

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

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22 **ABSTRACT**

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

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

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

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

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

48 INTRODUCTION

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

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

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

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

76

77 **METHODS**

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

85 Medline (Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2016), Embase (Embase 1996 to
86 2016 Week 24), and Cochrane Library (Issue 6 of 12, June 2016) databases were systematically
87 searched on June 15, 2016 with a strategy combining MeSH and free text terms for “neonate” AND
88 “colonisation” AND “bloodstream infection”. The full strategy is available as Supplementary Material.

89 Two assessments for included studies were performed. In the first one (baby-level) inclusion criteria
90 for studies were their reporting of: 1) data on neonates aged 0-28 days, 2) the total number of babies
91 colonised with GNs assessed by rectal swab/stool culture or skin swab culture, and 3) the total number
92 of GN-colonised babies who developed a concordant (caused by the same pathogen) GN-BSI. In the
93 second assessment (unit-level), inclusion criteria were studies reporting: 1) data on neonates aged 0-
94 28 days, 2) the total number of babies colonised with GNs assessed by rectal swab/stool culture or
95 skin swab culture during the study period, and 3) the total number of babies with GN-BSI in the same
96 unit during the same timeframe were considered eligible for inclusion. Studies were excluded if

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

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

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

108 This study did not receive any direct funding.

109 **Quality assessment**

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

117 **Statistical analysis**

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

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

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

141

142 **RESULTS**

143 **Study selection and description**

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

154 Apart from one study,[23] all papers assessed colonisation through rectal swab or stool culture (**Table**
155 **2S**). 24 (88.9%) out of 27 studies provided information about timing and frequency of microbiological
156 screening.[4, 6, 8, 9, 17-36] In nearly half of the studies, rectal/skin swabs were performed weekly
157 through the baby's NICU stay[4, 6, 17, 19, 20, 24-30, 32, 33] whereas in 6 studies neonates were
158 screened twice a week.[8, 21, 22, 31, 35, 36]

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

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

165 **Quality assessment of included studies**

166 A huge variation was highlighted in terms of study design (prospective vs retrospective, inclusion
167 criteria, different outcomes assessed), included population (gestational age, birth weight, sample
168 size), and investigated pathogens (different strains, different resistance pattern). Overall, according to
169 the STROBE-NI checklist,[12] the included studies reported adequately a mean of 44.8% (range 8.6-
170 67%) of the suggested items. A statistically significant difference was highlighted in terms of
171 compliance with the checklist between studies primarily designed for clinical and those mainly for
172 microbiological purposes (47.2% vs 32.4%, p=0.034). As summary considerations on study quality in
173 general, according to the Newcastle-Ottawa scale, all studies assessed the exposure and the outcome
174 by using secure records, and all of them selected the non-exposed cohort from the same community
175 as the exposed cohort. However, very few studies demonstrated that the outcome of interest was not
176 present at the start of the study and none of them reported a statement about proportion of patients
177 who completed the follow-up (Table 1S).

178 **Baby-level analysis**

179 15 studies were included in the baby-level analysis,[4, 6, 8, 17-28] 3 (20.0%; 3/15) of which were
180 carried out during NICU outbreaks.[21, 24, 28] 7 (46.7%; 7/15) studies provided information about
181 demographic characteristics of the included cohort (e.g. age at screening, birth weight or gestational
182 age) (**Table 3S**).[4, 6, 8, 19, 22, 25, 26] The length of follow-up was reported in 6 studies.[6, 22, 24-26,
183 28] Five studies reported the interval between colonization and onset of concordant BSI.[8, 13, 16, 21-
184 22]

185 Overall, a total of 8,421 neonates were screened for rectal and/or skin colonisation. Among them,
186 1,984 (23.6%) were found to be colonised by GNB. In total, 157 colonised babies experienced a BSI
187 concordant with the colonising pathogen (7.9%). A broad variation was found among the included
188 studies in terms of prevalence of concordant GN-BSIs in colonised babies (range 0.0 – 42.8%). In those
189 studies that also reported the number of non-colonized babies who developed a GN-BSI, the
190 proportion of neonates who experienced a GN-BSI was 2.4% (85/3,583).

