: *Atopic dermatitis*

Study or Subgroup	Topical emollient Events	Topical emollient Total	Control Events	Control Total	Weight	Risk Ratio 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: $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0\%$

Test for overall effect: Z = 4.05 (P < 0.0001)



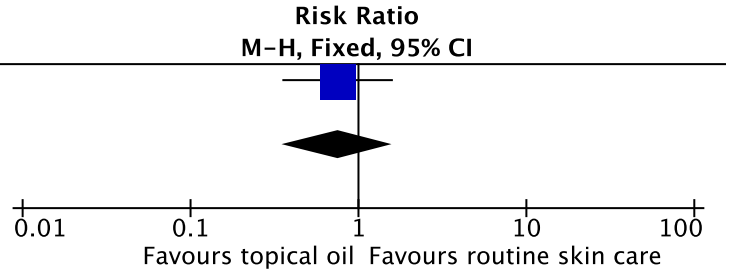
Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: *Invasive infection (any organism)*

Study or Subgroup	Topical oil Events	Topical oil Total	Routine skin care Events	Routine skin care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 applicable

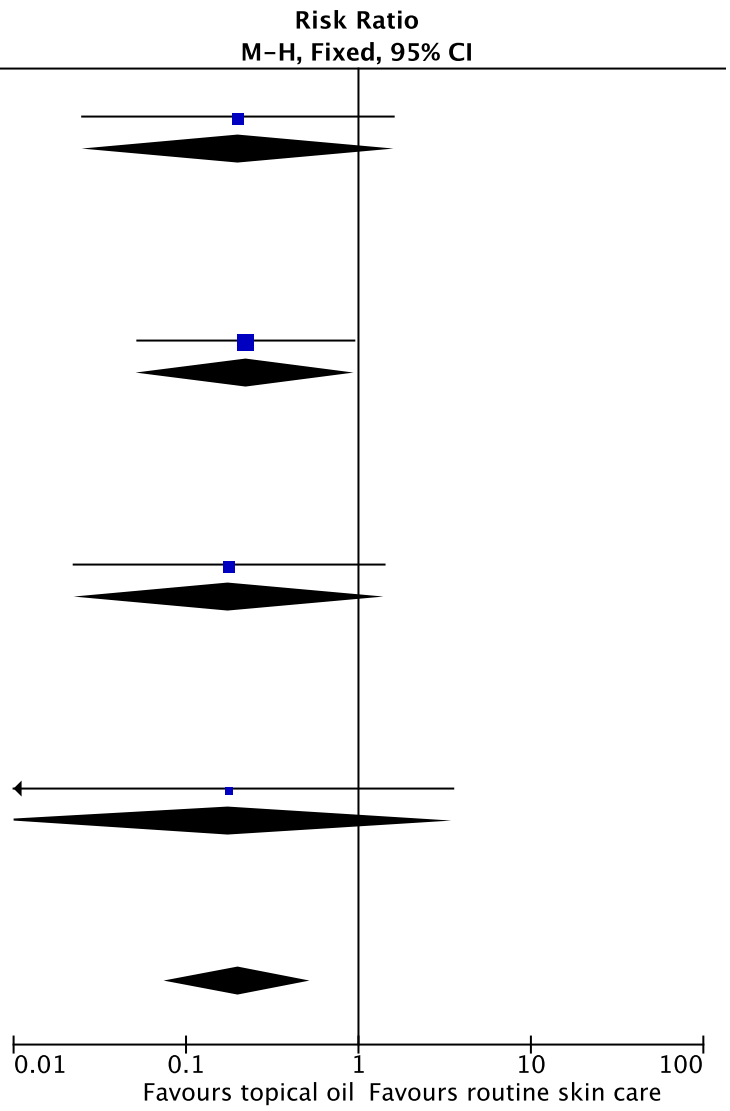
Test for overall effect: Z = 0.75 (P = 0.45)



