

Supplementary Results

Gram-negative bacteraemia in very low birth weight infants

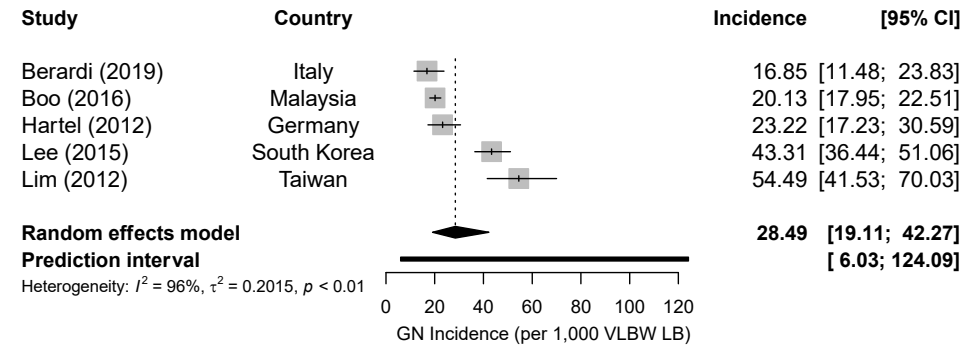
Eleven studies,¹⁻¹¹ all but two (from Bangladesh and Iraq)^{1,4} in HIC, reported Gram-negative infections in very low birthweight (VLBW) infants (<1,500g), one of which (from Italy) included extremely low birthweight infants (ELBW, <1,000g).² The overall incidence of GNB in VLBW infants (based on data from 5 studies) was 28.5 (95%CI 19.1-42.3) per 1,000 VLBW live births (see Figure SR1 below). The incidence reported by Berardi *et al.* for ELBW infants in Italy was 138.8 per 1000 live births.² The most commonly reported pathogens in VLBW infants were *Klebsiella* spp. (n=845 isolates, prevalence 8.89%, 95%CI 3.94-18.9%), *E. coli* (n=833, prevalence 5.77%, 95%CI 4.23-7.83%), and *Enterobacter* spp. (n=714, 3.85%, 95%CI 2.47-5.96%) (see Table SR1 below).

Gram-negative bacteraemia by gestational age

Ten studies, including 4 from LMIC, described GNB at different gestational ages.^{2,4,12-19} Berardi *et al.* was the only study that reported incidence for term (≥ 37 months), preterm (28-36 weeks) and extremely preterm infants (<28 weeks) infants.² Preterm and extremely preterm infants showed a higher incidence with 15.2 and 174.0 episodes per 1,000 live births, respectively, compared to those carried to term. Heterogeneity and non-reporting of gestational age cut-offs defining preterm and very/extremely precluded meta-analysis, but *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. tended to be the most reported species as for low birthweight infants (Supplementary Data, online supplemental file 1).

Gram-negative bacteria in cerebrospinal fluid cultures

Of the 17 studies reporting CSF culture results,^{2,17,20-34} three studies in HIC reported Gram-negative infection incidence, which ranged from 0.07-0.38 per 1,000 live births.^{25,29,30} The most frequently reported Gram-negative species in CSF cultures from all studies combined was *Escherichia coli* (n=433 isolates, prevalence 14.3%, 95%CI 9.97-20.0%), followed by *Klebsiella* spp. (n=58, 1.02%, 0.45-3.16%) and *Enterobacter* spp. (n=53, 1.02%, 0.40-2.60%) (Table SR2, Table SR3).

Figure SR1. Gram-negative (GN) bacteraemia incidence per 1,000 very low birth weight (VLBW) live births (LB)**Table SR1.** Aetiology of Gram-negative bacteraemia in very low birth weight infants by random-effects meta-analysis (11 studies)