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

193 Meta-analysis

194 All sub-group meta-analyses results are shown in **Figure 2**. The random-effects inverse variance meta-
195 analysis for all sub-groups demonstrated strong evidence of heterogeneity within sub-groups, and
196 heterogeneity between sub-groups. The overall estimated RRs in within sub-groups analyses did not
197 show any differences for GDP, pathogen, and outbreak. However, when conducting separate meta-
198 analysis for screening frequency, RR of GN-BSI in babies screened twice/week compared with once a
199 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
200 colonisation group. *I*-squared (I^2) estimates of 75.5% (screening twice) and 64.2% (screening once)
201 showed a different heterogeneity to the overall meta-analysis. To further explore heterogeneity
202 between studies, we performed multivariate meta-regression analysis (**Table 1**). All included variables
203 in the meta-regression analysis did not show statistically significant impact on GN colonisation and
204 GN-BSI in the baby-level.

205 **Unit-level analysis**

206 12 studies were included for the analysis at the unit-level,[9, 29-39] 5 (41.6%) of which were carried
207 out during outbreaks in the neonatal units.[29-31, 37, 38]

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

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

216 Meta-analysis

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

221

222 **DISCUSSION**

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

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

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

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

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

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

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

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

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

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

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

307 **TRANSPARENCY DECLARATION**

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

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313 collected the data. LF, YH, JB, and MS contributed to the analysis of the data. All authors contributed
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315 revised the manuscript critically for important intellectual content. All authors approved the final
316 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

