THE RELATIONSHIP BETWEEN GRAM-NEGATIVE COLONISATION AND BLOODSTREAM INFECTIONS IN NEONATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Intended category: Systematic Review

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Running title: Gram-negative bloodstream infections in colonised babies

Keywords: infant, newborn; Gram-Negative Bacteria; carrier state; bacteraemia; neonatal screening

Abstract: 321 words

Manuscript: 3,327 words

ABSTRACT

Objectives: Neonates admitted to Neonatal Intensive Care Units (NICU) are at significant risk of developing bloodstream infections (BSIs). Gram-negative bacteria (GNB) both colonise and infect, but the association between these entities is unclear. By conducting a systematic literature review, we aimed to explore the impact of factors on the association between GN colonisation and GN-BSI at both baby level and unit level.

Methods: We searched Medline, Embase, and Cochrane Library. Observational cohort studies published after 2000 up to June 2016 reporting data on the total number of neonates (0-28 days) colonised with GNB assessed by rectal/skin swab culture and the total number of neonates with GN-BSI (same bacteria) were included. Studies were excluded if data on skin/rectal colonisation, neonates, and GNB could not been identified separately. The meta-analyses along with multivariate meta-regression with random-effect model were performed to investigate factors associated with the GN colonisation and GN-BSI at baby-level and unit-level.

Results: 27 studies fulfilled our inclusion criteria, 15 for the baby-level and 12 for the unit-level analysis. Study heterogeneity was high, with suboptimal overall quality of reporting assessed by the STROBE-NI statement (44.8% of items adequately reported). In 1,984 colonised neonates, 157 (7.9%) developed GN-BSI compared with 85 of 3,583 (2.4%) non-colonised neonates. Considerable heterogeneity across studies was observed. Four factors were included in the meta-regression model: Gross domestic product (GDP), pathogen, outbreak, and frequency of screening. There was no statistically significant impact of these factors on GN colonisation and GN-BSI in baby level. We were unable to perform the multivariate meta-regression due to the insufficient reported data for unit level.

Conclusions: Study limitations include the small number and the high heterogeneity of the included studies. While this report shows a correlation between colonisation and BSI risk, this data currently doesn't support routinely screening for GNB. The analysis of large cohorts of colonised neonates with

clinical outcomes is still needed to define the major determinants leading from colonisation to infection.

INTRODUCTION

Babies admitted to Neonatal Intensive Care Unit (NICU) are at high risk of developing bloodstream infections (BSIs) and have been identified as a critical population for the acquisition and transmission of multidrug-resistant (MDR) pathogens.[1] Among them, Gram-negative bacteria (GNB) are of highest concern in the neonatal population, with a global increase in the incidence rate and very limited therapeutic options.[2] MDR-GNB have been found to be responsible for an increasing number of NICU outbreaks, with many implications for infection control policies and practices, and mortality rates reported around 30%.[3]

GNB can cause both colonisation and infections. In a colonised patient, the organism is found on the body but is not causing any symptoms or disease. At birth, healthy neonates have no endogenous microflora which is rapidly acquired through perinatal transfer of maternal vaginal and gastrointestinal flora (vertical transmission) and from environmental or human sources (horizontal transmission).[4] However, sick neonates who require prolonged hospitalisation are at high risk of colonisation with resistant or difficult-to-treat bacteria as a result of intense and long-term exposure to antibiotics and the hospital environment.[5, 6] Some studies have shown a positive association between gut overgrowth and neonatal sepsis.[7, 8] Studies conducted during hospital outbreaks are broadly consistent in showing a relationship between the microorganisms causing colonisation and those isolated from the blood cultures of septic neonates admitted to the same unit.[9] However, the mechanisms leading from colonisation to infection are still debated.

Screening for colonisation is usually discussed in the context of intensive care to prevent cross-infections and inform strategies, such as patient cohorting.[10] However, role of active surveillance for GNB in informing antimicrobial empirical treatment has not yet been fully explored and evaluated in neonates. Clarifying the link between GNB colonisation and infection might have a significant impact on the clinical management for hospitalised babies. If a link is demonstrated, carriage screening could potentially be used to stratify patients to different antibiotic regimens and, at the same time, to select

baseline treatment options at unit-level and potentially conserve broad spectrum antibiotics. By conducting a systematic literature review, we aimed to explore the impact of factors on the association between GN colonisation and GN-BSI at both baby level and unit level.