Comparison: Topical oil versus routine skin care in preterm neonates

Outcome: *Severe neurodevelopmental disability*

Study or Subgroup	Topical oil Events	Total	Routine skin care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.7.1 BSID (3rd Ed): Cognitive <70						
Konar 2019	1	27	5	27	23.4%	0.20 [0.02, 1.60]
Subtotal (95% CI)		**27**		**27**	**23.4%**	**0.20 [0.02, 1.60]**
Total events	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
5.7.2 BSID (3rd Ed): Language <70						
Konar 2019	2	27	8	24	39.6%	0.22 [0.05, 0.95]
Subtotal (95% CI)		**27**		**24**	**39.6%**	**0.22 [0.05, 0.95]**
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
5.7.3 BSID (3rd Ed): Motor <70						
Konar 2019	1	27	5	24	24.7%	0.18 [0.02, 1.42]
Subtotal (95% CI)		**27**		**24**	**24.7%**	**0.18 [0.02, 1.42]**
Total events	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
5.7.4 BSID (3rd Ed): Social-emotional <70						
Konar 2019	0	27	2	24	12.3%	0.18 [0.01, 3.54]
Subtotal (95% CI)		**27**		**24**	**12.3%**	**0.18 [0.01, 3.54]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**108**		**99**	**100.0%**	**0.20 [0.08, 0.53]**
Total events	4		20			
Heterogeneity: Chi^2 = 0.04, df = 3 (P = 1.00); I^2 = 0%						
Test for overall effect: Z = 3.22 (P = 0.001)						
Test for subgroup differences: Chi^2 = 0.04, df = 3 (P = 1.00), I^2 = 0%						



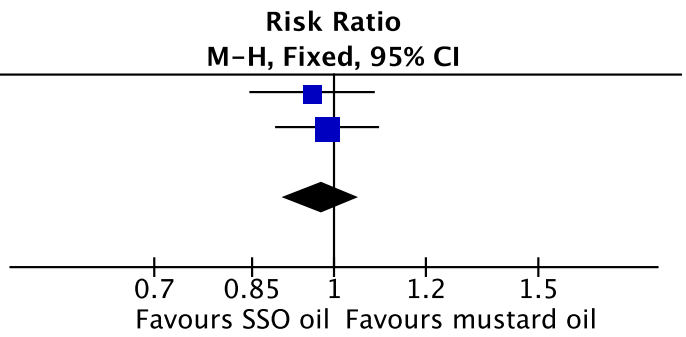
Comparison: Sunflower seed oil versus mustard oil in mixed term and preterm newborns

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

	Sunflower seed oil		Mustard oil			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**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: $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 0.65 (P = 0.51)



Footnotes

(1) Intention-to-treat analysis

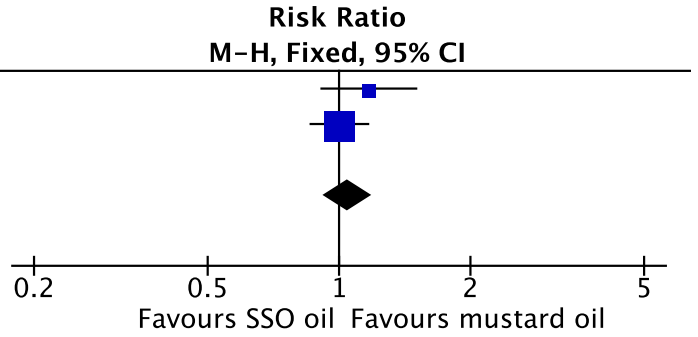
(2) Intention-to-treat analysis

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

	Sunflower seed oil		Mustard oil			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**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 = 0.30); $I^2 = 8\%$

Test for overall effect: Z = 0.67 (P = 0.50)



Footnotes

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

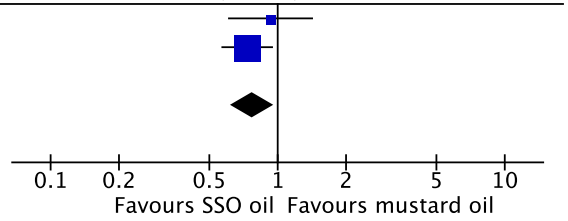
(2) newborns ≤2500 grams; intention-to-treat analysis

