

# Antimicrobial resistance—a threat to neonate survival



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Improvements in child survival have contributed much of the gains in life expectancy at birth during the last two decades. At a global level, neonatal mortality has decreased from 36 to 19 deaths per 1000 livebirths between 1990 and 2012.<sup>1</sup> However, the reduction in neonatal mortality between 1990 and 2015 (47%) has lagged behind that of postneonatal under-5 years mortality (58%) globally.<sup>2</sup> The Every Newborn Action Plan aims for countries to have ten or fewer neonatal deaths per 1000 livebirths by 2035 (or 12 or fewer neonatal deaths by 2030).<sup>3</sup>

40% of newborn deaths and stillbirths occur around the time of birth and interventions that focus on facility-based care during this period have been shown to effectively prevent deaths and disability.<sup>4</sup> A particular focus of these interventions is on the reduction of neonatal sepsis or meningitis, which accounted for 421 000 deaths<sup>5</sup> or roughly 16% of neonatal deaths in 2013,<sup>5</sup> in which rates of reduction between 1990 and 2012 have been among the slowest. Facility-based births could help to reduce the risk of sepsis but poor quality facilities are where the dangers of antimicrobial resistance are greatest. Estimates indicate that 56 524 neonates die each year from resistance-attributable neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in India; the toll in Pakistan is 25 692 neonates.<sup>6</sup>

Our understanding of the impact of antimicrobial resistance on sepsis outcomes comes from small single-centre studies. In Tanzania, 40% of the 300 neonates with sepsis at a neonatal unit tracked in one study had early onset sepsis and 47% had a positive blood culture.<sup>7</sup> Of those, 29% of neonates who were culture positive died compared with 9% who were culture negative. Mortality was increased in neonates with a Gram-negative bacterial infection, extended-spectrum  $\beta$  lactamase producing organism or meticillin-resistant *Staphylococcus aureus*. A single neonatal intensive care unit study from India reported that the proportion of culture positive sepsis was 14.8 per 1000 inborn neonates and 83.0 per 1000 outborn neonates based on 997 blood cultures. Overall sepsis-related mortality was 19%.<sup>8</sup> Most cultures showed Gram-negative bacteria, *Klebsiella pneumoniae* being the most common pathogen.

The Delhi Neonatal Infection Study (DeNIS)<sup>9</sup> followed up a cohort of 88 636 newborn infants for about 3 years in three large hospitals in Delhi, India, and represents one of the largest studies to date of neonatal sepsis and resistance in the Indian subcontinent. A few key results stand out. Rates of culture-proven sepsis were high—9.5 per 1000 livebirths compared with less than 5.0 per 1000 livebirths in high-income countries<sup>10</sup> but lower than the 15.6 per 1000 livebirths reported from the National Neonatal-Perinatal Database of India.<sup>8</sup> Early onset sepsis was common with nearly two-thirds of cases occurring within 72 h of birth. Three pathogens (*Klebsiella* spp, *Acinetobacter* spp, and *Escherichia coli*) were associated with more than half (53%) of the infections. 181 (82%) of 222 infections caused by *Acinetobacter* spp were multidrug resistant, confirming that pan-resistant untreatable *Acinetobacter* spp infections associated with high mortality in neonatal nurseries is a subcontinental-wide problem.<sup>11</sup> Sepsis accounted for nearly a quarter of all newborn deaths, higher than the 15% in global estimates noted in 2013.<sup>5</sup> Case fatality rates of culture-positive and culture-negative sepsis were similar to those observed in other low-income and middle-income country settings (figure 1).

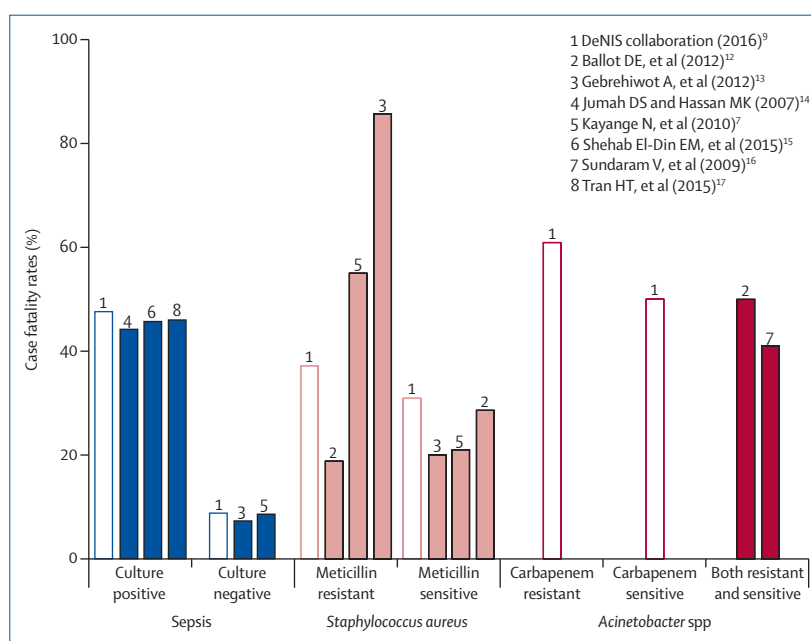


Figure: Case fatality rates from the DeNIS study (unshaded) compared with earlier studies (in solid colours)

There was a modest excess risk of mortality associated with multidrug-resistant organisms, which was lower than that previously recorded in south Asia.<sup>18</sup> There are methodological challenges in the attribution of excess neonatal mortality with antimicrobial resistance because of known confounding with severity of illness at presentation, treatment delay, and antibiotic choices. The fairly modest excess mortality (significant only for *Acinetobacter* spp and *Pseudomonas* spp) associated with antimicrobial resistance is also possibly accounted for by the high baseline mortality associated with culture-positive sepsis—as high as 67% in one facility.

Resistance among hospital acquired infections in Indian hospitals is a growing problem and driven by a combination of poor infection control and high, uncontrolled rates of antimicrobial prescribing.<sup>19</sup> Many neonates in hospitals in south Asia are now treated with carbapenems as a first-line therapy for sepsis or presumed sepsis. Against this backdrop, the widespread availability and antimicrobial use in community settings and the contribution of antimicrobial resistance as a complicating factor in neonate sepsis becomes extremely important.

Notwithstanding the importance of preventive strategies to reduce the risks and burden of neonatal infections,<sup>3</sup> early detection and prescribing of appropriate antibiotics will remain the cornerstone of management strategies. The DeNIS study highlights the serious risk associated with neonatal sepsis and resistance in health-care facilities that would rank among the better performing hospitals in a large middle-income country.

With an increased focus on institutionalising births in India and other low-income and middle-income countries, the quality of care and infection control in health-care institutions must receive greater attention and resources.

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