METHODS

A review protocol is available upon request. Studies were considered eligible for inclusion if reporting data on neonates aged 0-28 days (**P**opulation), rectal swab/stool culture or skin swab culture to assess GN colonisation (**I**ntervention), comparing the prevalence of GN-BSI among colonised and non-colonised neonates (**C**omparison), considering GN-BSI as clinical outcome (**O**utcome), in neonates admitted to NICU (**S**etting). The search was limited to studies published after 2000. Given the advances in modern neonatology, the aim was to capture publications that reflect policies and practices over the last 15 years. No language restriction was applied.

Medline (Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2016), Embase (Embase 1996 to 2016 Week 24), and Cochrane Library (Issue 6 of 12, June 2016) databases were systematically searched on June 15, 2016 with a strategy combining MeSH and free text terms for “neonate” AND “colonisation” AND “bloodstream infection”. The full strategy is available as Supplementary Material.

Two assessments for included studies were performed. In the first one (baby-level) inclusion criteria for studies were their reporting of: 1) data on neonates aged 0-28 days, 2) the total number of babies colonised with GNs assessed by rectal swab/stool culture or skin swab culture, and 3) the total number of GN-colonised babies who developed a concordant (caused by the same pathogen) GN-BSI. In the second assessment (unit-level), inclusion criteria were studies reporting: 1) data on neonates aged 0-28 days, 2) the total number of babies colonised with GNs assessed by rectal swab/stool culture or skin swab culture during the study period, and 3) the total number of babies with GN-BSI in the same unit during the same timeframe were considered eligible for inclusion. Studies were excluded if

reporting data on multiple colonisation sites but rectal and/or skin colonisation data could not be identified; studies also including children and/or adults where neonatal data could not be clearly extracted; and studies reporting data on both Gram positives and GNs if GN data could not be identified separately.

The primary outcome was to investigate the variables with an impact on the association between GN colonisation and GN-BSI at both baby-level and unit-level.

Data on study characteristics, demographic and clinical features of included neonates, inclusion and exclusion criteria, outcome definitions, microbiological methods, and total numbers of colonised/infected babies was independently extracted by two different authors (LF and CT), according to pre-specified criteria. In case of disagreements, these were resolved in discussion with a third author (JB).

This study did not receive any direct funding.

Quality assessment

To assess the quality of the included studies, the Newcastle-Ottawa scale was used (Table S1).[11] Moreover, to assess the quality of reporting of the included studies, the recently published *Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection* (STROBE-NI) statement was used.[12] This checklist is an extension of the STROBE statement aiming to improve scientific reporting of neonatal infection studies, with the ultimate goal to increase data utility and allow meta-analytical approaches. The proportion of STROBE-NI items adequately reported was calculated for each study. This review complies with the PRISMA guideline.[13]

Statistical analysis

The proportion of concordant GN-BSI in colonised babies was calculated as number of infections/colonised babies. Colonisation pressure was calculated as number of colonised babies/total

NICU admissions in the study period. The proportions of colonisation and infections were calculated using the crude data collected as the number of colonised or infected babies/total number of neonates admitted during the study period. The two-tailed Mann-Whitney U test for two independent samples was used to compare the STROBE-NI score between studies primarily designed for clinical and those mainly for microbiological purpose. A p-value of less than 0.05 was considered statistically significant.

We performed a sub-group meta-analysis along with multivariate meta-regression.[14, 15] Study characteristics extracted for sub-group and meta-regression were: 1) gross domestic product (GDP) (upper-middle-income countries (UMIC), lower-middle-income countries (LMIC), high-income countries (HIC)); 2) pathogen (*Klebsiella* spp. *vs* other Gram-negative pathogens); 3) screening timing (once *vs* twice a week); 4) outbreak (study carried out during outbreak *vs* not during outbreak). We carried out baby-level and unit-level meta-analyses separately. For baby-level, the meta-analysis was conducted to produce estimated risk ratio (RR) as the measure of group difference (colonisation *vs* non-colonisation) on the rate of infection. Due to the insufficient data reported for unit-level, we used the Freeman-Tukey double arcsine transformation (arcsine square root transformation [16]) to calculate the weighted proportion of overall infection rate. We performed the DerSimonian and Laird random-model effect using inverse variance weight method, which takes into account the within study variation and between study heterogeneity. The I^2 statistic was used to describe the variation across studies due to heterogeneity. We defined the level of heterogeneity as low, moderate, and high correspond to I^2 values of 25%, 50%, and 75%.[14] As the small number of included studies, we were unable to carry out publication bias in this present study.[14] The meta-analysis and meta-regression were carried out using STATA version 14.0 (StataCorp).

