

Supplementary Results

Gram-negative bacteraemia in very low birth weight infants

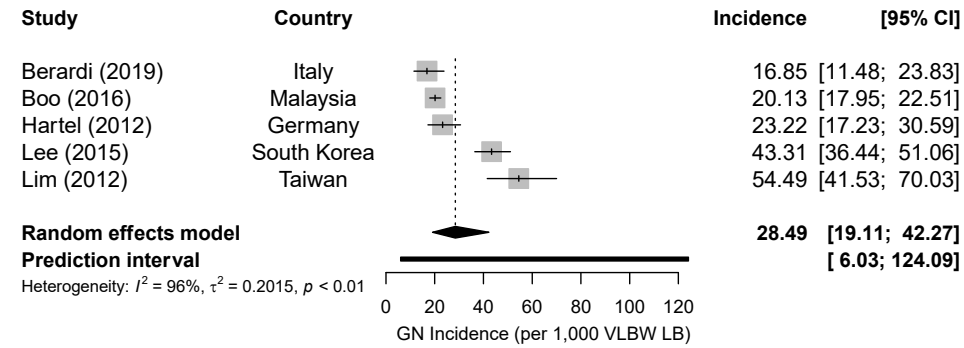
Eleven studies,¹⁻¹¹ all but two (from Bangladesh and Iraq)^{1,4} in HIC, reported Gram-negative infections in very low birthweight (VLBW) infants (<1,500g), one of which (from Italy) included extremely low birthweight infants (ELBW, <1,000g).² The overall incidence of GNB in VLBW infants (based on data 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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