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

Study or Subgroup	Sunflower seed oil Events	Total	Mustard oil Events	Total	Weight	Risk Ratio 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 (P = 0.34); $I^2 = 0\%$

Test for overall effect: Z = 2.32 (P = 0.02)



Footnotes

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

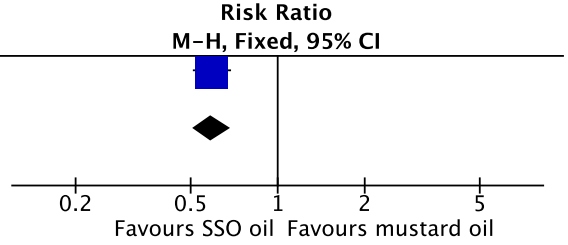
(2) newborns ≤1500 grams; intention-to-treat analysis

Outcome: *All-cause neonatal mortality (per protocol)*

Study or Subgroup	Sunflower seed oil Events	Total	Mustard oil Events	Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 7.09 (P < 0.00001)



Footnotes

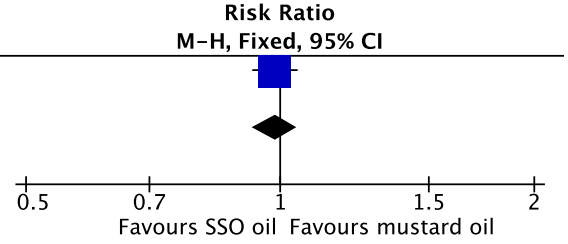
(1) Per protocol analysis

Outcome: *Possible serious bacterial infections*

Study or Subgroup	Sunflower seed oil Events	Total	Mustard oil Events	Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 0.47 (P = 0.64)



Footnotes

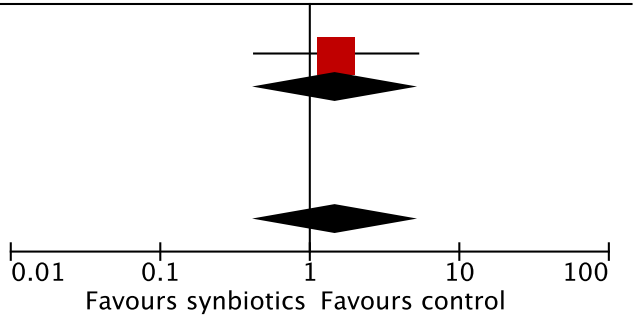
(1) Intention-to-treat analysis

4.3.3. Synbiotics Supplementation

Comparison: Synbiotics versus control in term newborns

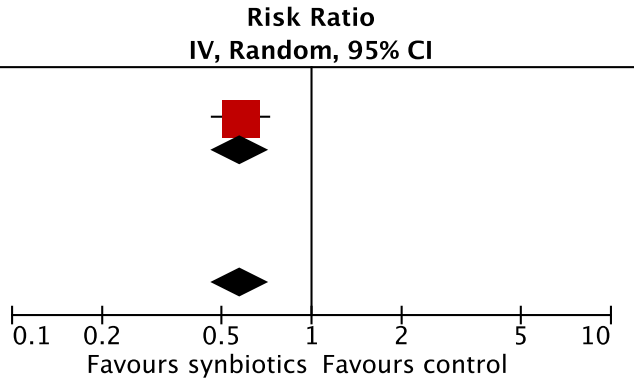
Outcome: *All-cause neonatal mortality*

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
10.1.2 Conducted at community-level				
Panigrahi 2016	0.4055	0.6448	100.0%	1.50 [0.42, 5.31]
Subtotal (95% CI)			**100.0%**	**1.50 [0.42, 5.31]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				
Total (95% CI)			**100.0%**	**1.50 [0.42, 5.31]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				
Test for subgroup differences: Not applicable				



Outcome: *Invasive infection*

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
10.2.2 Conducted at community level				
Panigrahi 2016	-0.5461	0.1123	100.0%	0.58 [0.46, 0.72]
Subtotal (95% CI)			**100.0%**	**0.58 [0.46, 0.72]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.86 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.58 [0.46, 0.72]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.86 (P < 0.00001)				
Test for subgroup differences: Not applicable				