RESULTS

Study selection and description

The search identified 8,543 studies. Among them, 25 papers and 2 conference abstracts fulfilled our inclusion criteria and were included in the final analysis. 5,254 studies were excluded based on the title, 1,338 were rejected on abstract, and 211 were rejected on full text (**Figure 1**). 15 studies were selected for the baby-level[4, 6, 8, 17-28] and 12 for the unit-level analysis.[9, 29-39] 18 out of 27 studies were carried out in high-income countries (HIC),[4, 6, 8, 18, 20, 22-24, 26-28, 30-32, 34-37] 5 in upper middle-income countries (UMIC),[17, 19, 21, 25, 29] and 2 in lower middle-income countries (LMIC)[9, 33], according to the 2016 World Bank Classification (**Table 1S**).[40] 20 were carried out as prospective[4, 6, 8, 9, 18, 20-22, 25-33, 35, 36, 38] and 5 as retrospective studies.[17, 19, 23, 34, 37] Two papers did not provide their study design.[24, 39] 8 studies were carried out during hospital outbreaks.[21, 24, 28-31, 37, 38]

Apart from one study,[23] all papers assessed colonisation through rectal swab or stool culture (**Table 2S**). 24 (88.9%) out of 27 studies provided information about timing and frequency of microbiological screening.[4, 6, 8, 9, 17-36] In nearly half of the studies, rectal/skin swabs were performed weekly through the baby's NICU stay[4, 6, 17, 19, 20, 24-30, 32, 33] whereas in 6 studies neonates were screened twice a week.[8, 21, 22, 31, 35, 36]

To evaluate the concordance between colonising and bloodstream isolates, 15 (55.6%) out of 27 studies performed genotyping analyses.[4, 9, 20-22, 24, 25, 28-32, 35, 37, 39] Twelve studies genotyped the isolates by pulsed field gel electrophoresis (PFGE)[4, 9, 20, 25, 28-32, 35, 37, 39] whereas 3 studies performed Polymerase Chain Reaction (PCR).[21, 22, 24] Only one study assessed the genotype by sequencing the pathogens.[39]

Only one study assessed the cost-effectiveness of the intervention.[30]

Quality assessment of included studies

A huge variation was highlighted in terms of study design (prospective *vs* retrospective, inclusion criteria, different outcomes assessed), included population (gestational age, birth weight, sample size), and investigated pathogens (different strains, different resistance pattern). Overall, according to the STROBE-NI checklist,[12] the included studies reported adequately a mean of 44.8% (range 8.6-67%) of the suggested items. A statistically significant difference was highlighted in terms of compliance with the checklist between studies primarily designed for clinical and those mainly for microbiological purposes (47.2% *vs* 32.4%, p=0.034). As summary considerations on study quality in general, according to the Newcastle-Ottawa scale, all studies assessed the exposure and the outcome by using secure records, and all of them selected the non-exposed cohort from the same community as the exposed cohort. However, very few studies demonstrated that the outcome of interest was not present at the start of the study and none of them reported a statement about proportion of patients who completed the follow-up (Table 1S).

Baby-level analysis

15 studies were included in the baby-level analysis,[4, 6, 8, 17-28] 3 (20.0%; 3/15) of which were carried out during NICU outbreaks.[21, 24, 28] 7 (46.7%; 7/15) studies provided information about demographic characteristics of the included cohort (e.g. age at screening, birth weight or gestational age) (**Table 3S**).[4, 6, 8, 19, 22, 25, 26] The length of follow-up was reported in 6 studies.[6, 22, 24-26, 28] Five studies reported the interval between colonization and onset of concordant BSI.[8, 13, 16, 21-22]

Overall, a total of 8,421 neonates were screened for rectal and/or skin colonisation. Among them, 1,984 (23.6%) were found to be colonised by GNB. In total, 157 colonised babies experienced a BSI concordant with the colonising pathogen (7.9%). A broad variation was found among the included studies in terms of prevalence of concordant GN-BSIs in colonised babies (range 0.0 – 42.8%). In those studies that also reported the number of non-colonized babies who developed a GN-BSI, the proportion of neonates who experienced a GN-BSI was 2.4% (85/3,583).

Only one study reported the relatedness between the genotype of colonising and invasive pairs of isolates.[20] In this study, 17 out of 19 strains (89.0%) had an indistinguishable PFGE pattern.

Meta-analysis

All sub-group meta-analyses results are shown in **Figure 2**. The random-effects inverse variance meta-analysis for all sub-groups demonstrated strong evidence of heterogeneity within sub-groups, and heterogeneity between sub-groups. The overall estimated RRs in within sub-groups analyses did not show any differences for GDP, pathogen, and outbreak. However, when conducting separate meta-analysis for screening frequency , RR of GN-BSI in babies screened twice/week compared with once a week was 1.24 (95CI: 1.12-1.37) in the non-colonisation group and 0.95 (95%CI: 0.94-0.97) in the colonisation group. *I*-squared (I^2) estimates of 75.5% (screening twice) and 64.2% (screening once) showed a different heterogeneity to the overall meta-analysis. To further explore heterogeneity between studies, we performed multivariate meta-regression analysis **(Table 1)**. All included variables in the meta-regression analysis did not show statistically significant impact on GN colonisation and GN-BSI in the baby-level.

