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Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC) Project: low adherence to WHO recommendations for neonatal sepsis treatment in developing countries

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Background: The neonatal mortality remains high with an estimated 2.9 million newborn deaths every year worldwide. It has been reported that approximately 23% of neonatal deaths are caused by infections (mainly sepsis). A detailed understanding of the treatment of neonatal sepsis is the first step to determine the scope of the problem and to define next steps to tackle it. Ampicillin in combination with gentamicin is recommended by WHO as the first-line treatment for neonatal sepsis. There is currently limited data on antibiotic use for neonatal sepsis treatment. This study describes antibiotic prescribing patterns for sepsis treatment in neonates globally.

Material/methods: Two Point Prevalence Surveys (PPSs) of antimicrobial prescribing were conducted between February and March, and May and June 2016. The surveys were conducted in 51 hospitals in 18 countries covering 5 WHO-regions: Africa (Nigeria, South Africa), Americas (Argentina, Brazil, Mexico, USA), Europe (Germany, Spain, Finland, Greece, Italy, Israel, Slovenia, UK), South-East Asia (Thailand, India), and Western Pacific (Australia, China). A web-based surveillance system was used for data collection across country. The surveys included children and neonates receiving an antimicrobial on the day of PPS. Data collected included demographics, antimicrobial agents, dose, frequency, mode of administration, and reasons for treatment. Neonates aged ≤ 30 days receiving at least one systemic antibiotic (ATC code: J01) for sepsis on the day of survey were included.

Results: A total of 253 neonates were surveyed. There was variation of antibiotic use for neonatal sepsis across the regions and the use of broad-spectrum antibiotics was high (Table 1). In Africa, the use of meropenem (33.3%) for neonatal sepsis treatment was higher compared to gentamicin (21.2%) and ampicillin (9.1%). Amikacin represented about 24% of prescriptions for sepsis treatment in South-East Asia, whereas the proportions of ampicillin and gentamicin use were low with 6.0% and 4.8%, respectively. In the West Pacific, gentamicin (24.1%) was frequently prescribed for sepsis treatment followed by benzylpenicillin (19.3%). Overall, only 29 neonates (11%; 29/253) received ampicillin in combination with gentamicin for sepsis treatment. Of these, 22.6% (7/31) were from the Americas, 19.4% (19/98) in Europe, 3.8% (2/53) from South-East Asia, and 2.0% (1/49) from Africa. No neonate was reported to receive ampicillin and gentamicin regimen in Western Pacific.

Conclusions: Antibiotic use for neonatal sepsis treatment varied globally. In this survey, many neonates received care from tertiary care hospitals introducing sampling bias. Despite the WHO recommendations, the regimen of ampicillin in combination with gentamicin for neonatal sepsis treatment was infrequently used. Understanding why WHO guidelines on neonatal sepsis are not more widely followed is important in order to design interventions to improve adherence to the guidelines.

Table 1. Antibiotics prescribing for sepsis treatment in neonates by WHO regions, presented by drug utilisation 90%

	Africa (n=22)	Americas (n=31)	Europe (n=98)	South-East Asia (n=53)	West Pacific (n=49)
<u>Meropenem</u>	33.3%	Gentamicin 27.3%	Ampicillin 21.9%	Amikacin 23.8%	Gentamicin 24.1%
Gentamicin	21.2%	Ampicillin 18.2%	Gentamicin 20.2%	<u>Piperacillin/inhib.</u> 15.5%	<u>Benzylpenicillin</u> 19.3%
Ceftriaxone	15.2%	Cefazolin 10.9%	Vancomycin 10.9%	<u>Meropenem</u> 15.5%	<u>Amoxicillin/inhib.</u> 16.8%
Ampicillin	9.1%	<u>Meropenem</u> 10.9%	Cefotaxime 10.4%	<u>Cefoperazone comb.</u> 10.7%	<u>Meropenem</u> 9.6%
Vancomycin	6.1%	Amikacin 9.1%	<u>Benzylpenicillin</u> 6.3%	Ampicillin 6.0%	<u>Ceftizoxime</u> 7.2%
Cefotaxime	3.0%	Vancomycin 7.3%	Amikacin 6.3%	Cefotaxime 6.0%	<u>Flucloxacillin</u> 6.0%
Procaine <u>benzylpenicillin</u>	3.0%	Oxacillin 7.3%	<u>Meropenem</u> 5.8%	Gentamicin 4.8%	<u>Latamoxef</u> 2.4%
			<u>Flucloxacillin</u> 4.6%	Ceftriaxone 3.6%	<u>Mezlocillin</u> 1.2%
			Amoxicillin 4.0%	<u>Colistin</u> 3.6%	<u>Pencillins comb.</u> 1.2%
					Amikacin 1.2%
					<u>Cefoperazone comb.</u> 1.2%