4.3.4. Community-Based Antibiotic Delivery for PSBIs

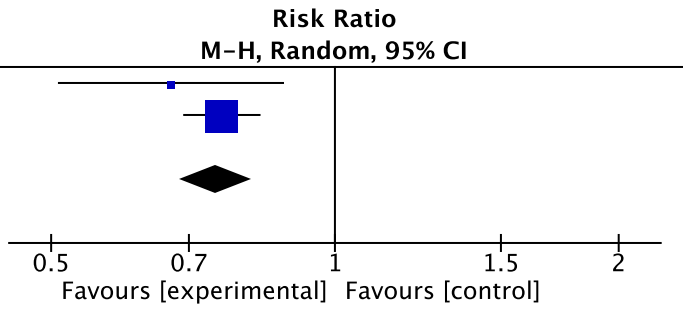
Comparison: Community-based antibiotic delivery versus standard care (i.e., hospital referral)

Outcome: *All-cause neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Baqui 2008	82	2812	125	2872	10.2%	0.67 [0.51, 0.88]
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: $Tau^2 = 0.00$; $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0\%$

Test for overall effect: Z = 6.49 (P < 0.00001)

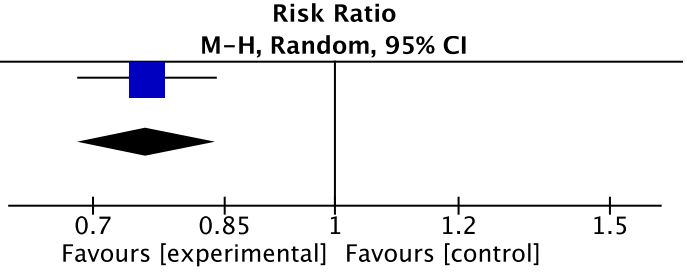


Outcome: *Early neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 5.35 (P < 0.00001)

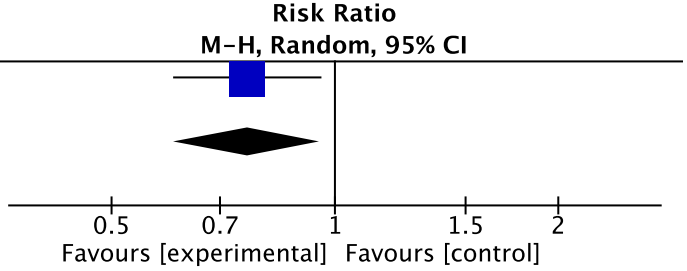


Outcome: *Late neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 2.35 (P = 0.02)

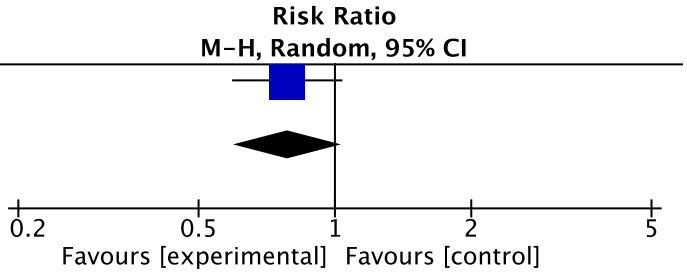


Outcome: *Sepsis-specific neonatal mortality*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio 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 applicable

Test for overall effect: Z = 1.73 (P = 0.08)



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 participants)**	**Effect estimate (95% CI)**	**Heterogeneity (I^2)**
Prophylactic systemic antifungals vs. control or placebo	Very preterm or VLBW neonates	Invasive fungal infection	Total*	12 (1,827)	**RR 0.41** (0.30, 0.55)	37%
Prophylactic systemic antifungals vs. control or placebo	Very preterm or VLBW neonates	Invasive fungal infection	Studies conducted in LMICs only	4 (474)	**RR 0.53** (0.35, 0.80)	67%

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

VLW, very low birth weight; bolded effect estimates are statistically significant (p<0.05)
**Leveraged HIC data to produce an HIC and LMIC combined estimate.*

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.

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