Unit-level analysis

12 studies were included for the analysis at the unit-level,[9, 29-39] 5 (41.6%) of which were carried out during outbreaks in the neonatal units.[29-31, 37, 38]

A total of 6,363 babies were included. Among them, 1,825 neonates (28.7%) had a rectal/skin swab positive for GNB (**Table 2**). The colonisation pressure varied widely among the selected studies, ranging from 1.0%[34] to 81.8%.[9] Overall, the prevalence of GN-BSIs among neonates admitted to the NICUs during the same timeframe was 8.1% (516 BSI episodes/6,363 admitted babies). The rate of BSIs among the different studies ranged from 0.0 to 19.8%.

In those studies evaluating the molecular epidemiology among colonising and invasive strains, PFGE analysis proved to be a very useful tool to investigate the spread and clonality of isolated pathogens, especially in the context of NICU outbreaks.[9, 29-32, 35, 37, 39]

Meta-analysis

The sub-group meta-analyses results for unit-level are shown in **Figure 1S**. Results for all within sub-group analyses have shown considerable high heterogeneity. This may be due to the insufficient reported data in the included studies. In addition, we were unable to perform the multivariable meta-regression model from the available unit-level data.

DISCUSSION

This systematic review included 27 studies, 15 were included in the baby-level and 12 in the unit-level analysis. The quality of reporting assessed by the STROBE-NI statement's checklist was suboptimal in the great majority of the published studies, with a significant difference between those primarily targeting clinical research questions and those focusing on microbiological research questions. Eight studies were carried out during NICU outbreaks. A total of 14,784 babies were screened for gut or skin colonisation. Among babies that were colonised, 7.9% developed a concordant BSI. The overall estimated RRs within sub-groups were similar for GDP, pathogen, and outbreak. In addition, the within-group I^2 estimates for these factors were similar. However, the RRs of GN-BSI comparing twice weekly with weekly screening were 1.24 in the non-colonisation group and 0.95 in the colonisation group with different I^2 estimates. To explore this further, meta-regression analyses were carried out. None of these factors were statistically significant associated with GN colonisation and GN-BSI at the baby-level. Only one study analysed the genotypic relatedness of colonising and invasive pairs of isolates. Due to the insufficient reported data for unit-level, we were not able to further explore the association of these factors and the outcome of interest in present study.

Many studies over the last decade have tried to assess the association between gastrointestinal (GI) bacterial flora and the onset of invasive infection in neonates. Direct translocation of bacteria from the GI tract to the bloodstream through immature or damaged bowel wall (such as in case of necrotizing enterocolitis) and indirect transfer via other pathways due to immaturity of defence mechanisms are some of the hypotheses that have been suggested.[7] Many factors associated with the NICU stay, both environment- and patient-related, have been shown to influence the status of the neonatal microbiome, therefore predisposing high-risk babies to nosocomial infections.[5]

Treatment with broad-spectrum antibiotics, frequently experienced by hospitalised neonates,[41] leads to gut colonisation with multidrug-resistant Gram-negative bacteria (MDRGN) by selecting resistant flora.[42] The GI tract provides an important reservoir for antibiotic-resistant GNB that can then persist throughout the NICU stay and can be easily transmitted between patients.[43]

The individual-level association between colonisation and BSI we observed may actually explain their ecological association at unit-level. For the unit-level analysis, we were unable to determine whether colonisation preceded infection in affected babies. However, there may be an additional impact of cross-infections with rapid transition from colonisation to invasive infection in the face of high colonisation pressure. Recently, colonisation pressure has been identified as an independent risk factor for ICU-acquired MDR-infections in adults.[44]

Conversely, the role of carriage screening to adjust empirical regimens in colonised patients in the non-epidemic setting has not been properly explored yet. Screening may have a particularly important role in NICUs, to closely monitor high-risk neonates, to inform empirical treatment when resistance patterns are identified, and to set up preventive interventions, such as decolonisation and decontamination, to reduce the risk of invasive infections.[45] Such potential interventions have to be interpreted in the light of a recent review of the interventions to control neonatal healthcare-associated infection outbreaks, which showed that enhanced swab-based surveillance did not prove to be effective at reducing case-fatality or outbreak duration.[46]

Our review showed the different RRs associated with the frequency of screening (once *vs* twice a week) in the infection rate of subsequent BSI in non-colonised and colonized babies. Despite the multivariate meta-regression failing to demonstrate a statistically significant finding for this factor, the screening time plays an important role in the clinical practice. A strategy of continuous surveillance of MDRGN colonization has been discussed extensively, both as a basis for preventing cross-infection and to facilitate infection control measures.[47] However, there is no consensus on the optimal timing and frequency of ongoing screening.