^aGDP: 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

^aBSI: Bloodstream infection

Figure 1

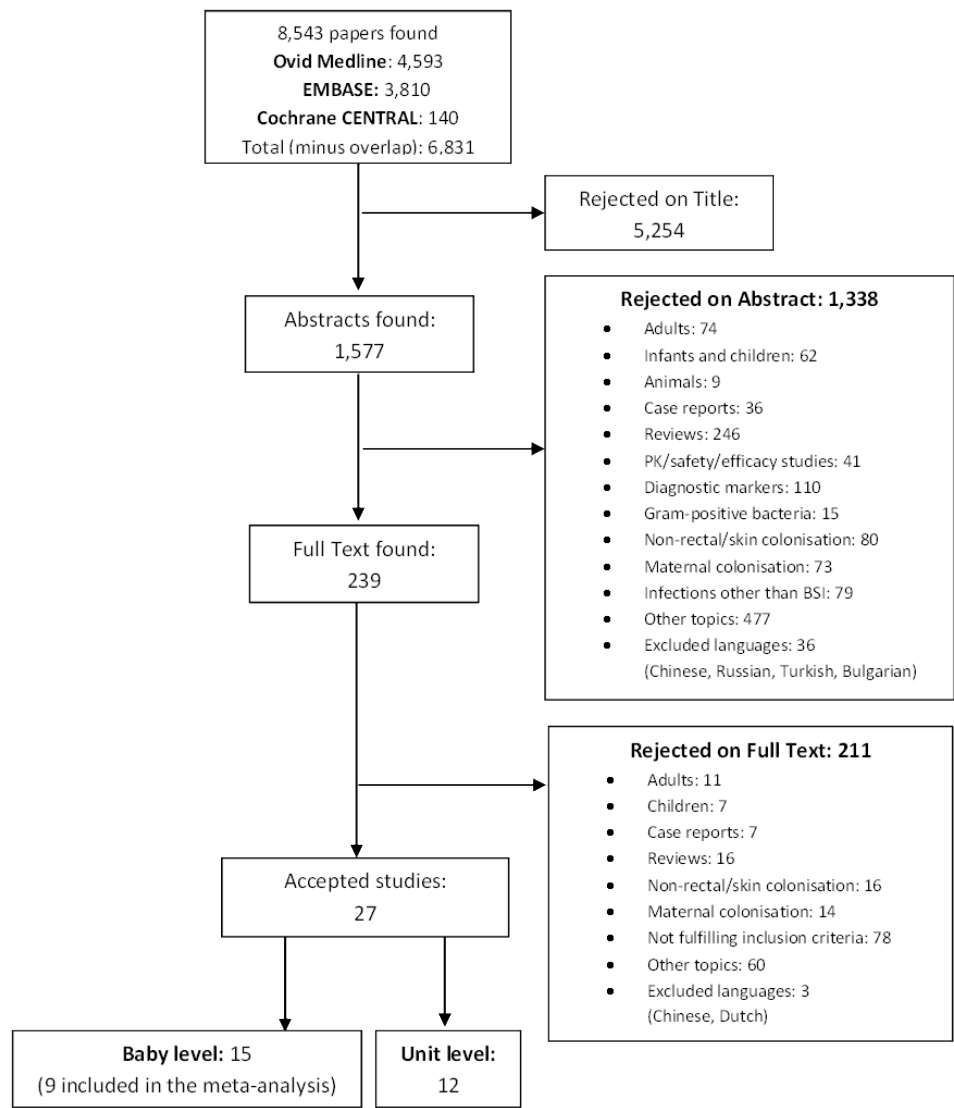


Figure 2

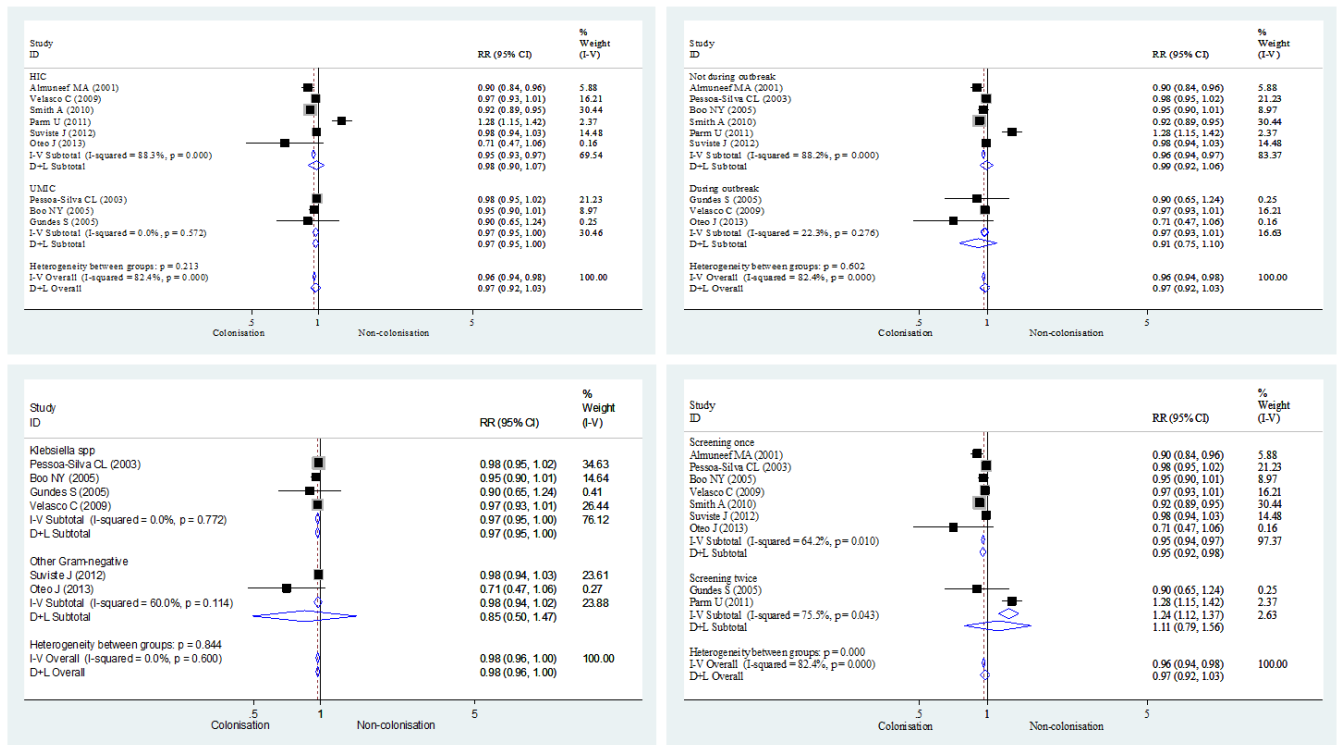


Figure legends

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