Antibiotic resistance genes in the gut microbiota of mothers and linked neonates with or without sepsis from low- and middle-income countries (BARNARDS)

Maria J Carvalho[1, 2], Kirsty Sands[1, 3], BARNARDS Group, Timothy R Walsh[1, 3], *et al.*

Sepsis is a primary cause of mortality in newborns, particularly in low – and middle-income countries (LMICs). The "Burden of Antibiotic Resistance in Neonates from Developing Societies" study – BARNARDS – established a network of 12 clinical sites across Bangladesh, India, Pakistan, Ethiopia, Nigeria, Rwanda, and South Africa and developed analytical tools to understand the burden of antimicrobial resistance, risk factors and microbiological causes of infant sepsis. Involving over 160 researchers, clinicians, nurses, and data managers, we produced unprecedent data on neonatal sepsis in LMICs by blending microbiology, whole genome sequencing, and sociodemographic and clinical data. BARNARDS was a combination of two research programs funded by the Bill & Melinda Gates Foundation aiming at reducing infant mortality in LMICs.

In this study, we characterized the Gram-negative gut microbiota of 15,217 mothers and 2,931 neonates with clinical signs of sepsis carrying clinically important antimicrobial resistance (AMR) genes ($bla_{\text{CTX-M-15}}$, bla_{NDM}, bla_{KPC} and $bla_{\text{OXA-48}}$-like genes). We showed that the incidence of AMR gut carriage is extremely worrying in these countries (Figure 1a-f) and that resistant bacteria are present in neonates after just a few hours of life (Figure 1g,h).

We showed that poorer WASH indicators, use of antibiotics and previous infection were probably associated with gut microbiota carriage of $bla_{\text{CTX-M-15}}$, bla_{NDM} or $bla_{\text{OXA-48}}$-like genes. Furthermore, the carriage of these genes was a predictor of neonatal sepsis and adverse birth outcomes.

Finally, using whole-genome sequencing (WGS), we characterized common Gram-negative bacteria carrying carbapenemase genes, detailing specific variants and plasmid types across the different study sites (Figure 2). We showed that transmission dynamics can be very complex, as we found links between carriage, infection, and sanitation and hygiene.

Reference

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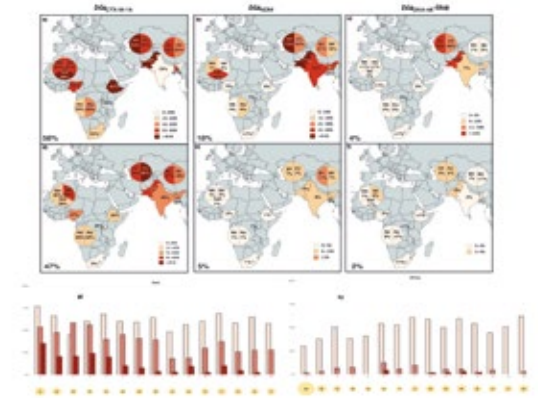

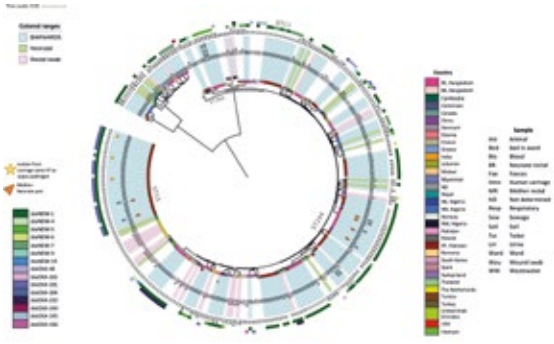

1 – Institute of Infection and Immunity, Cardiff University, United-Kingdom.

2 – Department of Medical Sciences & iBiMED, University of Aveiro.

3 – Ineos Oxford Institute of Antimicrobial Research, Department of Zoology, University of Oxford, United-Kingdom.

FIGURE 1

Prevalence of $bla_{\text{CTX-M-15}}$, bla_{NDM}, and $bla_{\text{OXA-48}}$-like genes among the rectal swabs of neonates and mothers. a-c, Prevalence of these genes among the rectal swabs of neonates. d-f, Prevalence of these genes among the rectal swabs of mothers. g,h, Carriage of $bla_{\text{CTX-M-15}}$, bla_{NDM}, and $bla_{\text{OXA-48}}$-like genes among neonates' rectal swabs against age of neonates at rectal swab collection per continent: Asia (g) and Africa (h). The prevalence of each AMR gene is plotted. The total number of samples collected per day is shown in the circles below the graphs.

FIGURE 2

The predominant gut isolates carrying ARG found were *E. coli, K. pneumoniae* and *E. cloacae* complex. *K. pneumoniae* isolates were also found to be the most common cause of sepsis in neonates enrolled in BARNARDS (Sands K*, Carvalho MJ* et al. doi: 10.1038/s41564-021-00870-7). This figure contains the phylogenetic tree based on the core genome of 268 *K. pneumoniae* genomes, including 161 from BARNARDS and 107 from other studies.