The predictive value of rectal MDRGN colonisation for subsequent MDRGN bacteraemia has been assessed in a number of studies in adults, with variable findings. Due to the significant implication of these highly resistant infections on healthcare costs and patients outcomes, the need to develop clinical prediction algorithms to identify patients potentially colonised with such organisms (and therefore candidates for screening) at hospital admission has been broadly recognised.[48]

At the moment, the cost-effectiveness of routine rectal screening cannot be fully elucidated. Frequent delays in laboratory reporting of microbiological results and increased exposure to broad-spectrum antibiotics are some of the potential limits for supporting colonisation-guided versus standard empiric antibiotic treatments. Without clear evidence of a significant impact on patient outcome, the implementation of routine surveillance cultures in those setting where MDRGNs are rare or endemic might not be warranted.

This review has several limitations. Firstly, the association between GNB colonisation and GN-BSI in neonates must be interpreted in the light of the small number of included studies and the high heterogeneity in terms of study design, included population, and investigated pathogens. Due to the low number of studies included in the meta-analysis, we were unable to assess publication bias. Different pathogens have been shown to have different impacts on the risk of developing invasive infections in colonised neonates, and pooling data on multiple strains could have biased the results.[42] Lastly, the quality of data reporting was assessed according to the STROBE-NI statement

checklist. However, this guideline was designed to improve the reporting of observational studies on the epidemiology of neonatal infections, and may not have been entirely suitable for some of the studies included in this review primarily designed for microbiological purpose. However, this is the only specific guidance currently available for the reporting of neonatal infections.

The analysis of large prospective cohorts of colonised neonates with their clinical outcomes is highly relevant in order to clarify the risk factors and determinants for invasive infections. This is evident from the observation that although we showed a correlation between colonisation and invasive disease, the majority of colonised babies do not develop systemic invasive infection. Previously published studies did not attempt to link WGS data with clinical outcome nor to ascertain the relatedness between colonising and invasive pathogens. Such information could assist in gaining evidence on pathogenicity determinants and might have a significant impact on the management of neonates with GN-BSIs. If a correlation between gut colonisation and invasive infections is confirmed, easy-to-collect rectal swab data could be used as a proxy, at the patients- or NICU-level, to inform empirical antibiotic treatment in neonates with suspected BSIs. In the LMIC setting, blood cultures are infrequently obtained from neonates, thus readily obtained rectal swabs could be used as a predictor of MDR pattern at unit-level and help identify the optimal antibiotic regimens to be used. In HIC, demonstrating a correlation between colonisation and invasive infections might help define the best strategies for Infection Prevention and Control (e.g. cohorting babies during hospital outbreaks) and to select babies who would benefit most from broad-spectrum antibiotics (for targeted clinical management) and those who can receive more narrow-spectrum antibiotics.

TRANSPARENCY DECLARATION

Conflict of Interests: Mike Sharland reports other from Pfizer, GSK, outside the submitted work; and Julia Bielicki declared that her husband is senior corporate counsel at Novartis International AG, Basel, Switzerland and owns stock and stock options.

Funding: This study did not receive any direct funding.

Contributors statement: All authors contributed to the conception and design of the study. LF and CT collected the data. LF, YH, JB, and MS contributed to the analysis of the data. All authors contributed to the interpretation of the data. LF, CT, and JB wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

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Table 1: Meta-regression to determine the factors that account for the heterogeneity between studies in the baby-level

Variable	Coefficient	p-value	95%CI lower	95%CI upper
Screening timing	0.197	0.594	-3.193	3.589
GDP[a] classification	-0.273	0.417	-2.939	2.392
During outbreak (Y/N)	0.275	0.412	-2.370	2.921
Pathogen	-0.266	0.422	-2.910	2.378

[a]GDP: Gross domestic product

Table 2: Colonisation pressure and rate of Bloodstream Infections in studies included in the unit-level analysis