	Isolates, n	proportion [95% CI]	τ^2	τ	I^2 [95% CI]	H [95% CI]
<i>Escherichia coli</i>	833	5.77% [4.23 - 7.83%]	0.24	0.49	91.8% [87.3% - 94.7%]	3.49 [2.80 - 4.34]
<i>Klebsiella</i> spp.	845	8.89% [3.94 - 18.9%]	2.04	1.43	96.6% [95.2% - 97.5%]	5.39 [4.56 - 6.37]
<i>Pseudomonas</i> spp.	234	0.94% [0.34 - 2.55%]	2.30	1.52	89.8% [83.8% - 93.6%]	3.13 [2.48 - 3.95]
<i>Enterobacter</i> spp.	714	3.85% [2.47 - 5.96%]	0.45	0.67	96.0% [94.4% - 97.2%]	5.02 [4.22 - 5.98]
<i>Serratia</i> spp.	209	1.53% [0.80 - 2.93%]	0.99	1.00	87.9% [80.4% - 92.6%]	2.88 [2.26 - 3.67]
<i>Proteus</i> spp.	3	0.0% [0.0 - 4.10%]	11.15	3.34	0.0%	1
<i>Salmonella</i> spp.	0	N/A	N/A	N/A	N/A	N/A
<i>Citrobacter</i> spp.	19	0.0% [0.0 - 0.51%]	10.28	3.21	0.0%	1
<i>Haemophilus</i> spp.	0	N/A	N/A	N/A	N/A	N/A
<i>Neisseria</i> spp.	0	N/A	N/A	N/A	N/A	N/A
<i>Acinetobacter</i> spp.	133	0.10% [0.01 - 1.78%]	13.31	3.65	92.3% [88.2% - 95.0%]	3.61 [2.91 - 4.47]
<i>Moraxella</i> spp.	0	N/A	N/A	N/A	N/A	N/A
Other spp. or unspecified Gram-negative	136	0.13% [0.01 - 2.09%]	13.11	3.62	91.0% [86.0% - 94.3%]	3.34 [2.67 - 4.17]

SR3

Table SR2: Gram-negative species as percentages of all infant cerebrospinal fluid (CSF) infections (Gram-negative and Gram-positive)*

Species isolated in CSF	Isolates, n	proportion [95%CI]
<i>Escherichia coli</i>	433	14.3% [9.97 - 20.0%]
<i>Klebsiella</i> spp.	58	1.20% [0.45 - 3.16%]
<i>Pseudomonas</i> spp.	28	0.94% [0.34 - 2.55%]
<i>Enterobacter</i> spp.	53	1.02% [0.40 - 2.60%]
<i>Serratia</i> spp.	8	0.09% [0.01 - 0.79%]
<i>Proteus</i> spp.	10	0.11% [0.02 - 0.68%]
<i>Salmonella</i> spp.	65	0.24% [0.04 - 1.63%]
<i>Citrobacter</i> spp.	3	0.11% [0.02 - 0.72%]
<i>Haemophilus</i> spp.	81	0.99% [0.28 - 3.44%]
<i>Neisseria</i> spp.	53	0.54% [0.14 - 1.99%]
<i>Acinetobacter</i> spp.	47	0.09% [0.01 - 1.05%]
<i>Moraxella</i> spp.	0	N/A
Other spp. or unspecified Gram-negative	74	1.03% [0.35 - 3.00%]

* Estimates obtained by random-effects meta-analysis; data from 17 studies (China x 2, India, Kenya, Malawi, Namibia, USA x 3, Canada x 2, France, Israel, Italy, Korea, Taiwan, UK); see Table SR3 for heterogeneity statistics

Table SR3. Heterogeneity statistics for infant invasive (CSF) Gram-negative bacterial infections by random-effects meta-analysis (corresponding to results in Table SR2)

	τ^2	τ	I ² [95% CI]	H [95% CI]
<i>Escherichia coli</i>	0.62	0.79	87.8% [82.0% - 91.7%]	2.86 [2.35 - 3.47]
<i>Klebsiella</i> spp.	2.45	1.57	41.4% [0.0% - 67.0%]	1.31 [1.00 - 1.74]
<i>Pseudomonas</i> spp.	2.31	1.52	89.8% [83.8% - 93.6%]	3.13 [2.48 - 3.95]
<i>Enterobacter</i> spp.	1.85	1.36	55.7% [23.6% - 74.3%]	1.50 [1.14 - 1.97]
<i>Serratia</i> spp.	2.15	1.47	0.0%	1
<i>Proteus</i> spp.	2.41	1.55	0.0%	1
<i>Salmonella</i> spp.	5.78	2.41	74.7% [59.3% - 84.3%]	1.99 [1.57 - 2.52]
<i>Citrobacter</i> spp.	0.10	0.32	0.0%	1
<i>Haemophilus</i> spp.	3.81	1.95	58.2% [28.4% - 75.6%]	1.55 [1.18 - 2.02]
<i>Neisseria</i> spp.	2.79	1.67	33.5% [0.0% - 62.9%]	1.23 [1.00 - 1.64]
<i>Acinetobacter</i> spp.	8.42	2.90	74.8% [59.6% - 84.3%]	1.99 [1.57 - 2.53]
<i>Moraxella</i> spp.	N/A	N/A	N/A	N/A
Other spp. or unspecified Gram-negative	2.89	1.70	68.7% [48.3% - 81.0%]	1.79 [1.39 - 2.30]

SR5

Supplementary References

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