Author, year	Population (n of screened babies)	N of colonised babies	Colonisation pressure (%)	N of infected babies (in the same period)	BSI rate (%)
Cassettari VC, 2009 [29]	120	27	22.5	7	5.8
Das P, 2011 [9]	242	198	81.8	32	13.2
Gbaguidi-Haore H, 2008 [30]	735	166	22.6	29	3.9
Gupta A, 2004 [31]	73	14	19.2	6	8.2
Haase R, 2014 [32]	635	27	4.3	4	0.6
Litzow JM, 2009 [33]	1,831	1,017	55.5	358	19.6
Macnow T, 2013 [34]	1,475	15	1.0	8	0.5
Mammina C, 2007 [35]	210	116	55.2	25	11.9
Parm U, 2011 [36]	276	154	55.8	27	9.8
Rettedal S, 2013 [37]	469	58	12.4	1	0.2
Richards C, 2004 [38]	69	8	11.6	0	0.0
Roy S, 2010 [39]	228	25	11.0	19	8.3

[a]**BSI: Bloodstream infection**

Figure 1

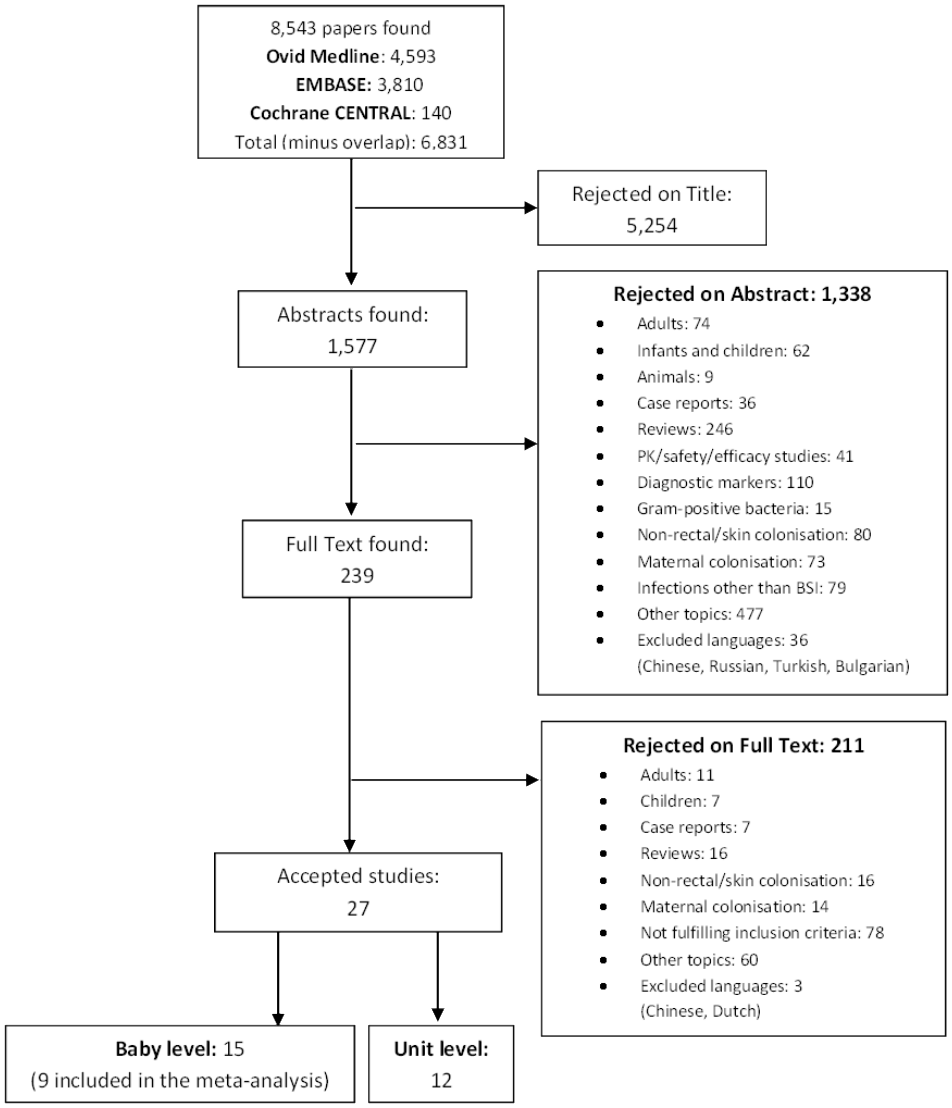
8,543 papers found
Ovid Medline: 4,593
EMBASE: 3,810
Cochrane CENTRAL: 140
Total (minus overlap): 6,831
Rejected on Title:
5,254
Abstracts found:
1,577
Rejected on Abstract: 1,338
Adults: 74
Infants and children: 62
Animals: 9
Case reports: 36
Reviews: 246
PK/safety/efficacy studies: 41
Diagnostic markers: 110
Gram-positive bacteria: 15
Non-rectal/skin colonisation: 80
Maternal colonisation: 73
Infections other than BSI: 79
Other topics: 477
Excluded languages: 36
(Chinese, Russian, Turkish, Bulgarian)
Full Text found:
239
Rejected on Full Text: 211
Adults: 11
Children: 7
Case reports: 7
Reviews: 16
Non-rectal/skin colonisation: 16
Maternal colonisation: 14
Not fulfilling inclusion criteria: 78
Other topics: 60
Excluded languages: 3
(Chinese, Dutch)
Accepted studies:
27
Baby level: 15
(9 included in the meta-analysis)
Unit level:
12

Figure 2

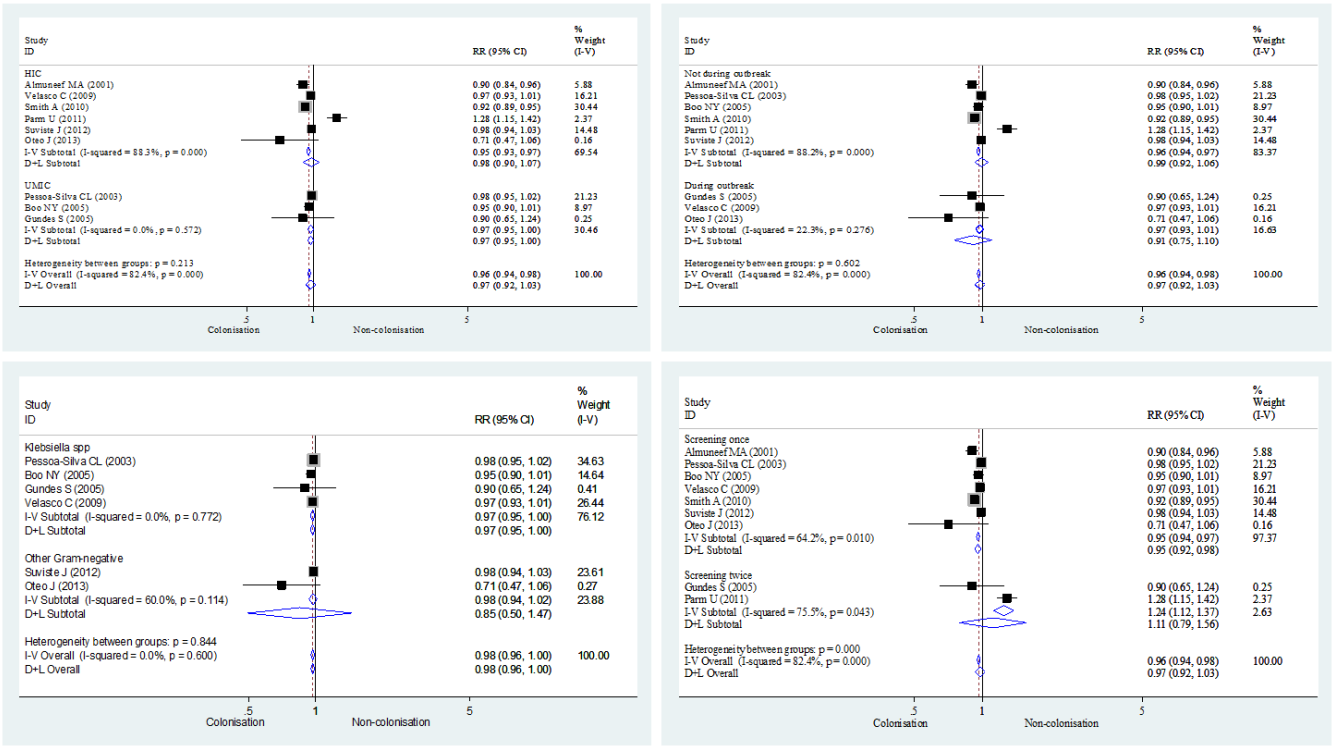
Study
ID
RR (95% CI)
% Weight (I-V)
HIC
Almuneef MA (2001) 0.90 (0.84, 0.96) 5.88
Velasco C (2009) 0.97 (0.93, 1.01) 16.21
Smith A (2010) 0.92 (0.89, 0.95) 30.44
Parm U (2011) 1.28 (1.15, 1.42) 2.37
Suviste J (2012) 0.98 (0.94, 1.03) 14.48
Oteo J (2013) 0.71 (0.47, 1.06) 0.16
I-V Subtotal (I-squared = 88.3%, p = 0.000) 0.95 (0.93, 0.97) 69.54
D+L Subtotal 0.98 (0.90, 1.07)
UMIC
Pessoa-Silva CL (2003) 0.98 (0.95, 1.02) 21.23
Boo NY (2005) 0.95 (0.90, 1.01) 8.97
Gundes S (2005) 0.90 (0.65, 1.24) 0.25
I-V Subtotal (I-squared = 0.0%, p = 0.572) 0.97 (0.95, 1.00) 30.46
D+L Subtotal 0.97 (0.95, 1.00)
Heterogeneity between groups: p = 0.213
I-V Overall (I-squared = 82.4%, p = 0.000) 0.96 (0.94, 0.98) 100.00
D+L Overall 0.97 (0.92, 1.03)
.5
1
5
Colonisation
Non-colonisation
Study
ID
RR (95% CI)
% Weight (I-V)
Not during outbreak
Almuneef MA (2001) 0.90 (0.84, 0.96) 5.88
Pessoa-Silva CL (2003) 0.98 (0.95, 1.02) 21.23
Boo NY (2005) 0.95 (0.90, 1.01) 8.97
Smith A (2010) 0.92 (0.89, 0.95) 30.44
Parm U (2011) 1.28 (1.15, 1.42) 2.37
Suviste J (2012) 0.98 (0.94, 1.03) 14.48
I-V Subtotal (I-squared = 88.2%, p = 0.000) 0.96 (0.94, 0.97) 83.37
D+L Subtotal 0.99 (0.92, 1.06)
During outbreak
Gundes S (2005) 0.90 (0.65, 1.24) 0.25
Velasco C (2009) 0.97 (0.93, 1.01) 16.21
Oteo J (2013) 0.71 (0.47, 1.06) 0.16
I-V Subtotal (I-squared = 22.3%, p = 0.276) 0.97 (0.93, 1.01) 16.63
D+L Subtotal 0.91 (0.75, 1.10)
Heterogeneity between groups: p = 0.602
I-V Overall (I-squared = 82.4%, p = 0.000) 0.96 (0.94, 0.98) 100.00
D+L Overall 0.97 (0.92, 1.03)
.5
1
5
Colonisation
Non-colonisation
Study
ID
RR (95% CI)
% Weight (I-V)
Klebsiella spp
Pessoa-Silva CL (2003) 0.98 (0.95, 1.02) 34.63
Boo NY (2005) 0.95 (0.90, 1.01) 14.64
Gundes S (2005) 0.90 (0.65, 1.24) 0.41
Velasco C (2009) 0.97 (0.93, 1.01) 26.44
I-V Subtotal (I-squared = 0.0%, p = 0.772) 0.97 (0.95, 1.00) 76.12
D+L Subtotal 0.97 (0.95, 1.00)
Other Gram-negative
Suviste J (2012) 0.98 (0.94, 1.03) 23.61
Oteo J (2013) 0.71 (0.47, 1.06) 0.27
I-V Subtotal (I-squared = 60.0%, p = 0.114) 0.98 (0.94, 1.02) 23.88
D+L Subtotal 0.85 (0.50, 1.47)
Heterogeneity between groups: p = 0.844
I-V Overall (I-squared = 0.0%, p = 0.600) 0.98 (0.96, 1.00) 100.00
D+L Overall 0.98 (0.96, 1.00)
.5
1
5
Colonisation
Non-colonisation
Study
ID
RR (95% CI)
% Weight (I-V)
Screening once
Almuneef MA (2001) 0.90 (0.84, 0.96) 5.88
Pessoa-Silva CL (2003) 0.98 (0.95, 1.02) 21.23
Boo NY (2005) 0.95 (0.90, 1.01) 8.97
Velasco C (2009) 0.97 (0.93, 1.01) 16.21
Smith A (2010) 0.92 (0.89, 0.95) 30.44
Suviste J (2012) 0.98 (0.94, 1.03) 14.48
Oteo J (2013) 0.71 (0.47, 1.06) 0.16
I-V Subtotal (I-squared = 64.2%, p = 0.010) 0.95 (0.94, 0.97) 97.37
D+L Subtotal 0.95 (0.92, 0.98)
Screening twice
Gundes S (2005) 0.90 (0.65, 1.24) 0.25
Parm U (2011) 1.28 (1.15, 1.42) 2.37
I-V Subtotal (I-squared = 75.5%, p = 0.043) 1.24 (1.12, 1.37) 2.63
D+L Subtotal 1.11 (0.79, 1.56)
Heterogeneity between groups: p = 0.000
I-V Overall (I-squared = 82.4%, p = 0.000) 0.96 (0.94, 0.98) 100.00
D+L Overall 0.97 (0.92, 1.03)
.5
1
5
Colonisation
Non-colonisation

Figure legends

Figure 1: Flowchart and study selection

Figure 2: Random effects meta-analysis for estimated risk ratio at the baby-level by groups (Abbreviations: CI, confident interval; RR, risk ratio; HIC, high income country; UMIC, upper middle income country)

Figure 1S: Random effect meta-analysis for infection rate at the unit-level by groups